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# A mild and easy one-pot procedure for the synthesis of 2-deoxysugars from glycals

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**Abstract**

Glycals can be converted into the corresponding 2-deoxysugars in good yields by treatment with *N*-iodosuccinimide in $CH_3CN$–$H_2O$ 95:5 and removal of the iodide group using $Na_2S_2O_4$ in DMF/$H_2O$ at room temperature. This method is easy to apply, sufficiently mild to allow the survival of acid-sensitive groups such as silyl and trityl ethers and less harmful to the environment than metal-based reactions.


2-Deoxysugars are ideal building blocks in the synthesis of a number of carbohydrate-based structures, such as glycolipids, glycoproteins and many other bio-active substances. The usual route to 2-deoxysugars involves direct or indirect hydration of the corresponding glycals. The synthetic value of this reaction has been greatly increased by the development of the Lewis acid-catalyzed diene-aldehyde cyclocondensation (LACDAC) reaction,[1] which provides an easy access to glycals of natural and non-natural sugars.

Within a synthetic project still in progress directed to the preparation of 2-deoxy analogs of agelasphin,[2] we needed to prepare the 6-*O*-TIPS-protected 2-deoxysugar **4** from the corresponding glycal. Several methodologies have been developed to synthesize 2-deoxysugars from glycals, but none are without drawbacks. The direct acid-catalyzed hydration requires rather drastic conditions that may affect many protecting groups (including TIPS), as does a procedure involving the phenylthio derivative[3] because of the high temperature (refluxing toluene) required for the reduction step. On the other hand, the hydration via oxymercuration-demercuration[4] is effective but not ideal from the environmental point of view. Therefore, we developed a simple two-step, one-pot procedure to carry out this transformation under very mild conditions.

As reported in Scheme 1, in the first step the protected galactal is treated with *N*-iodosuccinimide in the presence of water to obtain the corresponding protected 2-deoxy-2-iodosugar as a

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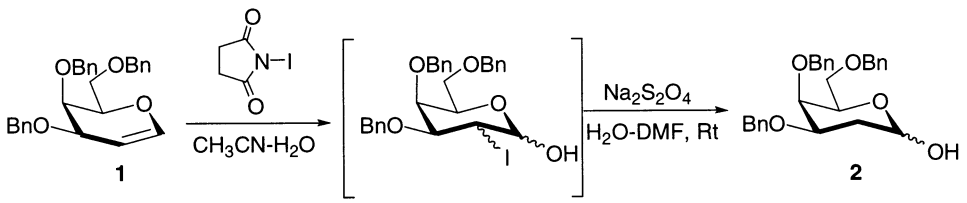
mixture of stereoisomers. The addition to glycals of $I^+$ from *N*-iodosuccinimide was first exploited by Thiem[5] in the synthesis of 2-deoxy-2-iodoglycosides, but, in that case, the $I^+$ addition was followed by the nucleophilic attack of an alcohol to the resulting cation. To complete the preparation of the 2-deoxysugar, the iodine atom in the 2-deoxy-2-iodosugar had to be removed. The usual way to accomplish this task is reduction with $(Ph)_3SnH$ in refluxing benzene.[6] Although the reaction works well it requires relatively high temperatures and a reagent containing a heavy metal that may be harmful to the environment, especially when the reaction is scaled up. Therefore, we examined the possibility of using sodium dithionite ($Na_2S_2O_4$) as an alternative reducing agent.




Scheme 1.

Sodium dithionite is a readily available, inexpensive and an easy-to-use reducing agent. The utility of sodium dithionite in dehalogenation reactions was not appreciated until 1982, when it was shown to remove selectively halogen atoms that are α to a ketone function.[7] The use of this reagent for the reductive displacement of iodine from 2-iodo-2-deoxysugars has never been reported in the literature, but it can be considered a reasonable extension of the above dehalogenation reaction if the aldehydic form of the iodosugar is considered. We actually found that sodium dithionite removes the iodine atom of 2-deoxy-2-iodosugars very effectively under very mild conditions, giving the target 2-deoxysugars in good yields. In addition, the yield was not lowered if the iodosugar produced in the first step was used without any purification, allowing us to develop a one-pot procedure.

