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A mild and efficient approach for the regioselective silyl-mediated protection–deprotection of C-4 hydroxyl group on carbohydrates

Andrea Graziani, Pietro Passacantilli,* Giovanni Piancatelli* and Simona Tani

Dipartimento di Chimica, Università 'La Sapienza' and Centro CNR di Studi per la Chimica delle Sostanze Organiche Naturali, Piazzale Aldo Moro, 5, Box 34-Roma 62, 00185 Rome, Italy

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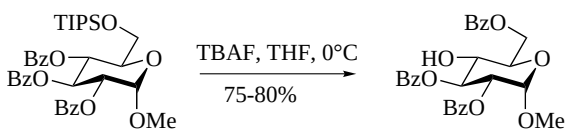
Abstract—A regioselective route is reported, which makes the free 4-OH group of hexopyranoses and derivatives easily and rapidly available. This protocol shows high efficiency on intermediates, such as **1a**, which contain a TIPS protective group at C-6 and necessarily a benzoyl group at C-4. Treatment of **1a** with TBAF cleaves the TIPS protecting group and gives rise to an intramolecular migration of the benzoyl group at C-4 to the less crowded C-6 position.

In the course of our efforts to synthesize azasugars, we needed a mild and efficient protocol for the regioselective preparation of carbohydrate intermediates, such as **2**, equipped in the 4-position with a free hydroxyl group, suitable for the introduction of an azide function. As is well known, the selective protection–deprotection of hydroxyl groups has occupied a key role in chemical synthesis.[1] Numerous methods and reagents have been developed for this purpose, particularly for carbohydrate chemistry.[2] Owing to their remarkable importance in organic chemistry, several methods for the functionalization of sugars have been continuously and extensively exploited in this field. A few unequivocal general routes are available for preparing hexopyranoses and pyranosides, *O*-protected at all positions, but with one free OH at C-4. A free 4-OH is traditionally obtained from a pyranosidic 4,6-*O*-benzylidene acetal by first blocking the 2,3-positions, then removing the 4,6-acetal, substituting the 6-position (primary OH) with a sterically demanding substituent, such as a trityl group[3] or a diphenyl-*tert*-butylsilyl group.[4] More recently procedures utilize a regioselective opening of cyclic derivatives, such as pyranosidic 4,6-*O*-benzylidene acetal[5] or 3,4-stannylidene acetals.[6–9] Usually, the above classical procedures have involved multiple steps, which include protection and deprotection strategies of the sugar moiety, and the use of a reaction promoter for the regioselective generation of the deprotected hydroxy group at C-4, such a Lewis acid as catalyst or reductive experimental conditions (for instance, $Me_3NBH_3/AlCl_3$ reagent combination). The yields are variable from poor to good.[2]

Now we report a practical and regioselective route, which makes easily and rapidly available the free 4-OH group of hexopyranoses and derivatives. In fact, the strategy of the present protocol focuses on the construction of intermediates, such as **1a**, which contain a triisopropylsilyl (TIPS) protective group at C-6 and necessarily a benzoyl group at C-4, starting from suitable monosaccharides. For their formation, the carbohydrates were selectively and quantitatively converted into the corresponding 6-TIPS derivatives by treatment with TIPSCl in DMF at rt for 1 h in the presence of imidazole, then the subsequent benzoylation reaction led to the starting compounds **1** in very high yields. The key step of our 'one-pot' procedure is the use of a mild reaction promoter, such as the fluoride anion, which allowed directly to obtain sugars with the free hydroxyl



1a **2a**

Scheme 1.

Keywords: selective protection–deprotection; carbohydrates; glycals.

* Corresponding authors. E-mail: pietro.passacantilli@uniroma1.it; giovanni.piancatelli@uniroma1.it

