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Regioselective Control in the Oxidative Cleavage of 4,6-*O*-Benzylidene Acetals of Glycopyranosides by Dimethyldioxirane

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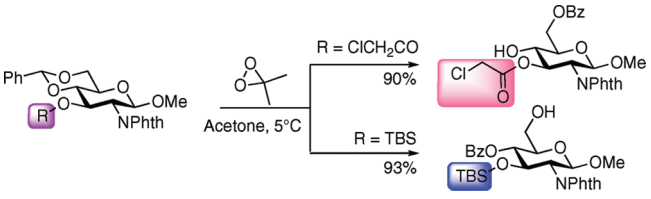
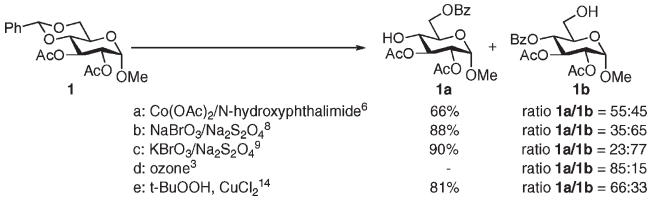
Received December 9, 2009



The oxidative cleavage of 4,6-*O*-benzylidene acetals of glycopyranosides using dimethyldioxirane (DMDO) leads to the corresponding hydroxy-benzoates in excellent yields. With a proper choice of the neighboring protecting groups, this oxidative fragmentation provides the 6- or 4-hydroxyl derivatives in a highly regioselective manner.

Carbohydrates contain many hydroxyl groups with similar chemical reactivities. It is often a difficult task to perform useful differential manipulations on such molecules, particularly the discrimination between secondary hydroxyl groups.[1] The regioselective opening of cyclic derivatives is an attractive approach for this purpose. Benzylidene acetal groups are widely used as protecting groups of diols because of their easy introduction and their tolerance to a variety of chemical conditions. These acetals provide a selective 4,6-*O*-protection of pyranoses such as glucose, 2-acetamido-2-deoxy-glucose, galactose, mannose, or altrose. Reductive opening of carbohydrate benzylidene acetals, furnishing benzyl ether at either the C4 or C6 hydroxyl group, was extensively investigated in the literature.[2] Selective cleavage of benzylidene acetals under oxidative conditions, allowing formation of a benzoate ester at either the C4 or C6 hydroxyl group, is less frequently employed because most known procedures suffer from rather harsh or environmentally unfriendly conditions. Oxidative cleavage of benzylidene acetals of nonsaccharidic acetals using tritylfluoroborate ($Ph_3C^+BF_4^-$),[3] pyridinium dichromate/*tert*-butyl hydroperoxide,[4] $NaBO_3$,[5] $Co(OAc)_2$/*N*-hydroxyphthalimide,[6] 2,2′-bipyridinium chlorochromate/*m*-CPBA,[7] $NaBrO_3/Na_2S_2O_4$[8] and $KBrO_3/Na_2S_2O_4$,[9] and more recently $RuCl_3/NaIO_4$[10] has been evaluated and gave varying degrees of regioselectivity. Similarly, many methods have been developed for the selective oxidative cleavage of 4,6-*O*-benzylidene acetals of pyranosides. Ozone,[3] 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[11,12] NBS/H_2O,[13] $Pd(OAc)_2$ or $CuCl_2$/t-BuOOH,[14] $NaBrO_3/Na_2S_2O_4$,[8] $Co(OAc)_2$/*N*-hydroxyphthalimide,[6] and $KBrO_3/Na_2S_2O_4$[9] gave, in most cases, the benzoyl esters in high yield but with moderate regioselectivity (Scheme 1).

SCHEME 1. Reported Methods for Oxidative Opening



As part of our ongoing interest to develop easy new methods for the regioselective protection of carbohydrates,[15] we now report conditions for the regioselective oxidative opening of 4,6-*O*-benzylidene acetals of glycopyranosides **A** using dimethyldioxirane (DMDO), leading to the corresponding 4-alcohols **B** or 6-alcohols **C** (Scheme 2), valuable intermediates as glycosyl acceptors in glycoside synthesis.[16]

(1) *Protecting Groups*, 3rd ed.; Kocienski, P. J., Ed.; Georg Thieme Verlag: Stuttgart, 2005.
(2) *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker, Inc.: New York, 1997; pp 53−65.
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(5) Bhat, S.; Ramesh, A. R.; Chandrasekaran, S. *Synlett* **1995**, 329.
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(10) Ponminor Senthil, K.; Amit, B.; Sundarababu, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 804–807.
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(15) Français, A.; Urban, D.; Beau, J.-M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8662–8665.
(16) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 2–37.

