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Polymethylhydrosiloxane (PMHS): A Convenient Option for Synthetic Applications of the Iodine/Silane Combined Reagent – Straightforward Entries to 2-Hydroxyglycals and Useful Building-Blocks of Glucuronic Acid and Glucosamine

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Dedicated to the memory of Professor Ernesto Fattorusso

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Polymethylhydrosiloxane (PMHS) proved to be a practically convenient alternative to triethylsilane in a large set of synthetic elaborations entailing the quick generation of glycosyl iodides with a iodine/silane combined reagent. In addition, the scope of this combined reagent was expanded to the especially fast generation of 2-acetoxyglycals, and the rapid synthesis of useful building-blocks of D-glucuronic acids and D-glucosamine. All the synthetic targets were obtained in especially short times either via one-pot procedures or through experimental sequences devoid of laborious chromatographical purifications of intermediates.

Introduction

In recent years, the iodine/triethylsilane reagent combination has proved to be a very effective tool for a wide range of synthetic applications, and it can be used under simple experimental conditions.[1] In this context, we have demonstrated the successful application of this reagent combination to a large set of transformations in carbohydrate chemistry. Many of these transformations go via glycosyl iodide intermediates, which can be quickly generated (generally in a few minutes) by exposing 1-*O*-acetylated sugars to a moderate excess of the two reagents (1.4 equiv.) in refluxing CH_2Cl_2. It is reasonable to assume that HI generated in situ is the actual promoter of the process. The crude glycosyl iodides thus obtained can, in turn, be converted into a wide variety of useful intermediates, such as 1,2-orthoesters,[2,3] 1,2-ethylidenes,[2] glycals,[2] thio- and selenoglycosides,[4,5] estradiol glycosides,[6] 2-*O*-deprotected allyl glycosides,[7] (selenophenyl)thioglycosides,[8,9] and glycosyl disulfides.[10] Advantages associated with all of these applications include the avoidance of chromatographic purification of the glycosyl iodide intermediates, and the especially high reactivity of these intermediates in the subsequent reactions.

Very recently, the combination of iodine and polymethylhydrosiloxane (PMHS) was found to promote the reductive Ferrier rearrangement, a reaction that was promoted equally effectively with iodine/triethylsilane.[11] The fact that polymeric PMHS has a lower cost per silane unit than triethylsilane (about 7–10 times less expensive) spurred us to evaluate this reagent in the wide repertoire of transformations previously mentioned. It should also be noted that PHMS has some additional advantages: (a) it is regarded as an easy to handle and environmentally friendly reducing agent; (b) it is more stable to air and moisture than other silanes; (c) it can be stored for long periods of time without loss of activity.[12]

In addition to establishing even more cost-effective procedures, another goal of the work reported in this paper was to extend the scope of the iodine/silane-based procedures to substrates and functional group manipulations that had not previously been examined.

Results and Discussion

At the outset of this investigation, we examined the ability of the iodine/PMHS combined system to promote the anomeric iodination of per-*O*-acetylated sugars. In this reaction, the replacement of Et_3SiH (1.4 equiv.) with PMHS (1.4 equiv. silane units) resulted in very similar iodination rates when keeping the same stoichiometric ratios of the reagents. The reactions were complete in 5–10 min in refluxing CH_2Cl_2 according to TLC analysis, starting from

