JOC*Note*

Facile Oxidative Cleavage of 4-*O*-Benzyl Ethers with Dichlorodicyanoquinone in Rhamno- and Mannopyranosides

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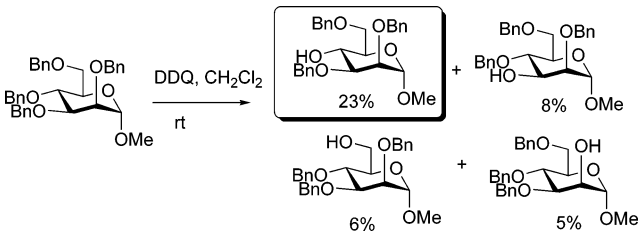
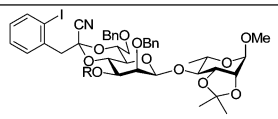
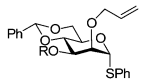
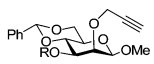
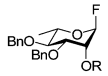
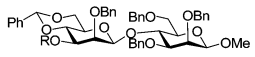
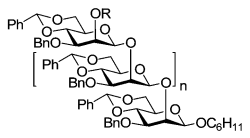
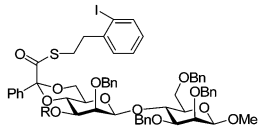
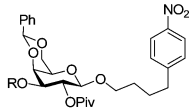
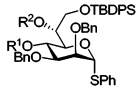
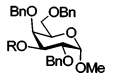


On exposure to dichlorodicyanoquinone in wet dichloromethane at room temperature, equatorial 4-*O*-benzyl ethers are removed with moderate selectivity in the presence of other benzyl ethers in glycopyranosides and glycothiopyranosides.

The *p*-methoxybenzyl (PMB) ethers and their somewhat less acid sensitive congeners, the 2-naphthylmethyl (Nap) ethers, are staple protecting groups in organic synthesis, in general, and especially in oligosaccharide synthesis, owing to their facile oxidative cleavage with either dichlorodicyanoquinone (DDQ) or ceric ammonium nitrate (CAN).[1−6] Simple benzyl ethers are not inert to these oxidative cleavage conditions but typically react significantly more slowly,[5−16] enabling the highly selective cleavage of the PMB or Nap ethers in their presence.[1,2] By way of illustration, we have collated some recent examples of this type from our own laboratory,[17−23] along with an oxidative cyclization[17] and a pertinent literature example[1] in Table 1.

TABLE 1. Examples of Selective Cleavage

Entry	Structure	Transformation, % yield
1[17]		R = Nap → R = H, 85%
2[18]		R = PMB → R = H, 93%
3[18]		R = PMB → R = H, 95%
4[19]		R = Nap → R = H, 54%
5[20]		R = PMB → R = H, 83%
6[21]		R = PMB → R = H, n = 0, 97%; n = 1, 91%; n = 2, 85%; n = 3, 80% n = 4, 85%
7[22]		R = Nap → R = H, 83%
8[23]		R = PMB → R = H, 85%
9[17]		R^1 = PMB, R^2 = H → R^1-R^2 = PMPCH,[a] 85%
10[1]		R = Nap → R = H, 80%

[a] PMPCH = *p*-methoxybenzylidene.

Accordingly, we were surprised when, in the course of an ongoing synthesis, we encountered significant cleavage of a

