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A new aspect of the reactivity of sodium dithionite provides a facile route to 2-deoxy-α-glycosides

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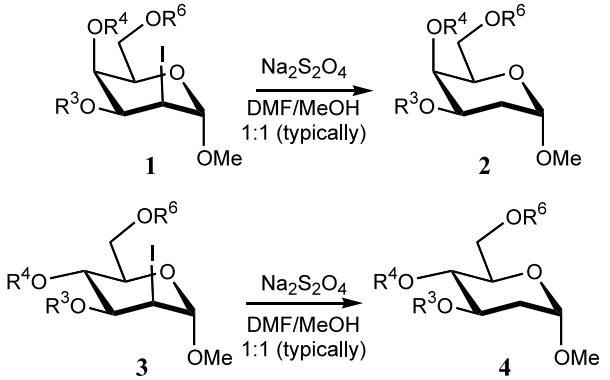
Abstract—Sodium dithionite, which is known to cause dehalogenation of α-halo carbonyl compounds, also induces dehalogenation of protected 2-iodo-2-deoxyglycosides. Combined with the well-known iodonium-mediated haloalkoxylation, this reaction provides an easy, mild and highly stereoselective route for preparation of 2-deoxy-α-glycosides from glycals.

Stereoselective synthesis of 2-deoxy-α-glycosides is an interesting and non-trivial goal. Over the years, several methods[1] have been proposed to accomplish α-glycosidation, but a general procedure to synthesize α-glycosides in good yield has not yet been developed.

Glycals have been employed as a versatile starting material in glycosidation reactions, when 2-deoxy-α-glycosides were required. A well established procedure involves the use of I^+ donors such as *N*-iodosuccinimide[2] or *sym*-collidine iodonium perchlorate[3] to induce coupling of glycals with alcohols. It is well known that the reaction is governed by a *trans*-diaxial addition of I^+ and the alcohol hydroxyl group to the double bond of the glycal. Subsequent removal of the iodine atom produces the α-linked 2-deoxyglycosides in good yield and stereoselectivity. The usual ways to remove the iodine atom are reduction with triphenyltin hydride[3] in refluxing benzene or catalytic hydrogenation.



	R^3	R^4	R^6		R^3	R^4	R^6
a	Ac	Ac	Ac	**e**	Ac	Ac	TIPS
b	Bz	Bz	Bz	**f**	TISP	Ac	Ac
c	Bn	Bn	Bn	**g**	TIPS	Ac	TIPS
d	Ac	Si(*t*-Bu)$_2$		**h**	Bn	Bn	Ac

Scheme 1. Dehalogenation of 2-iodo-2-deoxyglycosides with sodium dithionite.

In a recent paper,[4] we reported that sodium dithionite ($Na_2S_2O_4$), an inexpensive and easy-to-use reducing agent, removes the iodine atom of 2-deoxy-2-iodosugars under very mild conditions, giving the corresponding 2-deoxysugars in good yields. This reagent is particularly suited to substrates that can suffer at high temperatures and, in addition, it avoids the use of ecologically harmful heavy metals.

Dehalogenation using sodium dithionite has been first described by Chung and Hu in 1982 for α-haloketones.[5] The presence of a carbonyl function α to the halogen atom was claimed to be essential, and indeed dehalogenation of 2-deoxy-2-iodosugars can be explained considering the aldehydic equilibrium form of the sugars. As a consequence, 2-deoxy-2-iodoglycosides were not expected to react.

Surprisingly, we found that sodium dithionite does cause dehalogenation of many 2-iodo-2-deoxyglycosides. A typical experimental procedure is as follows: methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-α-taloside **1a**

