Chemoselective Hydrolysis of Terminal Isopropylidene Acetals and Subsequent Glycol Cleavage by Periodic Acid in One Pot

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Isopropylidene acetal formation is the most commonly used protection method for 1,2- and 1,3-diols, it has been used extensively in carbohydrate chemistry to selectively mask the hydroxyls of many different sugars.[1] Isopropylidene derivatives of sugars are frequently used as a chiral pool for enantiomerically pure compound synthesis.[2] In synthetic practice, a useful strategy is selective hydrolysis of the terminal isopropylidene acetal (from a primary alcohol) in the presence of an internal one (from two secondary alcohols). In these cases, the two-step sequence, selective hydrolysis by aqueous AcOH[3] or H_2SO_4 in methanol[4] followed by oxidative cleavage, has mostly been employed. However, this sequence is not entirely chemoselective and usually suffers from tedious workup, providing the product in moderate yield. Especially, the application of this strategy has limited value in some cases, such as in the presence of acid-sensitive (TBDMS) or migratable protecting group (Ac). Although a few attempts[5] have already been made to realize the direct transformation of isopropylidene acetals to aldehydes in one pot in recent years, it is rather surprising that all of those have been investigated only by using aqueous solvents, under which conditions internal acetals and acid-sensitive protecting groups are unstable.

Ethereal periodic acid can cleave *vic*-glycol or epoxide smoothly, especially in the case of water-insoluble compounds or where a cleavage product is sensitive to aqueous acid.[6] In this paper, we wish to report our new findings that this reagent in hydrate form can effect the selective hydrolytic cleavage of terminal isopropylidene acetal in one pot.

The results are summarized in Table I.

The present procedure appears to be quite efficient for selective hydrolytic cleavage of terminal acetals. For example, the reaction of acetal **1a** (**2a**) with H_5IO_6 (3 equiv) in ether gave the lactol **1b** (**2b**) in 92% (85%) yield, while it has been reported that the yield obtained by using a two-step procedure (aqueous AcOH hydrolysis followed by $NaIO_4$ cleavage) was 50% (52%).[7,8]

This method is successfully applicable to those substrates containing a variety of protecting groups (TBDMS, entry 4; AcO, entry 5; MOM, entry 6; BzO, entry 9) and the yields are generally high, but THP ether (entry 7) and ethoxyethyl ether (EE; entry 8) are cleaved under these conditions.

Because generation of aldehydes from oxidative fission of diols for further synthetic elaboration is generally more efficient than that from oxidation of the corresponding primary alcohols,[9] the sequence involving a selective hydrolysis of terminal isopropylidene acetal followed by a glycol cleavage in one pot is particularly attractive. The high conversion and chemoselectivity, the tolerance toward functionalities combined with the mild conditions, and the simplicity of the operation should make it potentially very useful in the synthesis of natural product.

Experimental Section

General. IR spectra were recorded with a Shimadzu 440 spectrometer. ^1H NMR were recorded with TMS as an internal standard at 200 MHz on a Varian XL-200 spectrometer or at 300 MHz on an AMX-300 MHz spectrometer. MS spectra were obtained on a Finnigan 4201 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 MS Autopol polarimeter. Flash column chromatography was performed on silica gel H (10–40 μm) and with petroleum ether–ethyl acetate system as eluent.

Preparation of Substrates 1a–11a. 1a: prepared according to the literature.[7]

2a, 3a: prepared according to the literature.[8]