DOI: 10.1021/jo9026098 Published on Web 02/08/2010
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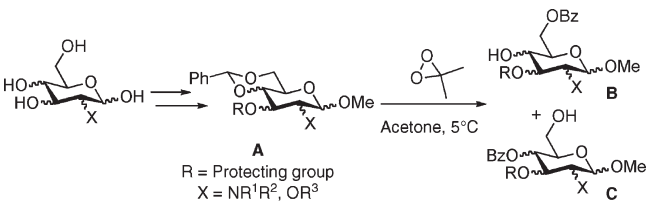
SCHEME 2. Oxidative Cleavage with DMDO



DMDO is a powerful oxidant prepared from Oxone and acetone and used as a dilute solution (~0.1 M) in acetone according to the literature.[17] The reaction is easy to perform and produces no waste other than acetone. DMDO can be employed under neutral, non-nucleophilic conditions that facilitate the isolation of products especially in cases of unstable intermediates.[18] Hayes et al.[19] have recently reported a selective benzylidene acetal cleavage with DMDO in order to access the primary alcohol during the total synthesis of (+)-lactacystin. They also extended this oxidative deprotection method to various benzylidene acetals derived from noncarbohydrate 1,2- and 1,3-diols.[20]

The preparation of a range of 4,6-*O*-benzylidene acetals of glucose, 2-amino-2-deoxy-glucose, galactose, mannose, and altrose derivatives was easily achieved from the corresponding glycopyranosides by standard acid-catalyzed condensation with benzaldehyde dimethyl acetal, furnishing the corresponding 4,6-*O*-benzylidene acetals (see Supporting Information).

In all cases, oxidation of the 4,6-*O*-benzylidene acetal derivatives was performed using an excess of DMDO[21] (0.1 M in acetone), and the resulting solution was stirred at 5 °C for 96 h. The slow rate of the cleavage explains the possibility of using DMDO for other oxidizing purposes in the presence of the benzylidene acetal group in the same molecule.[22] Removal of the volatiles *in vacuo* furnished the crude product that was purified by chromatography. The isolated yields of the 6-OH or 4-OH derivatives are provided in Table 1. $^1H-^1H$ COSY, $^1H-^{13}C$ HMQC, and $^1H-^{13}C$ HMBC spectra established unambiguously the structure of each regioisomer. In almost all cases no byproduct could be detected. The examples given show the chemoselectivity and functional group tolerance (except when the trichloroacetate group was used, Table 1, entry 10) of this oxidation in the carbohydrate series, with excellent discrimination of the glycosidic acetal.[23] In all cases the moderate to high regioselectivity was mostly determined by the nature of the protecting group at the C3 position. Also, the results are similar for the 2-deoxy-2-phthalimido-glucopyranoside series (Table 1, entries 1−9) and the glucopyranoside series (Table 1, entries 11−19).

O the basis of the experimental results, the following conclusions can be drawn. An increase of the electron-withdrawing character of the protecting group at C3 (Ac, $ClCH_2CO$, Cl_2CHCO) increases selectivity in favor of the formation of the primary benzoate at C6 (selectivities from 80:20 to 98:2, Table 1, entries 7−9 and 11, 14, 17). A bulky electron-withdrawing protecting group at C3 will however decrease the formation of the benzoate at C6 position (selectivities of 80:20, 62:38, and 56:44, respectively, with the Ac, Bz and Piv protecting groups at C3). Further, a bulkier electron-donating group at C3 (OTBS, OTBDPS, entries 5, 6, and 18) induces a reversal of selectivity with a high preference for the formation of the secondary benzoate at C4 (selectivities from 3:97 to 1:99 and higher).

A mesylate group[14] (Table 1, entry 16) at C3 gave poor regioselectivity in favor of the secondary benzoate at C6 similar to the benzoate group (Table 1, entry 12). Surprisingly, a tosylate group (Table 1, entry 15), a bulky electron-withdrawing group, at C3 led to good selectivity in favor of the secondary benzoate at C4. This result is in accordance with the regioselectivity observed with ozone by Deslongchamps et al.[3] and better than that obtained with *t*-BuOOH and $CuCl_2$ by Sato et al.[14]

The oxidation of epoxide **19** furnished with high selectivity (> 98:2) the benzoate at C6 contrary to the results of Sato et al.[14] with *t*-BuOOH and $CuCl_2$, who observed a poor selectivity in favor of the secondary benzoate at C4 (54:46). The half-chair conformation of **19** could explain this surprising regioselectivity.