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(430 mg, 1 mmol, prepared from 3,4,6-tri-*O*-acetyl-galactal as described[6]) was dissolved in 10 ml of DMF/H_2O 1:1, and solid $NaHCO_3$ (840 mg, 10 mol equiv.) and $Na_2S_2O_4$ (768 mg, 4 mol equiv.) were added. The reaction was allowed to proceed overnight under stirring at 25°C. After that, the reaction mixture was diluted with 400 ml of EtOAc and washed with water (3×400 ml), followed by brine (400 ml). The solvent was removed under reduced pressure and column chromatography of the residue (*n*-hexane/EtOAc 7:3) then provided methyl 3,4,6-tri-*O*-acetyl-2-deoxy-α-galactoside **2a** (215.8 mg, 71% yield), identified by comparison of its ^1H and ^{13}C NMR spectra with those reported.[6] As shown in Table 1 (entries 2–4), we obtained similar results using methyl 3,4,6-tri-*O*-benzoyl-2-iodo-2-deoxy-α-taloside **1b** as substrate, as well as with iodoglycosides deriving from protected glucals, such as methyl 3,4,6-tri-*O*-acetyl-2-iodo-2-deoxy-α-mannoside **3a** and methyl 3,4,6-tri-*O*-benzoyl-2-iodo-2-deoxy-α-mannoside **3b**.[7] In addition, we found that different solvent systems such as DMF/H_2O 2:1 and DMF/MeOH 1:1 could be used without affecting significantly the outcome of the reaction (entries 5–7). We selected the last solvent system for the subsequent experiments, because it was water-free and appeared to be the most suitable for dissolving most organic compounds.

However, no reaction took place using methyl 3,4,6-tri-*O*-benzyl-2-iodo-2-deoxy-α-taloside (**1c**) and methyl 3,4,6-tri-*O*-benzyl-2-iodo-2-deoxy-α-mannoside (**3c**), and we recovered only unreacted **1c** or **3c** even when we tried alternative solvent systems and/or raising the reaction temperature (entries 8–10).

In order to explore the potential applications of this methodology, we performed the dehalogenation reaction using differently protected methyl 2-iodo-2-deoxy-α-glycosides and different reaction conditions (Table 1). Even though the results do not allow to establish a sharp structure–reactivity relationship, some general trends can be outlined. The presence of electron-withdrawing (acetyl or benzoyl) protecting groups is essential for the substrate to be reactive (entries 11–13). Particularly, an acetyl protecting group at position 3 of the sugar is sufficient to promote the reaction (compound **3d**, entry 11,[9] and **1e**, entry 12[10]), but it is not strictly required at that very position, as shown by the deiodination of methyl 4,6-di-*O*-acetyl-3-*O*-TIPS-2-iodo-2-deoxy-α-taloside (compound **1f**, entry 13);[11] in contrast, a single acetyl group either at position 4 (compound **1g**) or 6 (compound **1h**) was not effective at all (entries 14 and 15).

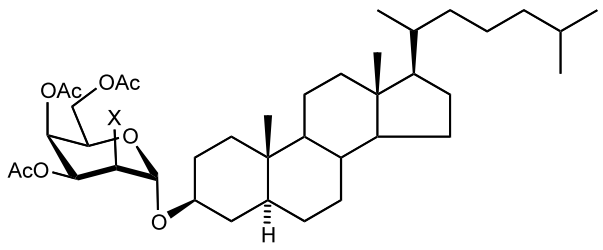
In spite of some limitations with the acceptable substrates, deiodination with sodium dithionite appears to be a promising alternative to complete the preparation of 2-deoxy-α-glycosides via iodoalkoxylation of glycals.

To test this reaction with a more complex substrate than methyl glycosides, we prepared 5α-cholest-3-β-yl-3,4,6-tri-*O*-acetyl-2-iodo-2-deoxy-α-taloside (**5**)[12] allowing 3,4,6-tri-*O*-acetylgalactal to react overnight with *N*-iodosuccinimide and 5-α-cholestan-3-β-ol. Compound **5** (786 mg, 1 mmol) was then dissolved in 16 ml of DMF/MeOH 1:1 and solid $NaHCO_3$ (840 mg, 10 mol equiv.) and $Na_2S_2O_4$ (1.54 mg, 8 mol equiv.) were added giving 5α-cholest-3-β-yl 3,4,6-tri-*O*-acetyl-2-deoxy-α-galactoside **6**. In this latter case gentle warming (40°C) of the reaction mixture was necessary to raise the yield to a satisfactory 74%.[13]