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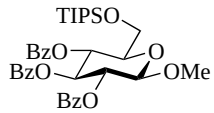
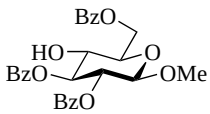
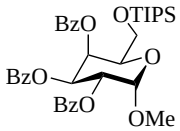
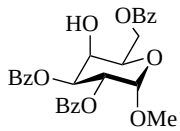
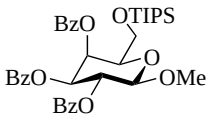
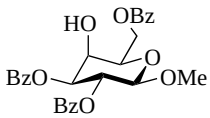
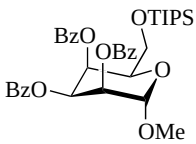
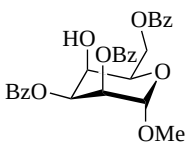
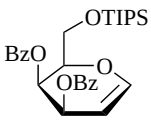
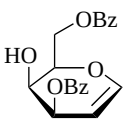
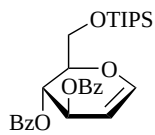
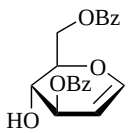
function at C-4, thus avoiding lengthy protocols for the protection–deprotection combination. In running experiments, methyl 2,3,4-tri-*O*-benzoyl-6-triisopropylsilyl-α-D-glucopyranoside **1a** (0.5 mmol in 5 ml of anhydrous THF) was stirred with TBAF 2 M (0.5 mmol) at 0°C under argon; after 15 min, 0.5 mmol of TBAF 2 M was added again and the mixture was stirred for an additional 30 min at 0°C. Usual work-up and column chromatography led to the pure compound **2a**[10] in 75–80% yield (Scheme 1).

The results showed that the reactions proceeded with high selectivity, giving the corresponding sugar derivatives with the free OH at C-4 in excellent yields (Table 1). However, methyl 2,3,4-tri-*O*-benzoyl-6-triisopropylsilyl-β-D-galactopyranoside **1d** gave the sugar derivative **3** with the free OH at C-6 in 20–25% yield, besides the expected **2d** (Table 1, entry 3).

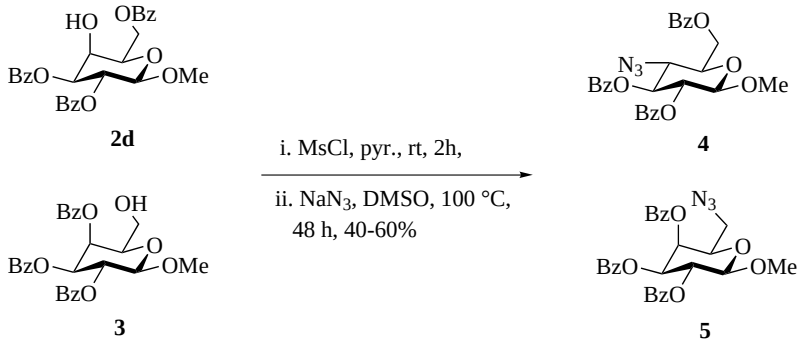
The structures of **2d** and **3** were confirmed by their conversion into the corresponding azido derivatives **4**[11] (^{13}C NMR: δ 61.03, CH-N_3) and **5**[12] (^{13}C NMR: δ 50.93, CH_2-N_3), respectively, by a well known procedure: first treatment with mesyl chloride and pyridine at rt for 2 h, then the nucleophilic substitution with NaN_3 in DMSO at 100°C for 48 h (Scheme 2).

For additional confirmation of the structure, **2f** was converted into the corresponding 4-keto derivative **6** by a two-step process, first the reduction of the olefinic

Table 1. Products of the desilylation reaction with TBAF

entry	substrate	product	yield (%)[a]
1	 **1b**	 **2b**	75-80
2	 **1c**	 **2c**	75-80
3	 **1d**	 **2d**	50-55[b]
4	 **1e**	 **2e**	80-90
5	 **1f**	 **2f**	75-80
6	 **1g**	 **2g**	75-80

[a] Yields were calculated on pure, chromatographically isolated products. [b] Also 20–25% of methyl 2,3,4-tri-*O*-benzoyl-β-D-galactopyranoside **3** was obtained.



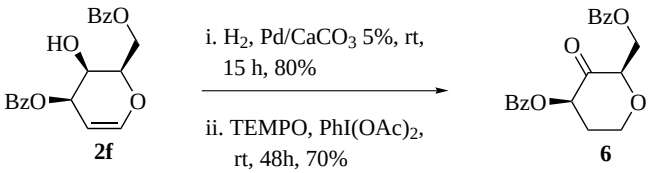
Scheme 2.

double bond of **2f** with H_2 and $Pd/CaCO_3$ 5% and then oxidation the secondary OH group with hypervalent iodine(III)/TEMPO reagent combination (Scheme 3).[13] The analytical and spectroscopic data were completely in agreement with the structure of **6**.[14]