Compound **4**. To a suspension of hexyltriphenylphosphonium bromide (17.1 g, 40 mmol) in THF (120 mL)–HMPA (18 mL) was added dropwise potassium bis(trimethylsilyl)amide [KN($SiMe_3$)$_2$] (40 mmol) at −10 °C. Stirring was continued for 1 h, and a red ylide solution was obtained. The solution was cooled to −70 °C, and a solution of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose[10] in THF (40 mL) was added dropwise. The reaction mixture was brought to 20 °C overnight. It was extracted with ether–petroleum ether (1:1) after addition of saturated solution of NH_4Cl. The combined extracts were concentrated, and the residue was chromatographed to give **4** (4.2 g, 80%): $[\alpha]^{20}_D$ −52.6° (*c* 0.7, $CHCl_3$); IR (film) 3480, 1660, 1380, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.89 (t, *J* = 6.8 Hz, 3H), 1.26 (m, 6H), 1.35 (s, 3H), 1.37 (s, 3H), 1.42 (s, 3H), 1.52 (s, 3H), 2.10 (m, 2H), 3.45 (m, 1H), 4.02 (m, 3H), 4.37 (d, *J* = 7.3 Hz, 1H), 5.08 (t, *J* = 7.4 Hz, 1H), 5.70 (m, 2H); MS (*m*/*z*) 313 (M^+ − Me, 1.8), 271 (M^+ − 59, 9.7), 253 ($M^+ - H_2O$ − 59, 34), 213 (63); HRMS calcd for $C_{17}H_{32}O_5$ 313.2015, obsd 313.1983.

4a. A mixture of compound **4** (0.328 g, 1 mmol), *tert*-butyldimethylsilyl chloride (0.2 g, 1.3 mmol), and imidazole (0.27 g, 4 mmol) in DMF (5 mL) was stirred at room temperature overnight. The mixture was diluted with Et_2O (30 mL) and water (15 mL), and the aqueous layer was separated. The organic layer was washed with 5% aqueous $NaHCO_3$ (10 mL) and brine (10 mL) and dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, the residue was purified by chromatography to give **4a** (0.39 g, 91%): $[\alpha]^{20}_D$ +36.9° (*c* 0.49, $CHCl_3$); IR (film) 1660, 1380, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.13 (s, 6H), 0.89 (t, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 1.30 (m, 6H), 1.32 (s, 3H), 1.35 (s, 3H), 1.39 (s, 3H), 1.47 (s, 3H), 1.95–2.20 (m, 2H), 3.74–4.05 (m, 5H), 4.78 (dd, *J* = 10.0, 5.6 Hz, 1H), 5.4–5.70 (m, 2H); MS (*m*/*z*) 442 (M^+, 0.3), 427 (M^+ − Me, 0.66), 327 (M^+ − $SiMe_2Bu$, 5.1), 269 (100); HRMS calcd for $C_{16}H_{31}O_4Si$ 328.2025, obsd 328.2029.

5a. A solution of compound **4** (492 mg, 1.5 mmol) in Ac_2O (1 mL) and pyridine (1 mL) was stirred at room temperature

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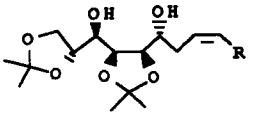
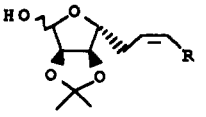
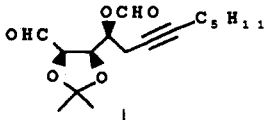
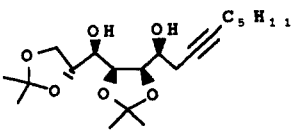
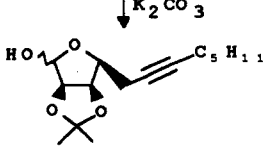
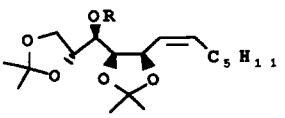
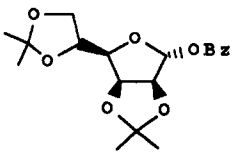
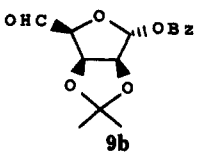
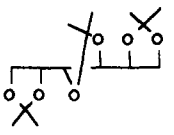
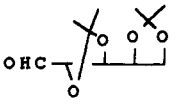
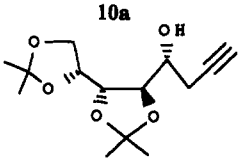
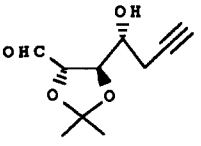
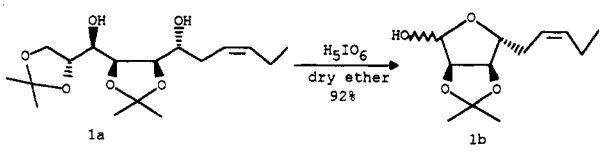
0022-3263/93/1958-3586$04.00/0

