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Reaction of acetylated carbohydrates with trimethylaluminum: concise synthesis of 1,2-*O*-isopropylidene D-ribofuranose

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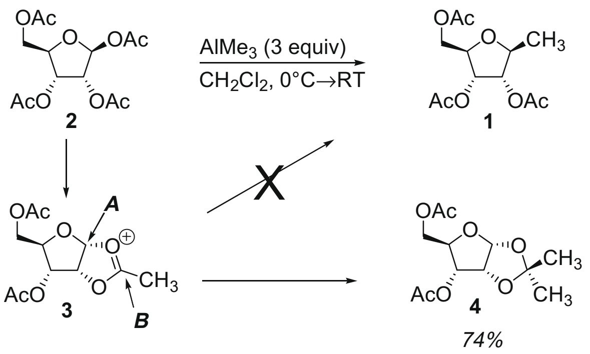
ABSTRACT

Treatment of β-D-ribose tetraacetate with trimethylaluminum gives α-3,5-*O*-acetyl-1,2-*O*-isopropylidene-D-ribofuranoside in excellent yield. This reaction allows for efficient and high-yielding installation of the 1,2-isopropylidene acetal (acetonide), which is difficult to prepare using more traditional acid-catalyzed methods. The reaction of trimethylaluminum with other *per*-acetylated carbohydrates is also described.

The temporary protection of functional groups is a necessary and often-used tactic in the synthesis of complex, polyfunctional organic molecules.[1] The adept use of such blocking groups is fundamental to the synthesis of carbohydrates, which are marked by the presence of several chemically and sterically similar hydroxyl groups. A large number of alcohol protecting groups with different stabilities and reactivities have been developed including ethers, esters, and acetals.[2] Isopropylidene acetals, or acetonides, are among the most useful diol-protecting groups, as they are easily introduced under a variety of conditions and removed using mild acid. We have discovered a novel method for the selective introduction of the 1,2-*O*-acetonide group onto ribose and we describe herein the scope of this reaction and its application to the protection of other carbohydrates.

In the context of a previous synthetic project, we needed to prepare the β-methyl-C-ribofuranoside **1** (Scheme 1). We reasoned that treatment of commercially available β-D-ribose tetraacetate **2** with trimethylaluminum ($AlMe_3$), acting as both Lewis acid and nucleophilic methyl source, should give **1** with the desired β -stereochemistry via acyloxonium ion **3**. Anchimeric assistance by a C2 acyl group (e.g., acetyl, benzoyl, and pivaloyl) is a common method for stereocontrol in glycosylation reactions, as the derived bicyclic oxonium ion (cf. **3**) directs nucleophilic attack to one face of the anomeric carbon.[3] In practice, when we treated a cold (0 °C) dichloromethane solution of **2** with 3 equiv of $AlMe_3$, followed by warming to room temperature we observed clean conversion to a new compound by thin-layer chromatography (TLC). After silica gel chromatography, ^{1}H and ^{13}C analysis revealed the product to not be **1**, but the known 3,5-*O*-acetyl-1,2-*O*-isopropylidene ribofuranoside **4** (74% yield).[4]

Oxonium ion **3** is an ambident electrophile; nucleophiles can react at the anomeric carbon (site **A**) or the carbonyl carbon (site **B**); under these conditions, $AlMe_3$ prefers site **B**. This alternate reactivity of ambident carbohydrate-derived acyloxonium ions (such as **3**) to give mixed acetals is well known in the field of O-glycosylation chemistry (Fig. 1). Reaction of a 2-*O*-acyl sugar with an alcohol under Lewis acid catalysis often gives rise to an orthoester (such as **5**) via an ambident oxonium ion.[5] These orthoesters are stable and can themselves be used as glycosyl acceptors in a subsequent glycosylation reaction. Nucleophilic attack by carbon nucleophiles with oxonium ions of type **3** usually occurs at the anomeric carbon,



Scheme 1. Reaction of **2** with Me_3Al; an unexpected result.

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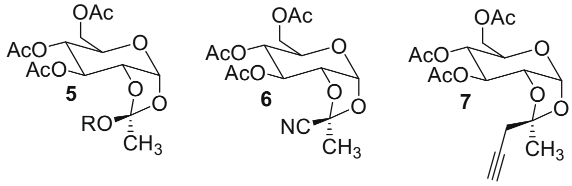
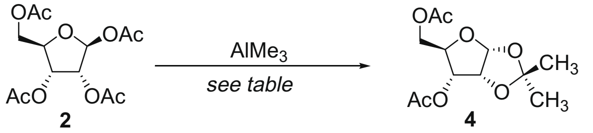


Figure 1. Carbohydrate mixed acetal derivatives.