A typical experimental procedure, as applied to 3,4,6-tri-*O*-benzyl-D-galactal **1**, is as follows. Compound **1** (416 mg, 1 mmol), prepared from 3,4,6-tri-*O*-acetyl-D-galactal according to the reported procedure,[8] was dissolved in 8 ml of $CH_3CN$–$H_2O$ 95:5 and cooled at 0°C. Then, the solution was treated with 1.1 equiv. (247.5 mg) of *N*-iodosuccinimide, allowed to rise to room temperature and left to stir for 15 minutes. The solvent was then removed in vacuo. The residue was dissolved in 10 ml of DMF and 10 ml of a solution of $H_2O/HCO_3^-$ (10 mol equiv.) was then added, followed by 4 equiv. (768.5 mg) of solid $Na_2S_2O_4$. The reaction was allowed to proceed under stirring for 5 hours at room temperature. After that, the reaction mixture was diluted with 400 ml of AcOEt and washed with water (three times, 400 ml each), followed by brine (400 ml). The organic layer was purified by column chromatography (*n*-hexane/EtOAc 7:3) to give 389 mg of 3,4,6-tri-*O*-benzyl-2-deoxygalactose **2** (90% yield) as a mixture of anomers, identified by comparison of its $^1H$ and $^{13}C$ NMR spectra with those reported.[4]


**3** R = Bn
**5** R = TIPS

**4** R = TIPS
**6** R = trityl

In order to evaluate the scope of this new procedure, several protected glycals were used as starting materials. The corresponding 2-deoxysugars (Chart 1) were purified by chromatography; compound **3** was identified by comparison with literature data,[9] while the structures of compounds **4**,[10] **5**,[11] and **6**[12] were elucidated by mass spectral and NMR (including two-dimensional COSY and HMQC experiments) data. As shown in Table 1, optimal reaction conditions may slightly change depending on starting material, but the yields are good with all the substrates.

Table 1
Protected 2-deoxysugars produced via Scheme 1

| Target compound | Starting material | Reaction time (hours) | Yield (%) |
|---|---|---|---|
| **2** | 3,4,6-Tri-*O*-benzyl-D-galactal | 5 | 90 |
| **3** | 3,4,6-Tri-*O*-benzyl-D-glucal | 5 | 94 |
| **4** | 6-*O*-TIPS-3,4-di-*O*-benzyl-D-galactal | 7 | 89 |
| **5** | 6-*O*-TIPS-3,4-di-*O*-benzyl-D-glucal | 7 | 80 |
| **6** | 6-*O*-Trityl-3,4-di-*O*-benzyl-D-galactal | 5 | 83 |

The ready availability and the low price of the reagents, the ease of the procedure, and the high yield of the products make this the method of choice for the preparation of 2-deoxysugars from glycals, if mild and neutral reaction conditions are required.

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## References

1. Danishefsky, S.; Bilodeau, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380–1419.
2. Costantino, V.; Fattorusso, E.; Mangoni, A. manuscript in preparation.
3. Wild, R.; Schmidt, R. *Liebigs Ann.* **1995**, 755–764.
4. Bettelli, E.; Cherubini, P.; D'Andrea, P.; Passacantilli, P.; Piancatelli, G. *Tetrahedron* **1998**, *54*, 6011–6018.
5. Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696–697.
6. Suzuki, K.; Sulikowski, G. A.; Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 8895–8902.
7. Chung, S.; Hu, Q. *Synth. Commun.* **1982**, *12*, 261–266.
8. Bovin, N. V.; Zurabyan, S. E.; Khorlin, A. Y. *Carbohydr. Res.* **1981**, *98*, 25–35.
9. Barnes, R. J.; Probert, M. A.; Wightman, R. H. *J. Chem. Soc., Perkin Trans 1* **1996**, *5*, 431–438.
10. 6-*O*-TIPS-3,4-di-*O*-benzyl-D-2-deoxygalactose **4**: $[\alpha]_D^{25}$ +32 ($CHCl_3$, $c=0.2$); $^1H$ NMR ($CDCl_3$, α anomer): $\delta$ 7.42–7.22 (10H, m, aromatic protons), 5.45 (1H, br. s, H-1), 4.96 (1H, d, $J=11.4$ Hz, benzylic proton), 4.70 (1H, d, $J=11.4$ Hz, benzylic proton), 4.62 (2H, s, benzylic protons), 4.01 (1H, br. s, H-4), 3.99 (2H, H-3 and H-5, overlapped), 3.84 (1H, dd, $J=9.7$ and 8.0 Hz, H-6a), 3.72 (1H, dd, $J=9.7$ and 5.9 Hz, H-6b), 2.22 (1H, br. t, $J=12.1$, H-2ax), 2.02 (1H, br. dd, $J=12.7$, 4.2 Hz, H-2eq), 1.10 (3H, m, TIPS methine protons), 1.05 (18H, d, $J=6.5$ Hz, TIPS methyl protons); $^{13}C$ NMR ($CDCl_3$, α anomer): $\delta$ 127.7 (aromatic carbons), 92.7 (C-1), 74.5 ($\underline{C}H_2Ph$), 74.3 (C-3), 71.7 (C-5), 70.3 ($\underline{C}H_2Ph$), 62.4 (C-6), 31.2 (C-2), 18.1 (TIPS methine groups), 18.0 (TIPS