(1) Xia, J.; Abbas, S. A.; Locke, R. D.; Piskorz, C. F.; Alderfer, J. L.; Matta, K. L. *Tetrahedron Lett.* **2000**, *41*, 169−173.
(2) Liao, W.; Locke, R. D.; Matta, K. L. *Chem. Commun.* **2000**, 369−370.
(3) Wuts, P. G. M. In *Handbook of Reagents for Organic Synthesis: Reagents for Glycoside, Nucleotide, and Peptide Synthesis*; Crich, D., Ed.; Wiley: Chichester, 2005; pp 425−428.
(4) Csávás, M.; Szabó, Z. B.; Borbás, A.; Lipták, A. In *Handbook of Reagents for Organic Synthesis: Reagents for Glycoside, Nucleotide, and Peptide Synthesis*; Crich, D., Ed.; Wiley: Chichester, 2005; pp 459−460.
(5) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.
(6) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Thieme: Stuttgart, 2005.
(7) Tanaka, T.; Oikawa, Y.; Nakajima, N.; Hamada, T.; Yonemitsu, O. *Chem. Pharm. Bull.* **1987**, *35*, 2203−2208.
(8) Horita, K.; Nagato, S.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron Lett.* **1987**, *28*, 3253−3256.
(9) Sviridov, A. F.; Ermolenko, M. S.; Yashunsky, D. V.; Borodkin, V. S.; Kochetkov, N. K. *Tetrahedron Lett.* **1987**, *28*, 3839−3842.
(10) Vedejs, E.; Buchanan, R. A.; Watanabe, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8430−8438.
(11) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 2524−2536.
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(13) Fujiwara, K.; Murai, A.; Yotsu-Yamashita, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 10770−10771.
(14) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653−5660.
(15) Zhu, B.; Panek, J. S. *Org. Lett.* **2000**, *2*, 2575−2578.
(16) Crimmins, M. T.; Emmitte, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 1533−1534.

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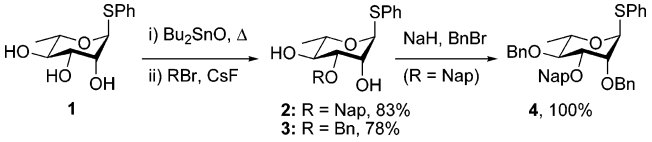
benzyl ether when removing a vicinal Nap ether with DDQ (Table 2, entry 1). Intrigued by this unusual observation, we carried out a more detailed investigation, the results of which are presented here.

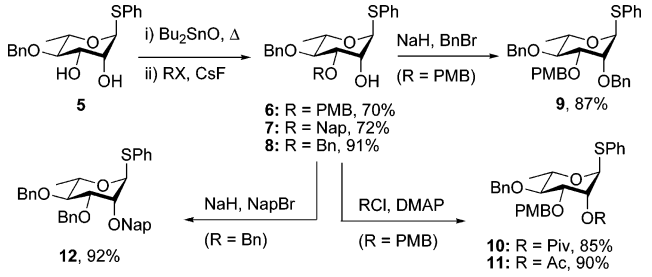
Substrate Preparation. Treatment of triol **1**[24] with dibutyltin oxide in toluene under Dean-Stark conditions gave an intermediate stannylene acetal, which, on quenching with either 2-bromomethylnaphthalene or benzyl bromide in the presence of cesium fluoride, gave the 3-*O*-naphthylmethyl and 3-*O*-benzyl ethers **2** and **3**, respectively. Exhaustive benzylation of **2** then gave the differentially protected substrate **4** (Scheme 1).

SCHEME 1



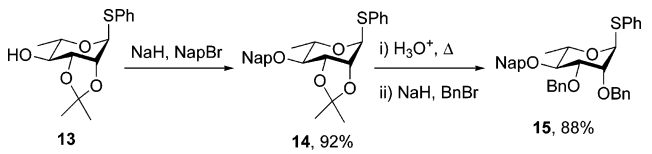
Reaction of the dibutylstannylene acetal derived from the known 4-*O*-benzyl ether **5**[25] with *p*-methoxybenzyl chloride in the presence of cesium fluoride and tetrabutylammonium bromide afforded the 4-*O*-benzyl-3-*O*-*p*-methoxybenzyl ether **6**, while reaction with naphthylmethyl bromide or benzyl bromide gave products **7** and **8**,[26] respectively (Scheme 2). The alcohol **6** was then converted to the fully protected systems **9**, **10**, and **11**, under standard conditions, whereas reaction of the 3,4-di-*O*-benzyl ether **8** with naphthylmethyl bromide and sodium hydride provided **12** (Scheme 2).