Table 1
Optimization of the conversion of **2**→**4**



Entry	Me_3Al (equiv)	Solvent	Temperature	Yield[a] (%)
1	3	CH_2Cl_2	0 °C→rt	74
2	1.5	CH_2Cl_2	0 °C→rt	79
3	3	CH_2Cl_2	4 °C	66
4	3	$PhCH_3$	0 °C→rt	61
5	3	THF	0 °C→rt	NR[b]
6	3	MeCN	0 °C→rt	NR[b]
7	2	CH_2Cl_2	0 °C→rt	83[c]
8	2.5	CH_2Cl_2	0 °C→rt	57[d]

[a] Isolated yield.
[b] NR = no reaction; reaction monitored by TLC.
[c] 1 g scale.
[d] 5 g scale.

although there are some examples of the abnormal acetal-type products being observed. Cyanoethylidene acetal **6** was formed by reaction of tetra-*O*-acetylglucopyranosyl bromide with potassium cyanide.[6a] Mixed acetals like **6** have been used as unique glycosyl donors under trityl cation activation by Kochetkov and coworkers.[6b] Acetal **7** has been isolated as the major product of the reaction of glucose pentaacetate and allenyl tributylstannane.[7] Although $AlMe_3$ has been used as a nucleophile in C-glycosylation reactions,[8] to our knowledge there are no examples of the reaction of $AlMe_3$ with a sugar containing a C2 participating group.

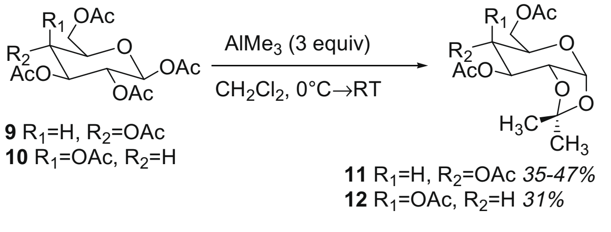
We immediately recognized the unexpected conversion of **2** to **4** as a convenient method for the synthesis of 1,2-isopropylidene acetals (acetonides) of carbohydrates. Both **4** and its derived diol **8** (Scheme 2) are valuable building blocks for synthesis, especially for the preparation of modified nucleosides and ligands for asymmetric catalysis.[9,10] The direct and selective synthesis of carbohydrate acetals from unprotected carbohydrates is challenging due to the presence of several hydroxyl groups and the ready equilibration between furanose and pyranose forms in the acidic medium in which acetals are usually made. 1,2-Acetonides are especially difficult to synthesize due to the attenuated nucleophilicity of the anomeric hemiacetal hydroxyl group. For example, reaction of D-ribose with acetone (*p*-toluene sulfonic acid, 4 Å MS) gives acetonide **8** in only 8% yield, along with other mono- and di-acetal isomers.[11]

Established methods for the synthesis of **4** or **8** involve multistep preparations from 1,2-isopropylidene xylose.[9a,12] These syntheses involve selective protection of the C5 primary alcohol, inversion of configuration (to achieve the ribose-stereochemistry) at C3 via oxidation-reduction, and then further protecting group manipulations. A similar sequence starting from diisopropylidene glucose has been reported.[13] Our synthesis of **4** from **2** is direct and high-yielding. Furthermore, diol **8** can be prepared in high yield using either of two common deacetylation methods (Scheme 2).

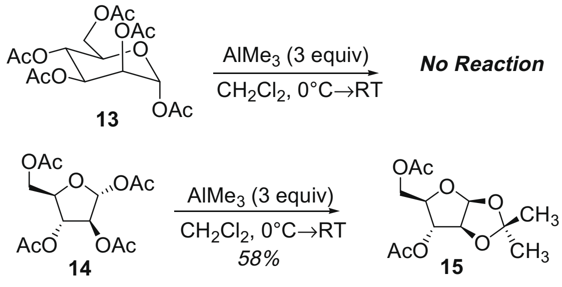
To examine further the conversion of **2** to **4**, we varied the reaction conditions as shown in Table 1. Most of our studies used 3 equiv of $AlMe_3$, but we found later that the reaction rate and yield remained similar with 1.5 equiv of $AlMe_3$ (entry 2). Lowering the temperature also had little effect on the reaction; maintaining the reaction at 4 °C gave only a slight diminution in yield (entry 3). Changing the solvent had a more profound effect. While the reaction worked almost equally as well in toluene as in dichloromethane (entry 4) the reaction failed to give any product in either tetrahydrofuran (THF) or acetonitrile (entries 5 and 6), as observed by TLC. In THF, only unreacted starting material was observed, while in acetonitrile, mainly decomposition to lower R_f material was seen. Importantly, we found that this reaction scales up very well. Reaction on a 1 g scale gives an 83% yield with only 2 equiv of trimethylaluminum (entry 7) while reaction on a 5 g scale gives a 57% yield (entry 8, unoptimized), which bodes well for preparative work in the synthesis of this valuable building block.