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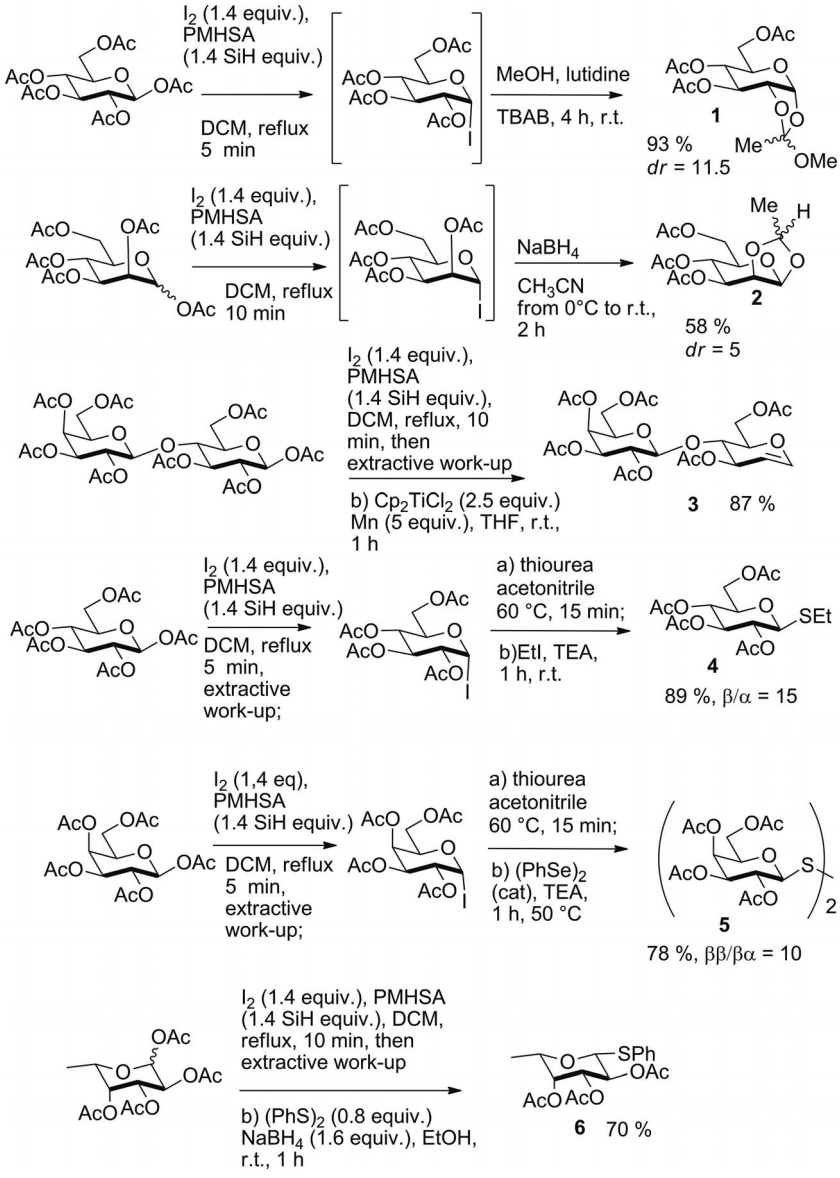


Scheme 1. Synthetic applications of the I_2/PMHS system.

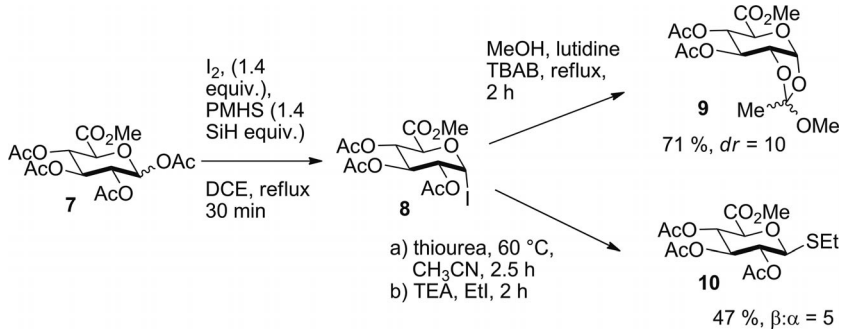
the diverse set of per-*O*-acetylated sugars shown in Scheme 1. Having obtained these promising preliminary results, a critical issue for the success of these modified conditions was to ascertain the reactivity of the resulting crude iodides in the wide range of protocols previously established with the iodine/Et_3SiH system.

Indeed, we had shown that iodides generated from the iodine/Et_3SiH combination did not need to be chromatographically isolated, but could be obtained by a simple extractive work-up, contaminated only by triethylsilane-derived by-products that proved to be inert in all the transformations mentioned above. In the case of the synthesis of 1,2-orthoesters and 1,2-ethylidenes, the two steps could be even performed in a one-pot mode by simple addition of the requisite reagents to the iodination vessel (a preliminary change of solvent was required for 1,2-ethylidene synthesis).[2]

Revisiting these synthetic sequences with the simple replacement of triethylsilane by PMHS was rewarding, and very good results were obtained in the synthesis of a wide range of model products, such as 1,2-orthoester **1**, 1,2-ethylidene **2**, 1,2-glycal **3**, alkylthioglycoside **4**, symmetrical glycosyl disulfide **5**, and phenyl thioglycoside **6** (Scheme 1).

These results show the versatility of this approach, as a varied set of saccharide building-blocks may be formed, but the results also highlight the fact that it is feasible to use structurally diverse per-*O*-acetylated starting materials, including *gluco*-, *galacto*-, or *manno*-configured hexoses, 6-deoxyhexoses, and disaccharides.