Table 1. Protected 2-deoxyglycosides produced via Scheme 1

Entry	Starting material	Reaction product	Protecting groups			Temp. (°C)	Solvent	Yield (%)
			R^3	R^4	R^6			
1	**1a**	**2a**	Ac	Ac	Ac	25	DMF/H_2O 1:1	71
2	**3a**	**4a**[a]	Ac	Ac	Ac	25	DMF/H_2O 1:1	76
3	**1b**	**2b**[b]	Bz	Bz	Bz	25	DMF/H_2O 1:1	82
4	**3b**	**4b**[b]	Bz	Bz	Bz	25	DMF/H_2O 1:1	83
5	**1a**	**2a**	Ac	Ac	Ac	25	DMF/H_2O 2:1	71
6	**1a**	**2a**	Ac	Ac	Ac	25	DMF/MeOH 1:1	81
7	**3a**	**4a**	Ac	Ac	Ac	25	DMF/MeOH 1:1	79
8	**1c**	–	Bn	Bn	Bn	25	DMF/H_2O 1:1	–
9	**1c**	–	Bn	Bn	Bn	25	DMF/H_2O 2:1	–
10	**1c**	–	Bn	Bn	Bn	40	DMF/MeOH 1:1	–
11	**3d**	**4d**[c]	Ac	$Si(t\text{-}Bu)_2$		25	DMF/MeOH 1:1	81
12	**1e**	**2e**[d]	Ac	Ac	TIPS	25	DMF/MeOH 1:1	85
13	**1f**	**2f**[e]	TIPS	Ac	Ac	25	DMF/MeOH 1:1	74
14	**1g**	–	Ac	Ac	TIPS	25	DMF/MeOH 1:1	–
15	**1h**	–	Bn	Bn	Ac	25	DMF/MeOH 1:1	–
16	**5**	**6**	Ac	Ac	Ac	40	DMF/MeOH 1:1	74

[a] Identified by comparison of spectral data with those reported (Ref. 7).
[b] Identified by comparison of spectral data with those reported (Ref. 8).
[c] Characterization: Ref. 9.
[d] Characterization: Ref. 10.
[e] Characterization: Ref. 11.



5 X = I
6 X = H

In conclusion, the dehalogenation of 2-iodo-2-deoxy-glycosides unveils a new aspect of the reactivity of sodium dithionite. Even though we do not feel to suggest any mechanistic hypothesis at this stage, it is clear that this dehalogenation reaction does not follow any of the mechanisms previously proposed. Combined with the I^+ promoted iodoalkoxylation of glycals, this reaction provides a route to 2-deoxy-α-glycosides characterized by high stereoselectivity and mild reaction conditions, particularly useful in molecules with functional groups that could be affected by the conditions previously used for the removal of the iodine atom.