We next examined the reaction of $AlMe_3$ with other commercially available *per*-acetylated carbohydrates. Notably, **2** is the ideal substrate; all the other acetylated carbohydrates we tested reacted more slowly, giving rise to greater decomposition and lower yield than with **2**. Reaction of β-D-glucose pentaacetate **9** with 3 equiv of $AlMe_3$ gave **11** in 35–47% yield after 48 h (Scheme 3). Increasing the amount of $AlMe_3$ to 6 equiv gave mainly decomposition and maintaining the reaction at 4 °C (6 equiv of $AlMe_3$) gave no reaction (not shown). Despite the modest yield, this represents the most efficient and highest yielding synthesis of **11** to date.[14,15]

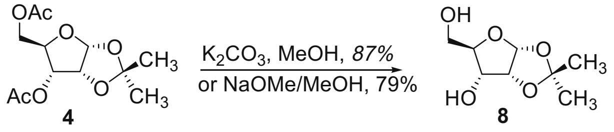
Reaction of β-D-galactose pentaacetate **10** was also slow and gave **12** in about 30% yield, contaminated with a minor, inseparable impurity (Scheme 3).[16] Increasing the equivalents of $AlMe_3$ and adding exogenous Lewis acids (TMSOTf, $BF_3{\cdot}OEt_2$, $TiCl_4$) gave intractable reaction mixtures. Reaction of α-D-mannose pentaacetate gave no reaction with either 3 or 6 equiv of $AlMe_3$ (Scheme 4). Addition of 3 equiv of $AlMe_3$ to α-D-arabinofuranose tetraacetate



Scheme 3. Reaction of glucose and galactose derivatives with $AlMe_3$.



Scheme 4. Reaction of mannose and arabinose derivatives with $AlMe_3$.



Scheme 2. Deacylation of **4**.

14 gave the previously unknown acetonide **15** in 58% yield.[17] Increasing the amount of $AlMe_3$ to 7 equiv gave complete conversion of starting material but increased decomposition; only 12% of **15** was isolated after chromatography (not shown).

In summary, we have discovered a novel and useful rearrangement-addition reaction of $AlMe_3$ with *per*-acetylated carbohydrates. This reaction allows for direct installation of the 1,2-acetonide onto ribose, glucose, and arabinose, thereby enabling a direct synthesis of these valuable building blocks. Our synthesis of 1,2-*O*-isopropylidene-D-ribofuranose is high-yielding, operationally simple,[18] and easily scalable, giving improved access to this valuable chiral synthon. Given the difficulty of preparing carbohydrate 1,2-acetonides, this reaction should be of general utility to the synthetic organic chemistry community.

Acknowledgments

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Supplementary data

Supplementary data (copies of ^{1}H NMR spectra for compounds **4**, **11**, and **15**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.116.