Having proved the reliable reproducibility of a large set of established protocols at a lower cost, our research was next directed towards expanding the repertoire of applicaitons of the iodine/silane reagent. The extension of the anomeric iodination protocol to per-*O*-acetylated methyl



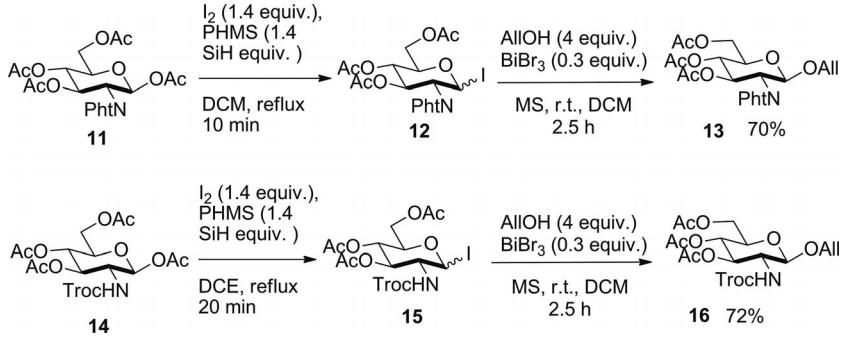
Scheme 2. Anomeric iodination of glucuronic acid and subsequent synthetic transformations.

uronate **7** (Scheme 2) initially proved difficult, as expected from the lower anomeric reactivity of uronic acid derivatives. Indeed, exposure of **7** to I_2 and Et_3SiH (1.4 equiv. each) in refluxing dichloromethane resulted in only partial anomeric iodination. A simple and effective solution was achieved by switching the solvent to the higher boiling 1,2-dichloroethane (DCE) under reflux conditions. With this modification, the precursor was smoothly converted into the corresponding iodide in about 30 min, and also underwent the same transformation when PHMS was used (Scheme 2). Notably, the efficacy of the protocol was not influenced by the anomeric composition of **7**, with the less reactive α-anomer also reacting under the reported conditions.[13,14]

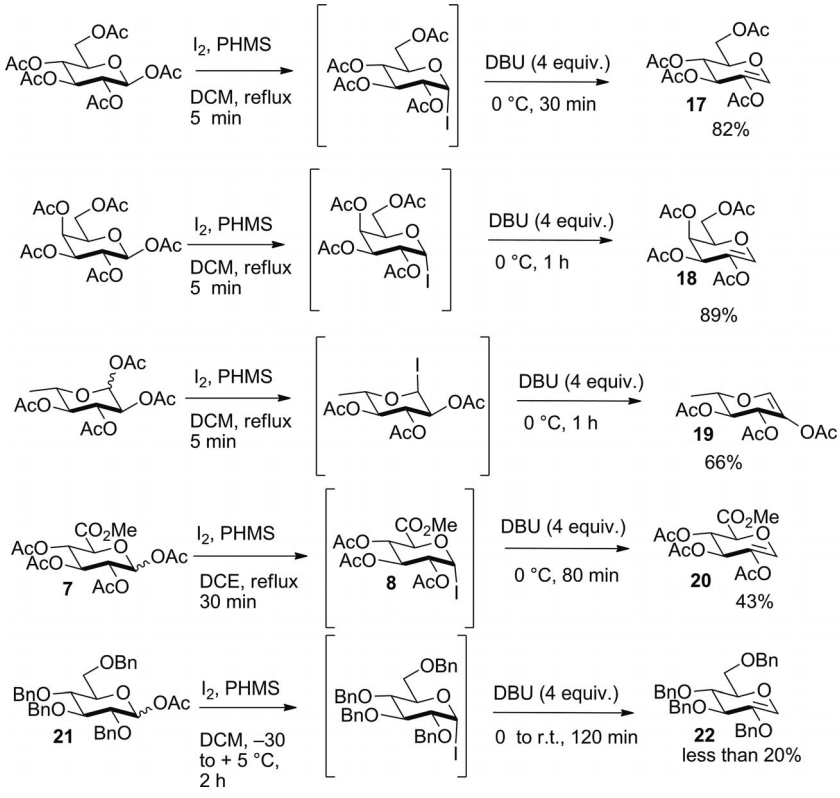
The utility of iodide intermediate **8** was demonstrated by its high-yielding conversion into orthoester **9** and thioglycoside **10** (Scheme 2). The orthoester was easily obtained in a one-pot approach by addition to the iodination mixture of MeOH, lutidine, and TBAB (tetrabutylammonium bromide)[2] at room temp., and immediately re-submitting the whole mixture to refluxing conditions. The thioglycosidation steps were performed after a rapid extractive work-up of the crude iodide, similarly to the corresponding procedures on other sugars.[4] As expected, the synthesis of thioethyl glycoside **10** took a longer time than had been seen for sugars not oxidized at C-6 (ca 6 h vs. ca 1–2 h). However, it should be noted that an alternative published procedure for the synthesis of the same target required an even longer reaction time, and suffered from the limitation that it worked only with the β-anomer of **7**.[15]