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9. Methyl 3-*O*-acetyl-4,6-di-*O*-*t*-butylsilanediyl-2-deoxy-α-glucoside **4d**: $[\alpha]_D^{25}=+30$ (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.19 (1H, m, H-3), 4.73 (1H, br d, $J=3.3$ Hz, H-1), 4.08 (1H, dd, $J=10.3$, 4.0 Hz, H-6a), 3.87 (1H, t, $J=10.3$ Hz, H-5), 3.78–3.74 (2H, m, H-6b), 3.33 (3H, s, methoxy group), 2.18 (1H, dd, $J=12.5$, 5.1 Hz, H-2eq), 2.05 (3H, s, Ac), 1.70 (1H, ddd, $J=12.5$, 12.5, 3.3 Hz, H-2ax), 1.03 (9H, s, *t*-butylsilyl group), 0.97 (9H, s, *t*-butylsilyl group); ^{13}C NMR ($CDCl_3$): δ 170.1 (acetyl CO), 98.9 (CH, C-1), 75.9 (CH, C-4), 66.7 (CH, C-5), 66.3 (CH_2, C-6), 54.3 (CH_3, methoxy group), 33.8 (CH_2, C-2), 27.4 (CH_3, *t*-butylsilyl group), 26.7 (CH_3, *t*-butylsilyl group), 20.7 (CH_3, Ac); HRESI MS (MeOH/$CHCl_3$ 1:1, positive ions): m/z 377.5669 ($[C_{18}H_{36}O_7Si+H]^+$, calcd 377.5683).
10. Methyl 3,4-di-*O*-acetyl-6-*O*-TIPS-2-deoxy-α-galactoside **2e**: $[\alpha]_D^{25}=+3.9$ (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.39 (1H, br s, H-4), 5.29 (1H, dt, $J=11.8$, 4.4 Hz, H-3), 4.87 (1H, br d, $J=3.3$ Hz, H-1), 3.96 (1H, t, $J=7.3$ Hz, H-5), 3.76–3.64 (2H, m, H-6a, H-6b), 3.34 (3H, s, methoxy group), 2.10 (3H, s, Ac), 2.03 (1H, dd, $J=13.2$, 4.4 Hz, H-2eq), 1.96 (3H, s, Ac), 1.85 (1H, dd, $J=11.8$, 4.8 Hz, H-2ax), 1.07–0.99 (21H, m, TIPS methyl and methine groups); ^{13}C NMR ($CDCl_3$): δ 170.4, 170.1 (acetyl CO), 95.6 (CH, C-1), 66.8 (CH, C-5), 64.3 (CH, C-4), 63.9 (CH, C-3), 59.4 (CH_2, C-6), 52.1 (CH_3, methoxy group), 27.8 (CH_2, C-2), 18.1 (CH_3, Ac), 18.0 (CH_3, Ac), 15.0 (CH_3, TIPS methyl groups), 9.3 (CH, TIPS methine group); HRESI MS (MeOH/$CHCl_3$ 1:1, positive ions): m/z 419.2454 ($[C_{20}H_{38}O_7Si+H]^+$, calcd 419.2465).
11. Methyl 4,6-di-*O*-acetyl-3-*O*-TIPS-2-deoxy-α-galactoside **2f**: $[\alpha]_D^{25}=+46$ (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.23 (1H, br s, H-4), 4.82 (1H, br d, $J=3.3$ Hz, H-1), 4.23 (1H, dt, $J=11.4$, 4.4 Hz, H-3), 4.04 (1H, t, $J=7.7$ Hz, H-5), 4.15–4.09 (2H, m, H-6a, H-6b), 3.29 (3H, s, methoxy group), 2.08 (3H, s, Ac), 2.03 (3H, s, Ac), 1.96 (1H, dd, $J=11.4$, 3.3 Hz, H-2ax), 1.84 (1H, dd, $J=13.2$, 4.4 Hz, H-2eq), 1.05 (3H, m, TIPS methine groups), 1.01 (18H, m, TIPS methyl groups); ^{13}C NMR ($CDCl_3$): δ 170.3, 170.1 (acetyl CO), 95.7 (CH, C-1), 68.4 (CH, C-4), 65.6 (CH, C-5), 62.8 (CH, C-3), 61.0 (CH_2, C-6), 51.1 (CH_3, methoxy group), 34.1 (CH_2, C-2), 18.6 (CH_3, Ac), 18.2 (CH_3, Ac), 18.0 (CH_3, TIPS methyl groups), 15.4 (CH, TIPS methine group); HRESI MS (MeOH/$CHCl_3$ 1:1, positive ions): m/z 419.2474 ($[C_{20}H_{38}O_7Si+H]^+$, calcd 419.2465).
12. 5α-Cholest-3-β-yl 3,4,6-tri-*O*-acetyl-2-iodo-2-deoxy-α-taloside **5**: $[\alpha]_D^{25}=+44.5$ (*c* 2.3, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.43 (1H, br s, H-1′), 5.35 (1H, m, H-4′), 4.92 (1H, t, $J=4.4$ Hz, H-3′), 4.38 (1H, t, $J=6.6$ Hz, H-5′), 4.21 (1H, br d, $J=4.8$ Hz, H-2′), 4.15 (2H, br d, $J=6.6$ Hz, H-6′a, H-6′b), 3.54 (1H, m, H-3), 2.16 (3H, s, Ac), 2.05 (3H, s, Ac), 2.03 (3H, s, Ac), 0.88 (3H, d, $J=6.6$ Hz, H-21), 0.85 (6H, d, $J=6.7$ Hz, H-26, H-27), 0.79 (3H, s, H-18), 0.63 (3H, s, H-19); ^{13}C NMR ($CDCl_3$): δ 169.0 (CO), 170.0 (CO), 170.3 (CO), 101.1 (CH, C-1′), 78.2 (CH, C-3), 66.8 (CH, C-5′), 65.6 (CH, C-4′), 65.4 (CH, C-3′), 62.3 (CH_2, C-6′), 56.5 (CH, C-14), 56.3 (CH, C-17), 54.4 (CH, C-9), 45.1 (CH, C-5), 42.6 (C, C-13), 40.0 (CH_2, C-16), 39.5 (CH_2, C-24), 36.9 (CH_2, C-1), 36.2 (CH_2, C-22), 35.8 (CH_2, C-4), 35.7 (CH, C-8), 35.6 (CH, C-20), 35.5 (C, C-10), 32.1 (CH_2, C-7), 28.8 (CH_2, C-6), 28.2 (CH_2, C-12), 28.0 (CH, C-25), 27.8 (CH_2, C-2), 24.2 (CH_2, C-15), 23.8 (CH_2, C-23), 22.8 (CH_3, C-27), 22.6 (CH, C-2′), 22.5 (CH_3, C-26), 21.2 (CH_2, C-11), 20.9–20.6 (CH_3, Ac), 18.7 (CH_3, C-21), 12.2 (CH_3, C-18), 12.1 (CH_3, C-19); ESI MS (1 mM LiCl in MeOH/$CHCl_3$ 4:1, positive ions): m/z 793 ($[M+Li]^+$).
13. 5α-Cholest-3-β-yl 3,4,6-tri-*O*-acetyl-2-deoxy-α-galactoside **6**: $[\alpha]_D^{25}=+61.7$ (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$): δ