Table I

entry	substrate (1 mmol)	H_5IO_6 (mmol)	product	isolated yield
1	 **1a** R = C_2H_5	3	 **1b**	92
2	**2a** R = C_5H_{11}	3	 **2b**	85
3	 **3a**	3	 **3b**	84
	 **4** R = H			
4	**4a** R = TBDMS	1.5	**4b**	92
5	**5a** R = Ac	1.5	**5b**	87
6	**6a** R = MOM	1.5	**6b**	91
7	**7a** R = THP	1.5	THP cleave	
8	**8a** R = EE	1.5	EE cleave	
9	 **9a**	1.5	 **9b**	98
10	 **10a**	1.3	 **10b**	58 + 30% S.M.
11	 **11a**	1.5	 **11b**	95

Scheme I



overnight. After evaporation under reduced pressure, chromatography of the residue gave **5a** (538 mg, 97%): $[\alpha]^{20}_D$ −76.6° (*c* 0.4, $CHCl_3$); IR (film) 1745, 1660, 1380, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.89 (t, *J* = 6.8 Hz, 3H), 1.26 (m, 6H), 1.36 (s, 3H), 1.39 (s, 3H), 1.43 (s, 3H), 1.54 (s, 3H), 2.05 (m, 2H), 2.09 (s, 3H), 3.95 (m, 2H), 4.18 (q, *J* = 6.4 Hz, 1H), 4.34 (dd, *J* = 5.3, 1.5 Hz, 1H), 5.0 (m, 2H), 5.3 (dd, *J* = 10.8, 8.1 Hz, 1H), 5.67 (m, 1H); MS (*m/z*) 355 (M^+ − Me, 4.4), 313 (M^+ − 57, 12), 195 (14); HRMS calcd for $C_{19}H_{31}O_6$ 355.2283, obsd 355.2273.

6a. To a solution of compound 4 (400 mg, 1.22 mmol) and methoxymethyl chloride (150 mg, 1.83 mmol) in dry methylene chloride (8 mL) was added diisopropylethylamine (240 mg, 1.83 mmol), and the mixture was stirred at room temperature for 24 h and then diluted with ether and washed with brine. After evaporation of the solvent, chromatography of the residue yielded **6a** (440 mg, 97%): $[\alpha]^{20}_D$ −9.7° (*c* 0.43, $CHCl_3$); IR (film) 1660, 1380, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.89 (t, *J* = 6.8 Hz, 3H), 1.2–1.45 (m, 6H), 1.33 (s, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 1.50 (s, 3H), 1.95–2.20 (m, 2H), 3.43 (s, 3H), 3.82 (m, 1H), 4.05 (m, 4H), 4.81 (s, 2H), 4.90 (dd, *J* = 8, 4.1 Hz, 1H), 5.65 (m, 2H); MS (*m/z*) 372 (M^+, 3.8), 357 (M^+ − Me, 5.2), 315 (M^+ − C_4H_9, 35), 257 (100); HRMS calcd for $C_{20}H_{36}O_6$ 372.2512, obsd 372.2546.

7a. A solution of 4 (0.49 g, 1.5 mmol) and dihydropyran (0.19 g, 2.25 mmol) in dry methylene chloride (10 mL) containing PPTS (38 mg, 0.15 mmol) was stirred for 4 h at room temperature. Then the solution was diluted with ether and washed once with half-saturated brine. After evaporation of the solvent, chromatography gave **7a** (525 mg, 85%): IR (film) 2920, 1660, 1380, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.87 (t, *J* = 3.8 Hz, 3H), 1.2–1.80 (complex, 24H), 1.9–2.2 (m, 2H), 3.45–3.70 (m, 2H), 3.9–4.3 (m, 5H), 4.8–5.05 (m, 2H); MS (*m/z*) 442 (M^+, 1), 356 (M^+ − 1 − C_5H_9O, 10.8), 271 (28), 253 (98.5).