Another original application of the glycosyl iodide intermediates that was pursued was the synthesis of allyl glycosides of glucosamine. The allyl group is a useful protecting group for the anomeric position of sugars, due both to its chemical versatility and its stability to a wide range of conditions. Anomeric allylation of *N*-protected amino sugars is commonly carried out under Fischer conditions, which requires prolonged reaction times and the use of toxic and high-boiling allyl alcohol as the solvent under refluxing conditions. Alternative approaches have been described in which *N*-phthalimido precursor **11** (Scheme 3) was converted into the corresponding β-allyl glycosides under the influence of $SnCl_4$ or $FeCl_3$.[16] Searching for alternative procedures that would avoid the use of moisture-sensitive promoters and tedious work-up procedures, we took advantage of the rapid conversion of **11** into iodide **12** under the influence of the I_2/PMHS system, which once again proceeded with a rate similar to the I_2/Et_3SiH reagent.[4]

It has been described previously that iodide **12** may be transformed into **13** (Scheme 3) upon prolonged exposure to an excess of toxic allyl alcohol (used as the solvent).[17] We pursued an alternative strategy that would require much lower amounts of allyl alcohol by aiming for the possible activation of the iodide leaving group. In fact, the anomeric allylation of **12** was achieved by adapting a recently reported procedure in which we showed that 2,3,4,6-tetra-*O*-acetylated glycosyl iodides can be *O*-allylated at the anomeric position, with concomitant 2-*O*-deprotection, by activation with substoichometric amounts (0.3 equiv.) of $BiBr_3$.[7] Under those conditions, a moderate excess of allyl



Scheme 3. Anomeric allylation of *N*-protected glucosamine derivatives.



Scheme 4. One-pot synthesis of 2-acetoxyglycals from the corresponding per-*O*-acetylated precursors.

alcohol (4 equiv.) was sufficient to obtain high yields of 1-*O*-allylated products. In addition, in the same study, we observed that 2-*O*-deacylation was largely suppressed when 2-*O*-benzoylated substrates were used.

On this basis, the robust *N*-phthalimido group was expected to survive the same conditions, while providing a significant participation effect leading to a β-selective allylation. Exposure of intermediate **12** to allyl alcohol and a sub-stoichiometric quantity of $BiBr_3$ resulted in the smooth generation of **13**, exclusively as the β-anomer (Scheme 3). Interestingly, this reaction proceeded quickly enough at room temp., whereas the $BiBr_3$ activation of 2-*O*-acetylated glycosyl iodides conditions required reflux conditions.[7]

Due to the frequent use of *N*-Troc-protected glucosamine building-blocks in oligosaccharide synthesis, the same sequence was applied to precursor **14** (in this case, only the β-anomer was reactive in the iodination reaction),[6] and the final allylated product (i.e., **16**) was obtained in almost the same yield as **13** (Scheme 3). In this latter sequence, the reaction time of the preliminary iodination step was shortened by using DCE in place of dichloromethane.

Another result of this investigation was the development of a very streamlined synthetic entry to per-*O*-acetylated 2-hydoxyglycals. These derivatives are versatile building-blocks that are amenable to a wide range of transformations,[18,19] and numerous applications of these compounds in the synthesis of complex targets have also been described.[20] These derivatives are commonly prepared either by base-induced elimination of glycosyl bromides,[21] or by related elimination schemes applied to thioglycosides[22] using appropriate thiophilic reagents.[23] As both glycosyl bromides and thioglycosides are commonly prepared from the corresponding per-*O*-acetylated precursors, we searched for a very streamlined approach to 2-acetoxyglycals based on an unprecedented one-pot sequence of anomeric iodination and base-promoted elimination. This sequence proved to be viable, and examples shown in Scheme 4 show that a simple addition of excess 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[21b,21c] to the iodination mixtures at 0 °C results in a very fast elimination. The procedure gave moderate to high yields of the 2-hydroxyglycal derivatives starting from a range of *O*-acetylated sugars, with a lower yield being recorded for glucuronate ester **9**, presumably due to other competing elimination pathways. The elimination procedure proved to be less effective when applied to highly *O*-benzylated model precursor **21**, and only modest amounts of the desired glycal (i.e., **22**)[24] could be detected in the resulting crude mixture. Interestingly, in this case, the main reaction was the DBU-promoted reattachment of the acetate moiety to C-1, a process favoured by the enhanced anomeric electrophilicity of highly *O*-benzylated sugars.[25]

Conclusions

In this paper, we have shown that polymethylhydrosiloxane (PMHS) can be a practically convenient alternative to triethylsilane in a large set of synthetic transformations going via glycosyl iodides, which can be quickly generated

using an iodine/silane reagent combination. PMHS has numerous practical advantages, such as a low cost per silane unit, ease of handling and storage, and a higher stability to air and moisture than other silanes.