5.34–5.29 (2H, m, H-3′, H-4′), 5.16 (1H, d, $J=2.6$ Hz, H-1′), 4.24 (1H, t, $J=6.6$ Hz, H-5′), 4.11–4.03 (2H, m, H-6′a, H-6′b), 3.51 (1H, m, H-3), 2.12 (3H, s, Ac), 2.04 (3H, s, Ac), 1.97 (3H, s, Ac), 0.89 (3H, d, $J=6.6$ Hz, H-21), 0.85 (6H, d, $J=6.6$ Hz, H-26, H-27), 0.79 (3H, s, H-18), 0.64 (3H, s, H-19); ^{13}C NMR ($CDCl_3$): δ 170.4 (CO), 170.1 (CO), 170.0 (CO), 95.7 (CH, C-1′), 76.9 (CH, C-3), 66.9 (CH, C-4′), 66.7 (CH, C-5′), 66.4 (CH, C-3′), 62.7 (CH_2, C-6′), 56.5 (CH, C-14), 56.3 (CH, C-17), 54.4 (CH, C-9), 45.1 (CH, C-5), 42.6 (C, C-13), 40.0 (CH_2, C-16), 39.5 (CH_2, C-24), 36.9 (CH_2, C-1), 36.2 (CH_2, C-22), 35.9 (CH_2, C-4), 35.8 (CH, C-8), 35.6 (C, C-10), 35.5 (CH, C-20), 32.1 (CH_2, C-7), 30.8 (CH_2, C-2′), 28.9 (CH_2, C-6), 28.2 (CH_2, C-12), 28.0 (CH, C-25), 27.7 (CH_2, C-2), 24.2 (CH_2, C-15), 23.8 (CH_2, C-23), 22.8 (CH_3, C-27), 22.5 (CH_3, C-26), 21.2 (CH_2, C-11), 20.9–20.7 (CH_3, Ac), 18.7 (CH_3, C-21), 12.3 (CH_3, C-18), 12.1 (CH_3, C-19), ESI MS (1 mM LiCl in MeOH/$CHCl_3$ 4:1, positive ions): m/z 667 ($[M+Li]^+$).