SCHEME 2



Naphthylmethylation of acetonide **13**[27] gave **14**, which was heated to reflux in a mixture of acetic acid and aqueous dioxane followed, without isolation of the intermediate 2,3-diol, by exposure to sodium hydride and benzyl bromide to give the 2,3-di-*O*-benzyl-4-*O*-naphthylmethyl system **15** (Scheme 3).

SCHEME 3



Oxidative Cleavage Reactions. Exposure of the 2,4-di-*O*-benzyl-3-*O*-naphthylmethyl system **4** to DDQ in wet dichloromethane at 0 °C for 30 min, followed by stirring at room temperature for 3 h, gave 63% of the anticipated mono-ol **16**, along with 13% of diol **17**[28] (Table 2, entry 1). Comparable results were obtained with the corresponding 2,4-di-*O*-benzyl-3-*O*-*p*-methoxybenzyl ether **9** (Table 2, entry 2). When the alcohol **16** was subjected to the standard reaction conditions, the diol **17** was again formed in amounts depending on the reaction conditions and stoichiometry employed (Table 2, entry 3). When the 2,3,4-tri-*O*-benzyl ether **18**[29] was similarly treated, a complex reaction mixture was obtained in which the product arising from selective removal of the 4-*O*-benzyl ether **19** predominated significantly (Table 2, entry 4). With the 2-*O*-pivalate ester **10** and the 2-*O*-acetate **11**, the pattern was continued with cleavage of the 3-*O*-*p*-methoxybenzyl ether, accompanied by partial loss of the benzyl ether at the 4-*O*-position (Table 2, entries 5 and 6). Analysis of the initial reaction mixture from the reaction of **11** with DDQ was complicated by migration of the acetate group but was facilitated by saponification.

With the 3,4-di-*O*-benzyl-2-*O*-naphthylmethyl system **12**, regioisomeric with the initial substrate **4**, partial cleavage of the 4-*O*-benzyl ether was again observed (Table 2, entry 7). However, the trend did not extend to the third regioisomer in the series, the 2,3-di-*O*-benzyl-4-*O*-naphthylmethyl system **15**, where the oxidative cleavage reaction was much cleaner and only minor amounts of debenzylated products were observed under the standard conditions (Table 2, entry 8).

The methyl 2,4-di-*O*-benzyl rhamnopyranoside **24**[30] (Table 2, entry 9) performed much as the corresponding *S*-phenyl thioglycoside **16** (Table 2, entry 3) with considerable cleavage of the 4-*O*-benzyl ether depending on the stoichiometry employed. Finally, methyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside **26**[31] was explored as a substrate for the oxidative cleavage reaction. All four possible mono-ols were obtained from this reaction, but it is noteworthy that the 4-ol **27**[32] is by far the most significant product with a yield surpassing that of 2-, 3-, and 6-ols combined (Table 2, entry 10).

It is apparent from the entirety of results presented in Table 2 that benzyl ethers located on the 4-position of rhamno- and mannopyranosides are cleaved oxidatively with DDQ significantly more easily than benzyl ethers located at other positions around the ring. In hindsight, the moderate yield recorded for the example of entry 4 of Table 1 can most likely be ascribed to the same phenomenon. From entry 3 of Table 2, it is clear that the oxidative cleavage of the 4-*O*-benzyl ether is an inherent characteristic of that group and does not require