8a. A solution of 4 (0.43 g, 1.3 mmol) and ethyl vinyl ether (0.14 g, 0.195 mmol) in dry methylene chloride (8 mL) containing PPTS (33 mg, 0.13 mmol) was stirred for 4 h at room temperature. Usual workup and chromatography afforded **8a** (484 mg, 92%): IR (film) 1660, 1380, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.89 (t, *J* = 6.7 Hz, 3H), 1.20 (t, *J* = 7 Hz, 3H), 1.3–1.5 (complex, 21H),

1.95–2.2 (m, 2H), 3.5–4.15 (complex, 7H), 4.8–5.1 (complex 2H), 5.5–5.7 (m, 2H).

9a: prepared according to the literature.[11]

10a: prepared according to the literature.[12]

11a. Into a stirred mixture of aldehyde **10b** (5.6 g, 24.3 mmol) and prop-2-ynyl bromide (4.2 g, 35 mmol) in DMF–Et_2O (1:1, 80 mL) was added zinc dust (3.3 g, 50 mmol) slowly. An exothermic reaction started within a few minutes, and the reflux was allowed to continue until most of compound **10b** had been consumed. Then, the reaction mixture was poured into a solution of saturated aqueous NH_4Cl. Usual workup and chromatography provided pure **11a** (5.64 g, 86%): $[\alpha]^{20}_D$ +10.7° (*c* 0.8, $CHCl_3$); IR (film) 3450, 3290, 1380, 1370 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 1.38 (s, 6H), 1.43 (s, 3H), 1.47 (s, 3H), 2.07 (t, J = 2 Hz, 1H), 2.4–2.6 (m, 2H), 3.70–4.25 (complex m, 6H); MS (*m/z*) 271 (M^+ + 1, 3.7), 255 (M^+ – Me, 45.5), 253 (M^+ + 1 – H_2O, 2). Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.39; H, 8.23.

Reaction of Acetals 1a–11a with Periodic Acid in Ether. A general procedure is as follows: the acetal compound (1 mmol) was added at room temperature under nitrogen atmosphere to a well-stirred suspension of periodic acid (1.5-3.0 mmol) in dry ether. Stirring was continued for 4–10 h, and the reaction mixture was worked up by simply filtering and evaporating the solution. The residue was chromatographed to give the product.

1b, 2b. The physical and spectroscopic data are agreement with that reported previously.[7,8]

3b: $[\alpha]^{20}_D$ +6.2° (*c* 0.8, $CHCl_3$); IR (film) 3450, 1380, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.90 (t, J = 7 Hz, 3H), 1.20–1.60 (m, 12H), 2.15 (m, 2H), 2.54 (m, 2H), 4.28 (m, 1H), 4.43–4.65 (m, 3H); MS (*m/z*) 268 (M^+, 0.6), 253 (M^+ – Me, 29), 251 (M^+ + 1 – H_2O,2), 59 (100); HRMS calcd for $C_{14}H_{21}O_4$ 253.1440, obsd 253.1496.

4b: $[\alpha]^{20}_D$ –99.5° (*c* 0.4, $CHCl_3$); IR (film) 2720, 1740, 1660, 1380, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.06 (s, 6H), 0.89 (t, J = 6.6 Hz, 3H), 0.94 (s, 9H), 1.2–1.5 (m, 6H), 1.36 (s, 3H), 1.53 (s, 3H), 1.95–2.20 (m, 2H), 4.03 (dd, J = 4.4, 1 Hz, 1H), 4.32 (dd, J = 6.6, 4.3 Hz, 1H), 5.06 (dd, J = 8.3, 6.6 Hz, 1H), 5.5 (m, 2H), 9.67 (d, J = 1 Hz, 1H); MS (*m/z*) 370 (M^+, 1.6), 356 (M^+ + 1 – Me, 13.3), 313 (M^+ – C_4H_9, 22.8), 255 (M^+ – $SiMe_2Bu$, 40.3).