References and notes

1. Kocienski, P. G. *Protecting Groups*, 3rd Edition; Georg Thieme: Stuttgart, 2003.
2. *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; CRC: New York, 1997.
3. (a) Demchenko, A. In *Handbook of Chemical Glycosylation*; Demchenko, A., Ed.; Wiley-VCH: Weinheim, 2008; pp 5–6; (b) Hunig, S. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 548–560.
4. Chittenden, G. J. F. *Carbohydr. Res.* **1972**, *22*, 491–493.
5. For a review, see: (a) Kong, F. *Carbohydr. Res.* **2007**, *342*, 345–373; (b) Kochetkov, N. K.; Khorlin, A. J.; Bochkov, A. F. *Tetrahedron* **1967**, *23*, 693–707.
6. (a) Betaneli, V. I.; Ovchinnikov, M. V.; Backinowsky, L. V.; Kochetkov, N. K. *Carbohydr. Res.* **1979**, *68*, C11–C13; (b) Betaneli, V. I.; Ovchinnikov, M. V.; Backinowsky, L. V.; Kochetkov, N. K. *Carbohydr. Res.* **1979**, *76*, 252–256.
7. Chan, K. L.; Coumbarides, G. S.; Islam, S.; Wyatt, P. B. *Tetrahedron Lett.* **2005**, *46*, 61–65.
8. Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. *Tetrahedron* **1989**, *45*, 4293–4308.
9. (a) Puech, F.; Gosselin, G.; Imbac, J-L. *Tetrahedron Lett.* **1989**, *30*, 3171–3174; (b) Ma, T.; Pai, B.; Zhu, Y. L.; Lin, J. S.; Shanmuganathan, K.; Du, J.; Wang, C.; Kim, H.; Newton, M. G.; Cheng, Y. C.; Chu, C. K. *J. Med. Chem.* **1996**, *39*, 2835–2843; (c) Choo, H.; Chen, X.; Yadav, V.; Wang, J.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2006**, *49*, 1635–1647.
10. (a) Pàmies, O.; Net, G.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **1999**, *10*, 2007–2014; (b) Lu, Y.; Just, G. *Tetrahedron Lett.* **2000**, *41*, 9223–9227; (c) Guimet, E.; Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2247–2251.
11. He, D. Y.; Li, Z. J.; Li, Z. J.; Liu, Y. Q.; Qiu, D. X.; Cai, M. S. *Synth. Commun.* **1992**, *22*, 2653–2658.
12. (a) Tsutsumi, H.; Kawai, Y.; Ishido, Y. *Carbohydr. Res.* **1979**, *73*, 293–296; (b) Kim, J.; Weledji, Y. N.; Greenberg, M. M. *J. Org. Chem.* **2004**, *69*, 6100–6104; (c) Koth, D.; Fiedler, A.; Scholz, S.; Gottschaldt, M. *J. Carbohydr. Res.* **2007**, *26*, 267–278.
13. Xie, M.; Berges, D. A.; Robins, M. J. *J. Org. Chem.* **1996**, *61*, 5178–5179.
14. (a) Lemieux, R. U.; Detert, D. H. *Can. J. Chem.* **1968**, *46*, 1039–1040; (b) Dick, W. E.; Weisleder, D.; Hodge, J. E. *Carbohydr. Res.* **1972**, *23*, 229–242.
15. Lohman, G. J. C.; Seeberger, P. H. *J. Org. Chem.* **2003**, *68*, 7541–7543.
16. Cano, F. H.; Foces-Foces, C.; Jiminez-Barbero, J.; Bernabe, M.; Martin-Lomas, M. *Carbohydr. Res.* **1987**, *170*, 100–105.
17. *Characterization data for* **15**: $R_f = 0.49$ (1:1 ethyl acetate/hexane). IR (cm^{-1}) 2962, 2919, 2849, 1745, 1371, 1261, 1224, 1163, 1096, 1020. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (d, $J = 4$ Hz, 1H), 5.08 (s, 1H), 4.60 (d, $J = 4$ Hz, 1H), 4.26–4.31 (m, 3H), 2.09 (s, 6 H), 1.56 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.8, 113.1, 105.9, 84.3, 83.0, 77.3 (overlapping with solvent), 63.7, 26.7, 25.9, 20.8 (two carbons). HRMS (EI) *m/z* calculated for $C_{11}H_{15}O_7$ (M–CH_3): 259.0818. Found: 259.0815.
18. *Preparation of* **4**: A flame-dried 25 mL round-bottomed flask was charged with **2** (0.20 g, 0.63 mmol, 1 equiv) and 5.0 mL anhydrous dichloromethane. The flask was placed under argon (balloon) and cooled to 0 °C. Trimethylaluminum(2.0 M in hexane, 0.47 mL, 0.94 mmol, 1.5 equiv) was added dropwise via syringe. The reaction was allowed to slowly warm to room temperature and stirred for 15 h, at which point TLC analysis showed the absence of **2** and the appearance of a new spot (R_f 0.49, 1:1 ethyl acetate/hexane). The reaction was re-cooled to 0 °C and quenched by the dropwise addition of 5 mL of saturated aqueous sodium-potassium tartrate (Rochelle's salt), diluted with 10 mL dichloromethane, and stirred for 2 h. The organic layer was removed and the aqueous layer was extracted once with dichloromethane. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. Flash column chromatography on silica gel (40% ethyl acetate in hexane) gave **4** (0.14 g, 79%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (d, $J = 4$ Hz, 1H), 4.81 (t, $J = 4$ Hz, 1H), 4.66 (dd, $J = 5$ Hz, 9 Hz, 1H), 4.35 (dd, $J = 2$ Hz, 12 Hz), 4.28–4.32 (m, 1H), 4.13 (dd, $J = 5$ Hz, 12 Hz), 2.12 (s, 3H), 2.08 (s, 3H), 1.55 (s, 3H), 1.33 (s, 3H).