(17) Crich, D.; Banerjee, A. *J. Am. Chem. Soc.* **2006**, *128*, 8078−8086.
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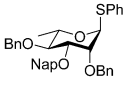
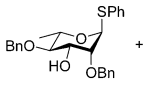
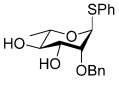
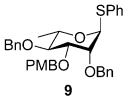
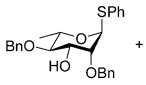
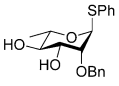
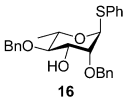
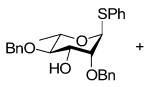
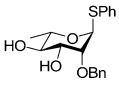
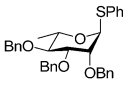
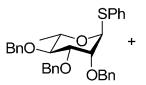
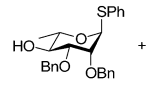
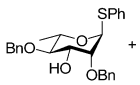
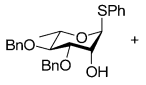
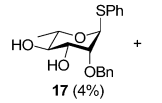
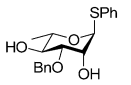
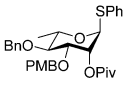
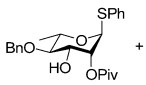
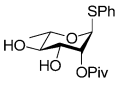
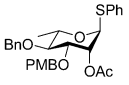
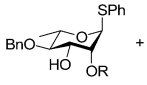
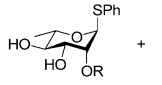
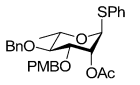
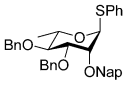
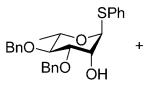
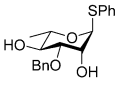
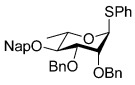
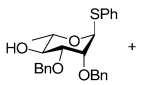
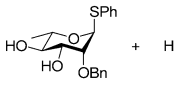
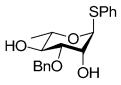
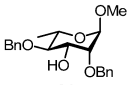
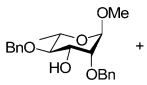
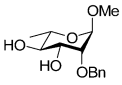
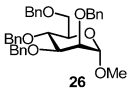
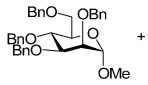
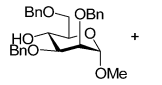
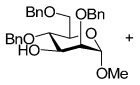
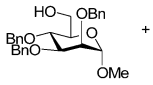
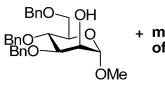
(19) Crich, D.; Hutton, T. K.; Banerjee, A.; Jayalath, P.; Picione, J. *Tetrahedron: Asymmetry* **2005**, *16*, 105−119.
(20) Crich, D.; Li, W.; Li, H. *J. Am. Chem. Soc.* **2004**, *126*, 15081−15086.
(21) Crich, D.; Banerjee, A.; Yao, Q. *J. Am. Chem. Soc.* **2004**, *126*, 14930−14934.
(22) Crich, D.; Yao, Q. *J. Am. Chem. Soc.* **2004**, *126*, 8232−8236.
(23) Crich, D.; Li, H. *J. Org. Chem.* **2002**, *67*, 4640−4646.
(24) Groneberg, R. D.; Miyazaki, T.; Stylianides, N. A.; Schulze, T. J.; Stahl, W.; Schreiner, E. P.; Suzuki, T.; Iwabuchi, Y.; Smith, A. L.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1993**, *115*, 7593−7611.
(25) Pozsgay, V. *J. Org. Chem.* **1998**, *63*, 5983−5999.
(26) Lau, R.; Schüle, G.; Schwaneberg, U.; Ziegler, T. *Liebigs* **1995**, 1745−1754.
(27) Pozsgay, V. *Carbohydr. Res.* **1992**, *235*, 295−302.
(28) Maloney, D. J.; Hecht, S. M. *Org. Lett.* **2005**, *7*, 1097−1099.
(29) Furukawa, J.-I.; Kobayashi, S.; Nomizu, M.; Nishi, N.; Sakairi, N. *Tetrahedron Lett.* **2000**, *41*, 3453−3457.
(30) Pozsgay, V. *Carbohydr. Res.* **1979**, *69*, 284−286.
(31) Girard, C.; Miramon, M.-L.; de Solminihac, T.; Herscovici, J. *Carbohydr. Res.* **2002**, *337*, 1769−1774.
(32) Schie, C.-R.; Tzeng, Z.-H.; Kulkarni, S. S.; Uang, B.-J.; Hsu, C.-Y.; Hung, S.-C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1665−1668.