In addition, in this study, we have also expanded the scope of the iodine/silane reagent combination to allow the straightforward and high-yielding generation of per-*O*-acetylated 2-hydroxyglycals, as well as useful building blocks based on D-glucuronic acid and D-glucosamine. All the synthetic targets were obtained in particularly short reaction times, either in one-pot procedures or following reaction sequences devoid of laborious chromatographic purification of intermediates.

Experimental Section

General Remarks: Commercially available PMHS (average M_n = 1700–3200) was used as supplied in all the experiments described. The spectroscopic data of known compounds **2**,[2] **3**,[2] **4**,[4] **5**,[10] and **13**[16] were consistent those reported in the literature.

General Procedure for the Synthesis of the Glycosyl Iodide Intermediates: I_2 (356 mg, 1.4 mmol) and PMHS (85 μL, 1.4 mmol silane units) were added to a solution of a per-*O*-acetylated sugar (1 mmol) in anhydrous CH_2Cl_2 or 1,2-dichloroethane (see the schemes for the selected solvent; 4–6 mL) (***Caution:*** exothermic reaction). The mixture was heated to reflux until complete consumption of the starting material was observed (monitored by TLC, see the schemes for the times). For the synthesis of 1,2-orthoesters and 2-acetoxyglycals, the appropriate reagents were directly added to the iodination mixture (see specific procedures below), whereas for the synthesis of 1,2-ethylidenes, dichloromethane was replaced by acetonitrile before addition of the reagents (see below). For the remaining targets (thioglycosides, disulfides, glycals, and glucosamine allyl glycosides), the mixture was submitted to the following extractive work-up: it was diluted with CH_2Cl_2, and the organic phase was washed with aqueous sodium carbonate containing sodium thiosulfate (the latter reagent was added portionwise until complete consumption of the residual iodine in the organic phase was observed). The aqueous phase was then re-extracted with dichloromethane, and the combined organic extracts were dried and concentrated in vacuo. The residue was used directly in subsequent elaborations.

Synthesis of 1,2-Orthoesters 1 and 9: Lutidine (465 μL, 4 mmol), methanol (245 μL, 6 mmol), and tetrabutylammonium bromide (129 mg, 0.4 mmol) were added sequentially to the iodination mixture. The resulting mixture was left to stir at room temp. (synthesis of **1**, Scheme 1) or under reflux (synthesis of **9**, Scheme 2). When the reaction was complete (TLC), the mixture was concentrated and purified by chromatography on silica gel (eluent: hexane/ethyl acetate mixtures).

Synthesis of 1,2-Ethylidene 2:[26] The glycosyl iodide intermediate was synthesised as described above, then the dichloromethane was removed with a stream of nitrogen. The residue was dissolved in acetonitrile (5 mL), and then sodium borohydride (190 mg, 5 mmol) was added, keeping the vessel in an ice bath (*Note*: exothermic reaction). On completion of the reaction (TLC), the mixture was diluted with dichloromethane, and washed with water. The aqueous phase was then re-extracted with dichloromethane, and the combined organic extracts were dried and concentrated in vacuo. The residue was purified by silica gel chromatography (eluent: hexane/ethyl acetate, 6:4).

Synthesis of Glycal 3:[27] The crude glycosyl iodide residue from the extractive work-up was dissolved in THF (2.5 mL), and Cp_2Cl_2Ti (610 mg, 2.5 mmol) and manganese (50 mesh, 275 mg, 5 mmol) were added at room temperature under argon. After completion of the reaction (TLC), the mixture was concentrated and the residue was purified by chromatography on silica gel (eluent: hexane/ethyl acetate, 1:1).

Synthesis of Ethyl Thioglycosides 4 and 10:[28] Thiourea (114 mg, 1.5 mmol) was added to the crude glycosyl iodide residue from the exctractive work-up, and the mixture was suspended in acetonitrile (2 mL) and then heated to 60 °C. When TLC analysis indicated the consumption of the iodide and the generation of a polar product (see Schemes for the times), the vessel was cooled to room temp., and then ethyl iodide (160 μL, 2 mmol) and Et_3N (0.55 mL, 4 mmol) were sequentially added. When the reaction was complete (TLC), the mixture was concentrated under vacuum. The resulting residue was dissolved in CH_2Cl_2, and the organic phase was washed with water. The aqueous phase was then re-extracted with dichloromethane and the combined organic extracts were dried and concentrated in vacuo. The residue was purified by flash silica gel chromatography (eluent: hexane/ethyl acetate mixtures).