methyl groups); HRFABMS (thioglycerol/*m*-nitrobenzyl alcohol matrix, positive ions): $m/z$ 501.3003 ($C_{29}H_{45}SiO_5$, calcd 501.3036).

11. 6-*O*-TIPS-3,4-di-*O*-benzyl-D-2-deoxyglucose **5**: $[\alpha]_D^{25}$ +28 ($CHCl_3$, $c=0.3$); $^1H$ NMR ($CDCl_3$, α anomer): $\delta$ 7.40–7.28 (10H, m, aromatic protons), 5.38 (1H, br. s, H-1), 4.95 (1H, d, $J=11.4$ Hz, benzylic proton), 4.72 (1H, d, $J=11.4$ Hz, benzylic proton), 4.68 (2H, s, benzylic protons), 4.05 (1H, ddd, 11.9, 8.9, and 4.9 Hz, H-3), 3.98 (1H, dd, $J=11.2$ and 4.4 Hz, H-6a), 3.89 (1H, br. d, $J=11.2$ Hz, H-6b), 3.87 (1H, m, H-5), 3.61 (1H, t, $J=8.9$ Hz, H-4), 2.29 (1H, br. dd, $J=13.1$ and 4.9 Hz, H-2eq), 1.67 (1H, br. t, $J=12.1$ Hz, H-2ax), 1.10 (3H, m, TIPS methine protons), 1.07 (18H, d, $J=6.5$ Hz, TIPS methyl protons); $^{13}C$ NMR ($CDCl_3$, α anomer): $\delta$ 126–128 (aromatic carbons), 92.0 (C-1), 78.5 (C-4), 76.9 (C-3), 75.3 ($\underline{C}H_2Ph$), 72.9 (C-5), 72.2 ($\underline{C}H_2Ph$), 62.9 (C-6), 35.6 (C-2), 18.1 (TIPS methine groups), 18.0 (TIPS methyl groups); HRFABMS (thioglycerol/*m*-nitrobenzyl alcohol matrix, positive ions): $m/z$ 501.3015 ($C_{29}H_{45}SiO_5$, calcd 501.3036).
12. 6-*O*-Trityl-3,4-di-*O*-benzyl-D-2-deoxygalactose **6**: $[\alpha]_D^{25}$ +33 ($CHCl_3$, $c=0.3$); $^1H$ NMR ($CDCl_3$, α anomer): $\delta$ 7.43–7.15 (25H, m, aromatic protons), 5.40 (1H, br. d, $J=3.1$ Hz, H-1), 4.82 (1H, d, $J=11.6$ Hz, benzylic proton), 4.63 (1H, d, $J=11.4$ Hz, benzylic proton), 4.60 (1H, d, $J=11.4$ Hz, benzylic proton), 4.49 (1H, d, $J=11.4$ Hz, benzylic proton), 4.09 (1H, m, H-5), 3.98 (1H, br. s, H-4), 3.97 (1H, overlapped, H-3), 3.37 (1H, dd, $J=9.4$ and 5.8 Hz, H-6a), 3.22 (1H, dd, $J=9.4$ and 7.3 Hz, H-6b), 2.16 (1H, ddd, $J=12.3$, 12.3, and 3.3 Hz, H-2ax), 2.02 (1H, br. dd, $J=12.3$ and 4.4 Hz, H-2eq); $^{13}C$ NMR ($CDCl_3$, α anomer): $\delta$ 128.4–128.0 (aromatic carbons), 92.4 (C-1), 74.3 (-$\underline{C}H_2Ph$), 73.9 (C-3), 73.2 (C-4), 70.3 (C-5), 63.0 (C-6), 30.9 (C-2); ESI MS (MeOH solution, positive ions): $m/z$ 609 ($[M+Na]^+$); ESI MS/MS (positive ions, precursor ion at $m/z$ 609): $m/z$ 374 $[M+Na–trityl]^+$, 234 $[trityl]^+$.