TABLE 2. Oxidative Cleavage Reactions with DDQ

entry	substrate	conditions	products (% yield)		
1	 **4**	0 °C, 30 min, rt, 3 h	 **16** (63%)	 **17** (13%)	
2	 **9**	0 °C, 30 min, rt, 1.5 h	 **16** (78%)	 **17** (14%)	
3	 **16**				
		0 °C, 30 min, rt, 5 h	**16** (58%)	**17** (35%)	
		0 °C, 30 min, 3 h	**16** (60%)	**17** (30%)	
		3 h (0.3 eq DDQ)	**16** (81%)	**17** (3%)	
4	 **18**		 **18** (28%)	 **19** (40%)	 **16** (6%)
		0 °C, 30 min, rt, 5 h	 **8** (4%)	 **17** (4%)	 **3** (4%)
5	 **10**	0 °C, 30 min, rt, 4 h	 **20** (74%)	 **21** (13%)	
6	 **11**		 **22:** R = Ac	 **23:** R = Ac	 **11**
		0 °C, 30 min, rt, overnight	**5:** R = H (69%)	**1:** R = H (30%)	-
		0 °C, 30 min, rt, 4 h	**5:** R = H (82%)	**1:** R = H (12%)	**11** (2%)
7	 **12**	0 °C, 30 min, rt, 2.5 h	 **8** (60%)	 **3** (11%)	
8	 **15**	0 °C, 30 min, rt, 2 h	 **19** (85%)	 **17** (~3%)	 **3** (~6%)
9	 **24**				
		0 °C, 30 min, rt, 3 h	**24** (62%)	**25** (30%)	
		3 h (0.3 eq DDQ)	**24** (89%)	**25** (3%)	
10	 **26**	0 °C, 30 min, rt, 3 h	 **26** (40%)	 **27** (23%)	 **28** (8%)
			 **29** (6%)	 **30** (5%)	+ **mixture of the products of dibenzyl deprotection** (7%)

the presence of the Nap or PMB ethers; that is, the mechanism must involve direct oxidation of the benzyl ether rather than hole transfer from a more readily oxidized neighboring group.[33,34] Likewise, entries 9 and 10 of Table 2 reveal that the thioglycoside is not the site of the initial oxidation step. Comparison of entries 9 and 10 of Table 2 indicates that the absence of a C6−O bond is not a requirement for the selective removal of the 4-*O*-benzyl ether.

While we have restricted our study to the rhamno- and mannopyranosyl systems of greatest interest to our laboratory, useful indications may also be gleaned from the literature. Thus, as set out in Table 1, entry 10, Matta and co-workers reported the selective cleavage of a 3-*O*-Nap ether in the presence of a 4-*O*-benzyl ether in the galactopyranose series,[1] leading to the implication that an axial benzyloxy group at the 4-position of a pyranose is less readily oxidized than the equatorial counterpart. This postulate is reinforced by the apparent need for more forcing conditions: 30 equiv of DDQ and 10 h at room temperature, to obtain a 70% yield in the cleavage of a 4-*O*-benzyl ether from an α-fucopyranoside noted in the course of a total synthesis of polycavernoside A.[13] While we have not studied the glucopyranose series here, we do expect that selective cleavage of 4-*O*-benzyl ethers will be a feature of that system based on our results so far.

Overall, we are led to the conclusion that the selective cleavage of the 4-*O*-benzyl ether derives from the fixed antiperiplanar nature of the C4−O4 and C5−O1 bonds, which maximizes the electron-withdrawing properties of the latter, and accelerates decomposition of the radical cation, just as the disarming effect of a 4,6-*O*-alkylidene acetal in glycosylation reactions is attributed to the enforcement of the more electron-withdrawing *tg* conformation.[35,36] Selective protection strategies are key features of the enormous majority of work in the carbohydrate and oligosaccharide fields,[37−43] and it is possible that, with optimization, perbenzylation and selective debenzylation at O4 might provide a short, cost-effective entry into the 4-OH systems.