Synthesis of Symmetrical Disulfide 5: Thiourea (114 mg, 1.5 mmol) was added to the crude glycosyl iodide residue from the exctractive work-up, and the mixture was suspended in acetonitrile (2 mL) and then heated to 60 °C. When the reaction was complete (TLC), The vessel was cooled to room temp., and then phenyl diselenide (0.03 mmol, 9.4 mg) and Et_3N (0.55 mL, 4 mmol) were sequentially added. After 10 min, the reaction vessel was placed in an oil bath at 50 °C, and kept for 1 h at this temperature. The mixture was then concentrated in vacuo, the residue was dissolved in CH_2Cl_2, and the organic phase was washed with water. The aqueous phase was then re-extracted with CH_2Cl_2, and the combined organic extracts were dried and concentrated. The residue was purified by flash silica gel chromatography (eluent: hexane/ethyl acetate, 6:4).

Synthesis of Phenyl Thioglycoside 6:[29] Ethanol (12 mL) was added to a mixture of phenyl disulfide (152 mg, 0.7 mmol) and $NaBH_4$ (53 mg, 1.4 mmol). The mixture was stirred until the evolution of hydrogen ceased, and then was briefly heated at 50 °C to ensure completion of the reduction. The mixture was then added to the crude glycosyl iodide obtained from the extractive work-up as described above. Upon completion of the reaction (TLC), acetic acid was added until neutrality was reached, and then the mixture was diluted with CH_2Cl_2, and washed with water. The aqueous phase was re-extracted with CH_2Cl_2, and the combined organic extracts were dried anc concentrated under vacuum. The residue was purified by silica gel flash chromatography (eluent: hexane/ethyl acetate, 7:3).

Synthesis of Allyl Glycosides 13 and 16: Freshly activated 4 Å molecular sieves were added to the crude iodide (obtained from 0.3 mmol of 1-*O*-acetylated precursor), and the mixture was suspended in anhydrous dichloromethane (4 mL) under argon. After stirring for 15 min, allyl alcohol (80 μL, 1.2 mmol) and $BiBr_3$ (39 mg, 0.090 mmol) were added, and the mixture was stirred at room temp. until TLC analysis indicated complete consumption of the UV-detectable glycosyl iodide (see Scheme 3 for the times). Some drops of pyridine were added, and the mixture was filtered through a short pad of silica gel (eluent: ethyl acetate). The filtrate was concentrated, and the residue was purified by silica gel flash chromatography (eluent: hexane/ethyl acetate mixtures).

Synthesis of 2-Acetoxyglycals 17–20: The iodination vessel was placed in an ice-bath, and then DBU was added dropwise (0.6 mL, 4 mmol). Upon completion of the reaction (TLC) the mixture was

diluted with CH_2Cl_2 and washed with water. The aqueous phase was re-extracted with CH_2Cl_2, and combined organic extracts were dried and concentrated under vacuum. The residue was purified by silica gel flash chromatography (eluent: hexane/ethyl acetate mixtures).

3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-methoxyethylidene)-α-D-glucopyranose (1): Diastereoisomeric ratio 11:1. ^{1}H NMR (500 MHz, $CDCl_3$) signals of the major diastereoisomer: δ = 5.67 (d, J = 5.0 Hz, 1 H, 1-H), 5.17 (t, J = 3.0 Hz, 1 H, 3-H), 4.85 (dd, J = 3.0 and 9.5 Hz, 1 H, 4-H), 4.28 (m, 1 H, 2-H), 4.20–4.10 (m, 2 H, 6-H_2), 3.91 (m, 1 H, 5-H), 3.24 (s, 3 H, -OCH_3), 2.07, 2.05 (×2) (3 s, 9 H, 3 -$COCH_3$), 1.67 (s, 3 H, orthoester -CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 169.6, 169.1 (-*C*OCH_3), 121.5, 96.8 (C-1), 73.0, 70.0, 68.2, 66.9, 63.0, 20.7, 20.0 ppm. MALDI-TOF MS: m/z = 385.30 [M + Na]$^+$. $C_{15}H_{22}O_{10}$ (362.33): calcd. C 49.72, H 6.12; found C 49.85, H 6.05.

Phenyl 2,3,4-Tri-*O*-acetyl-1-thio-β-L-fucopyranoside (6): $[\alpha]_D$ = –10.1 (c = 1.3, in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60–7.20 (aromatic H), 5.25 (bd, J = 3.0 Hz, 1 H, 4-H), 5.22 (t, J = 10.0 Hz, 1 H, 2-H), 5.05 (dd, J = 3.0 and 10.0 Hz, 1 H, 3-H), 4.70 (d, J = 10.0 Hz, 1 H, 1-H), 3.83 (br. q, J = 6.5 Hz, 1 H, 5-H), 2.14, 2.08, 1.97 (3 s, 9 H, 3 -$COCH_3$), 1.23 (d, J = 6.5 Hz, 3 H, 6-H_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 170.0, 169.4 (-*C*OCH_3), 132.3, 128.8, 127.9 (aromatic CH), 86.5 (C-1), 73.1, 72.4, 70.2, 69.0, 67.3, 20.7, 20.5 (×2), 16.3 ppm. MALDI-TOF MS: m/z = 405.15 [M + Na]$^+$. $C_{18}H_{22}O_7S$ (382.43): calcd. C 56.53, H 5.80; found C 56.40, H 5.90.