In terms of regioselectivity and efficiency, our mild protocol is superior to the above reported conventional methods, as it uses a tin-free reaction sequence which makes it possible to extend the procedure to more reactive carbohydrate derivatives, such as glycals. Glycals are emerging as a major frontier area for organic chemistry.[15,16] In addition to their well-appreciated roles in finding new biologically active compounds, glycals are cast in a variety of interesting new reactions, due to their easily manipulated nature.[17]

The reaction mechanism should be explained in terms of a previously unreported domino process, initiated by the fluoride, which cleaves the TIPS protecting group and generating a primary C-6 alkoxy anion, which in turns gives rise to an intramolecular migration of the benzoyl group from C-4 to the less crowded C-6 position. Furthermore, all the results clearly showed that the reaction is site-selective, since only the C-4 benzoyl group was involved in the migration, probably due to a more accessible six-membered transition state. A steric hindrance due a *cis*-decaline like transition state should explain the formation of **3** as a by-product (Table 1, entry 3).

In conclusion, our method opens new possibilities for further protecting group manipulations, and it represents a substantial advance, when compared with described strategies for obtaining a single free 4-OH in a pyranosidic ring. We hope this elegant protection method will see many applications in general carbohydrate chemistry and even in natural product synthesis. Works are in progress in this area.



Scheme 3.

Acknowledgements

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10. Compound **2a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.18–7.97 (fs, 6H, Ph-C=O); 7.68–7.30 (fs, 9H, Ph-C=O); 5.83 (t, $J_{3,2}=J_{3,4}=10$ Hz, 1H, H3); 5.28 (dd, $J_{2,1}=4$ Hz, $J_{2,3}=10$ Hz, 1H, H2); 5.17 (d, $J_{1,2}=4$ Hz, 1H, H1); 4.80 (dd, $J_{6A,6B}=16$ Hz, $J_{6A,5}=4$ Hz, 1H, $H6_A$); 4.16 (dd, $J_{6B,6A}=16$ Hz, $J_{6B,5}=2$ Hz, 1H, $H6_B$); 4.12 (m, 1H, H5); 3.90 (t, $J_{4,3}=J_{4,5}=10$ Hz, 1H, H4); 3.48 (s, 3H, OCH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 167.39, 167.02, 166.08 (C=O); 133.47, 133.38 (CquatPh-C=O); 129.98–128.48 (Ph); 97.21 (C1); 73.98, 71.53, 70.18, 69.80 (C2, C3, C4, C5); 63.60 (C6); 55.53 (OCH_3).
11. Compound **4**: ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 166.58, 166.53, 166.25 (C=O); 133.70, 133.35, 133.20 (CquatPh-C=O); 130.00–128.40 (Ph-C=O); 102.03 (C1); 75.66, 71.63, 69.60 (C2, C3, C5); 62.30 (C6); 61.03 (C4); 56.30 (OCH_3).
12. Compound **5**: ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 165.63, 165.55, 165.30 (C=O); 133.72, 133.30, 133.24 (CquatPh-C=O); 130.02–128.28 (Ph-C=O); 102.41 (C1); 73.66, 71.63, 69.60, 68.86 (C2, C3, C4, C5); 57.32 (OCH_3); 50.93 (C6).

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14. Compound **6**: $[\alpha]_D = +29.0$ (*c* 1.8, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$): δ 8.10 (fs, 4H); 7.53 (m, 6H); 5.72 (dd, $J_{3,4} = 10$ Hz, 1H, H3); 4.85 ($J_{A,B} = 12$ Hz, $J_{A,1} = 4$ Hz, 1H, CH_A-OBz); 4.59 ($J_{B,A} = 12$ Hz, $J_{B,1} = 7.5$ Hz, 1H, CH_B-OBz); 4.43 (dd, $J_{1,A} = 4$ Hz, $J_{1,B} = 7.5$ Hz, 1H, H1); 4.30 (m, 1H, $H5_A$); 4.03 (fs, 1H, $H5_B$); 2.58 (m, 2H, $CH_2$4). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 198.20 (C2); 167.10 (C=O); 133.00–130.00 (CquatPh-C=O); 129.83, 128.75 (Ph-C=O); 81.00 (C1, C3); 66.45 (C5); 63.20 (CH_2-OBz); 29.89 (C4).
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