5b: $[\alpha]^{20}_D$ –87.2° (*c* 0.45, $CHCl_3$); IR (film) 3450, 2720, 1745, 1730, 1660, 1380, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.89 (t, J = 6.8 Hz, 3H), 1.2–1.6 (m, 12H), 1.95–2.2 (m, 2H), 2.22 (s, 3H), 4.65 (dd, J = 6.7, 2.7 Hz, 1H), 4.91 (d, J = 2.6 Hz, 1H), 5.11 (dd, J = 8.0, 6.6 Hz, 1H), 5.38 (m, 1H), 5.69 (m, 1H), 9.51 (s, 1H); MS (*m/z*) 298 (M^+, 1), 283 (M^+ – Me, 10.3), 241 (M^+ – C_4H_9, 23), 239 (M^+ – MeCOO, 2.9); HRMS calcd for $C_{15}H_{23}O_5$ 283.1547, obsd 283.1529.

6b: $[\alpha]^{20}_D$ –49.4° (*c* 0.45, $CHCl_3$); IR (film) 3450, 1730, 1660, 1380, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.89 (t, J = 6.5 Hz, 3H), 1.25-1.45 (m, 6H), 1.37 (s, 3H), 1.53 (s, 3H), 1.95–2.20 (m, 2H), 3.43 (s, 3H), 3.84 (dd, J = 4.4, 1.4 Hz, 1H), 4.43 (dd, J = 4.5, 6.3 Hz, 1H), 4.76 (q, J = 6.6 Hz, 2H), 5.06 (dd, J = 9.1, 6.6 Hz, 1H), 5.51 (dd, J = 10.8, 9 Hz, 1H), 5.64 (m, 1H), 9.69 (d, J = 1.4 Hz, 1H); MS (*m/z*) 300 (M^+, 0.4), 285 (M^+ – Me, 10.3), 243 (M^+ – C_4H_9, 7.7), 181 (13), 168 (54); HRMS calcd for $C_{15}H_{25}O_5$ 285.1702 obsd 285.1699.

Entries 7 and 8. The reaction was complicated due to partial cleavage of the THP (EE) protecting group, and the products were not identified. TLC showed the presence of compound **4**.

9b:[11] $[\alpha]^{20}_D$ +23.1° (*c* 0.8, $CHCl_3$); IR (film) 3450, 1735, 1720, 1380, 1370 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 1.36 (s, 3H), 1.50 (s, 3H), 4.15 (dd, J = 7, 5.0 Hz, 1H), 4.57 (dd, J = 2, 4 Hz, 1H), 4.95 (d, J = 5 Hz, 1H), 5.2 (dd, J = 7, 4 Hz, 1H), 7.5 (m, 3H), 8.0 (m, 2H), 9.66 (d, J = 2 Hz, 1H); MS (*m/z*) 293 (M^+ + 1, 1), 277 (M^+ – Me, 15), 187 (M^+ – C_6H_5CO, 17), 105 (100).

10b:[12] $[\alpha]^{20}_D$ –11.6° (*c* 1.1, $CHCl_3$); IR (film) 3400, 1730, 1380, 1370 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 1.37 (s, 3H), 1.39 (s, 3H), 1.42 (s, 3H), 1.48 (s, 3H), 3.9–4.2 (m, 5H), 9.8 (d, J = 2 Hz, 1H); MS (*m/z*) 230 (M^+, 5), 215 (M^+ – Me, 60), 143.

11b: $[\alpha]^{20}_D$ –8.6° (*c* 0.5, $CHCl_3$); IR (film) 3400, 3290, 2100, 1730, 1380, 1370 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 1.2–1.50 (m, 6H), 2.06 (m, 1H), 2.4–2.70 (m, 2H), 3.5–4.20 (m, 3H), 4.8–5.2 (m, 1H), 9.81 (s, 1H); MS (*m/z*) 199 (M^+ + 1, 17), 183 (M^+ – Me, 18), 181 (3), 81 (100); HRMS calcd for $C_9H_{11}O_4$ 183.0657, obsd 183.0701.

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Supplementary Material Available: ^1H NMR spectra of compounds **1a–8a**, **11a**, **4**, **1b–6b**, and **9b–11b** (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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