Methyl 3,4-Di-*O*-acetyl-1,2-*O*-(1-methoxyethylidene)-α-D-glucopyranuronate (9): Diastereoisomeric ratio 10:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85 (d, J = 4.8 Hz, 1 H, 1-H), 5.23 (t, J = 2.4 Hz, 1 H, 3-H), 5.15 (ddd, J = 1.2, 2.4, and 7.6 Hz, 1 H, 4-H), 4.32–4.25 (2 H, 2-H and 5-H), 3.74 (s, 3 H, -CO_2CH_3), 3.26 (s, 3 H, orthoester -OCH_3), 2.07, 2.06 (2 s, 6 H, 2 -$COCH_3$), 1.70 (s, 3 H, orthoester CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 168.7 (×2) (-*C*OCH_3 and -*C*O_2CH_3), 122.5 (orthoester C), 95.8 (C-1), 73.0, 70.3, 68.9, 68.3, 52.5, 50.5, 21.0, 20.6 ppm. MALDI-TOF MS: m/z = 371.35 [M + Na]$^+$. $C_{14}H_{20}O_{10}$ (348.31): calcd. C 48.28, H 5.79; found C 48.40, H 5.70.

Methyl (Ethyl 2,3,4-Tri-*O*-acetyl-1-thio-β-D-glucopyranoside)uronate (10): Anomeric ratio β/α, 5:1, ^{1}H NMR (500 MHz, $CDCl_3$) signals of the β-anomer: δ = 5.24 (t, J = 10.0 Hz, 1 H, 3-H), 5.18 (t, J = 10.0 Hz, 1 H, 4-H), 5.03 (t, J = 10.0 Hz, 1 H, 2-H), 4.51 (d, J = 10.0 Hz, 1 H, 1-H), 4.02 (d, J = 10.0 Hz, 1 H, 5-H), 3.72 (s, 3 H, -CO_2CH_3), 2.80–2.60 (m, 2 H, -S*C*H_2CH_3), 2.03, 1.99 (×2) (2 s, 9 H, 3 -$COCH_3$), 1.24 (t, J = 7.5 Hz, 3 H, -SCH_2CH_3) ppm. Significant signals of the α-anomer: δ = 5.71 (d, J = 5.0 Hz, 1 H, 1-H), 5.34 (t, J = 9.5 Hz, 1 H, 3-H), 5.15 (t, J = 9.5 Hz, 1 H, 4-H), 4.98 (dd, J = 5.00 and 10.0 Hz, 1 H, 2-H), 4.73 (d, J = 9.5 Hz, 1 H, 5-H), 2.04, 2.02, 2.00 (3 s, 9 H, 3 -$COCH_3$), 1.24 (t, J = 7.5 Hz, 3 H, -SCH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) signals of the β-anomer: δ = 169.9, 169.2 (×2), 166.9 (-*C*OCH_3 and -*C*O_2CH_3), 83.5 (C-1), 76.2, 73.0, 69.5, 69.3, 52.7, 24.0, 20.6, 20.5, 14.6 ppm. MALDI-TOF MS: m/z = 401.20 [M + Na]$^+$. $C_{15}H_{22}O_9S$ (378.39): calcd. C 47.61, H 5.86; found C 47.50, H 5.95.

Allyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranoside (16): $[\alpha]_D$ = +4.3 (c = 1.4, in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.80–5.65 (m, 1 H, -OCH_2-C*H*=CH_2), 5.35–5.25 (overlapping signals, 2 H, 3-H and -CH_2-CH=$CH_{cis}H_{trans}$), 5.18 (bd, J = 10.0 Hz, 1 H, CH_2CH=CH_{cis}-H_{trans}), 5.06 (t, J = 9.5 Hz, 1 H, 4-H), 4.67 (d, J = 9.0 Hz, 1 H, 1-H), 4.77–4.65 (AB, J = 11.5 Hz, 1 H, -OCH_2CCl_3), 4.35 (br. dd, J = 3.2 and 12.5 Hz, 1 H, -O*C*$H_a$$H_b$CH=$CH_2$), 4.27 (dd, J = 4.5 and 12.5 Hz, 1 H, 6a-H), 4.13 (br. d, J = 12.5 Hz, 1 H, 6b-H), 4.09 (br. dd, J = 6.0 and 12.5 Hz, 1 H, -OCH_aH_bCH=CH_2), 3.74–3.64 (overlapping signals, 2-H and 5-H), 2.08, 2.02 (×2) (3 s, 9 H, 3 -$COCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7 (×2) (-*C*OCH_3), 154.1 (-*C*$OCCl_3$), 133.3 (*C*H=CH_2), 118.0 (CH=*C*H_2), 99.6 (C-1), 95.4, 74.4, 71.7 (×2), 70.2, 68.7, 62.0, 56.1 (C-2), 20.6 ppm. MALDI-TOF MS: m/z = 542.80 [M + Na]$^+$. $C_{18}H_{24}Cl_3NO_{10}$ (520.75): calcd. C 41.52, H 4.65; found C 41.25, H 4.75.