Experimental Section

General Procedure for the Deprotection with DDQ. To a solution of the substrate (0.03 M) in a mixture of CH_2Cl_2/H_2O (17/1) was added DDQ (2.3 or 0.3 equiv) at 0 °C. After 30 min, the reaction mixture was warmed to room temperature and further stirred for the specified time (Table 2) before it was diluted with CH_2Cl_2 and quenched with saturated aqueous Na_2CO_3. The organic phase was separated, washed (saturated aqueous Na_2CO_3), dried (Na_2SO_4), and concentrated. The crude reaction mixture was filtered through a pad of silica gel (with ethyl acetate as an eluent) and then purified by chromatography on SiO_2.

Reaction of *S*-Phenyl 2,4-Di-*O*-benzyl-3-*O*-(2-naphthylmethyl)-α-L-thiorhamnopyranoside (4) with DDQ. Compound **4** (737 mg, 1.28 mmol) was deprotected with 2.3 equiv of DDQ (667 mg, 2.9 mmol) for 3 h. Purification by radial chromatography (SiO_2, hexanes to 2:3 ethyl acetate/hexanes) gave **16** (351 mg, 63%) and **17** (59 mg, 13%).

Reaction of *S*-Phenyl 2,4-Di-*O*-benzyl-3-*O*-(4-methoxybenzyl)-α-L-thiorhamnopyranoside (9) with DDQ. Compound **9** (88 mg, 0.16 mmol) was deprotected with 2.3 equiv of DDQ (83 mg, 0.37 mmol) for 1.5 h. Purification by radial chromatography (SiO_2, hexanes to 2:3 ethyl acetate/hexanes) gave **16** (54 mg, 78%) and **17** (8 mg, 14%).

Reaction of *S*-Phenyl 4-*O*-Benzyl-3-*O*-(4-methoxybenzyl)-2-*O*-pivaloyl-α-L-thiorhamnopyranoside (10) with DDQ. Compound **10** (96 mg, 0.17 mmol) was deprotected with 2.3 equiv of DDQ (91 mg, 0.40 mmol) for 4 h. Radial chromatography (SiO_2, hexanes to 3:7 ethyl acetate/hexanes) gave **20** (55 mg, 74%) and **21** (8 mg, 13%).

Reaction of *S*-Phenyl 3,4-Di-*O*-benzyl-2-*O*-(2-naphthylmethyl)-α-L-thiorhamnopyranoside (12) with DDQ. Compound **12** (69 mg, 0.12 mmol) was deprotected with 2.3 equiv of DDQ (62 mg, 0.27 mmol) for 2.5 h. Radial chromatography (SiO_2, hexanes to 3:7 ethyl acetate/hexanes) gave **8** (41 mg, 60%) and **3** (5 mg, 11%).

Reaction of *S*-Phenyl 2,3-Di-*O*-benzyl-4-*O*-(2-naphthylmethyl)-α-L-thiorhamnopyranoside (15) with DDQ. Compound **15** (104 mg, 0.18 mmol) was deprotected with 2.3 equiv of DDQ (94 mg, 0.42 mmol) for 2 h. Radial chromatography (SiO_2, hexanes to 2:3 ethyl acetate/hexanes) gave **19** (67 mg, 85%), **3** (4 mg, 6%), and **17** (2 mg, 3%).

Acknowledgment. We thank the NIH (GM62160) for support of this work, and an anonymous reviewer for insight into the origin of the phenomenon.

Supporting Information Available: Full experimental details for substrate preparation and copies of spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(33) For examples of hole (radical cation) transfer and delocalization and its consequences, see the extensive work on the oxidative cleavage of DNA: *Charge Transfer in DNA: From Mechanism to Application*; Wagenknecht, H.-A., Ed.; Wiley-VCH: Weinheim, Germany 2005; and ref 34.

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