2,3,4,6-Tetra-*O*-acetyl-2-hydroxy-D-glucal (17): $[\alpha]_D$ = –32.5 (c = 1.6, in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.57 (s, 1-H), 5.49 (d, J = 4.4 Hz, 1 H, 3-H), 5.16 (dd, J = 4.4 and 5.6 Hz, 1 H, 4-H), 4.36 (dd, J = 6.4 and 11.6 Hz, 1 H, 6a-H), 4.35–4.25 (m, 1 H, 5-H), 4.16 (dd, J = 3.2 and 11.6 Hz, 1 H, 6b-H), 2.04 (×2), 2.03, 1.99 (3 s, 12 H, 4 -$COCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 169.8, 169.3, 169.2 (-*C*OCH_3), 139.1 (C-1), 127.2 (C-2), 74.0, 67.3, 66.2, 60.8, 20.5 (×3), 20.2 ppm. MALDI-TOF MS: m/z = 353.20 [M + Na]$^+$. $C_{14}H_{18}O_9$ (330.29): calcd. C 50.91, H 5.49; found C 50.75, H 5.55.

2,3,4,6-Tetra-*O*-acetyl-2-hydroxy-D-galactal (18): $[\alpha]_D$ = –3.8 (c = 1.6, in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.59 (s, 1-H), 5.80 (d, J = 4.5 Hz, 1 H, 3-H), 5.45 (dd, J = 2.0 and 5.0 Hz, 1 H, 4-H), 4.38–4.34 (m, 1 H, 5-H), 4.25 (dd, J = 3.2 and 12.0 Hz, 1 H, 6a-H), 4.16 (dd, J = 3.6 and 12.0 Hz, 1 H, 6b-H), 2.09, 2.07, 2.05, 2.00 (4 s, 12 H, 4 -$COCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 169.8, 169.7, 169.2 (-*C*OCH_3), 138.7 (C-1), 127.1 (C-2), 73.1, 63.8 (×2), 61.2, 20.5, 20.4 (×2), 20.2 ppm. MALDI-TOF MS: m/z = 353.20 [M + Na]$^+$. $C_{14}H_{18}O_9$ (330.29): calcd. C 50.91, H 5.49; found C 50.75, H 5.55.

2,3,4-Tri-*O*-acetyl-2-hydroxy-L-fucal (19): $[\alpha]_D$ = –6.2 (c = 1.1, in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.60 (d, J = 1.2 Hz, 1-H), 5.87 (d, J = 5.2 Hz, 1 H, 4-H), 5.32 (d, J = 1.2 and 5.2 Hz, 1 H, 3-H), 4.29 (q, J = 6.4 Hz, 1 H, 5-H), 2.15, 2.10, 2.01 (3 s, 9 H, 3 -$COCH_3$), 1.29 (d, J = 6.4 Hz, 3 H, 6-H_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 169.9, 169.3 (-*C*OCH_3), 139.3 (C-1), 126.8 (C-2), 72.1, 66.3, 64.5, 20.5, 20.3, 16.0 ppm. MALDI-TOF MS: m/z = 295.20 [M + Na]$^+$. $C_{12}H_{16}O_7$ (272.25): calcd. C 52.94, H 5.92; found C 52.85, H 5.95.

2,3,4-Tri-*O*-acetyl-2-hydroxy-D-glucuronal Methyl Ester (20): $[\alpha]_D$ = –26.4 (c = 1.2, in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81 (d, J = 1.2 Hz, 1-H), 5.45 (m, 1 H), 5.37 (m, 1 H), 4.82 (m, 5-H), 3.79 (s, 3 H, -OCH_3), 2.14, 2.09, 1.99 (3 s, 9 H, 3 -$COCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 169.3, 169.2, 166.6 (-*C*OCH_3 and -*C*O_2CH_3), 139.5 (C-1), 127.5 (C-2), 72.3, 69.0, 63.5, 52.4, 20.6 (×2), 20.5 ppm. MALDI-TOF MS: m/z = 339.20 [M + Na]$^+$. $C_{13}H_{16}O_9$ (316.26): calcd. C 49.37, H 5.10; found C 49.45, H 5.00.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra of all synthesized products (**1–6**, **9**, **10**, **13**, **16**–**20**).

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