Similar yields were obtained with the 2-acetamido-2-deoxy-D-glucopyranoside series, with however a decrease in the regioselectivity of the reaction by comparison with the 2-deoxy-2-phthalimido series [for R = $ClCH_2CO$, ratio of 8:2 (Table 1, entry 22) vs 94:6 (Table 1, entry 8) and for R = TBS, a ratio of 10:90 (Table 1, entry 23) vs 1:99 (Table 1, entry 5)]. In the *altro* series, with an axial orientation of the protecting group at C3, the regioselectivity of the reaction was lost (Table 1, entries 24, 25). Finally, the regioselectivity was not sensitive to the configuration at C4 (compound **26** of the *galacto* series) or C2 (compound **27** of the *manno* series) (Table 1, entries 26, 27).

The putative first step[24] of this oxidative fragmentation is the formation of the *O*-insertion transition state **D** *via* a direct concerted electrophilic oxygen insertion process (Scheme 3) or the formation of intermediate **E** *via* a radical

(17) (a) Adam, W.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377. (b) Murray, R. W.; Singh, M. *Org. Synth.* **1997**, *74*, 91−97. CAUTION: DMDO is a very volatile peroxide that should be handled in a hood and behind a shield.

(18) (a) Boyer, F. D.; Descoins, C. L.; Thanh, G. V.; Descoins, C.; Prange, T.; Ducrot, P. H. *Eur. J. Org. Chem.* **2003**, 1172–1183. (b) Boyer, F. D.; Beauhaire, J.; Martin, M. T.; Ducrot, P. H. *Synthesis* **2006**, 3250–3260.

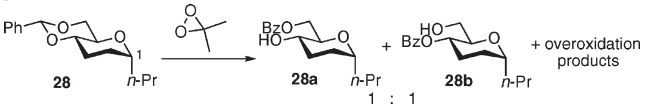
(19) Hayes, C. J.; Sherlock, A. E.; Green, M. P.; Wilson, C.; Blake, A. J.; Selby, M. D.; Prodger, J. C. *J. Org. Chem.* **2008**, *73*, 2041–2051.

(20) Mycock, D. K.; Sherlock, A. E.; Glossop, P. A.; Hayes, C. J. *Tetrahedron Lett.* **2008**, *49*, 6390−6392 and references therein.

(21) The reaction of compound **1** was also performed directly with Oxone and wet Al_2O_3 in refluxing CH_2Cl_2. After 48 h, this provided only 8% yield of the primary benzoate **1a** with the starting material **1**. See: Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Synlett* **1999**, 777–779.

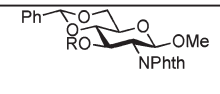
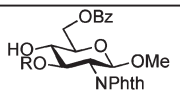
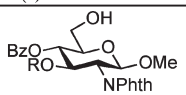
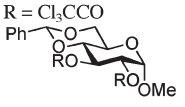
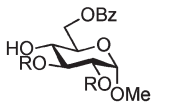
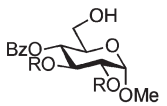
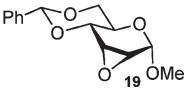
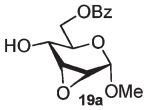
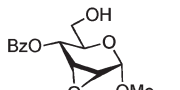
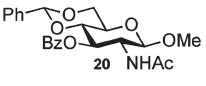
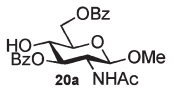
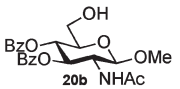
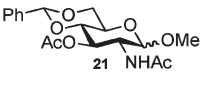
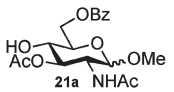
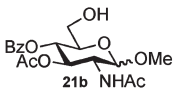
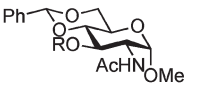
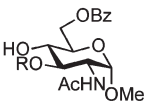
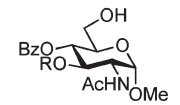
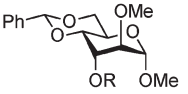
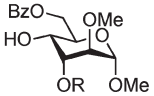
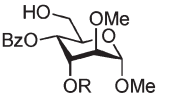
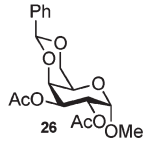
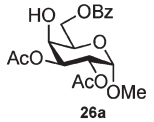
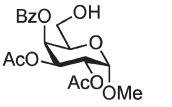
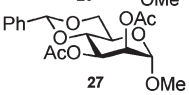
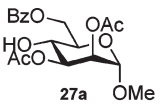
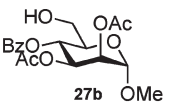
(22) Despite its high reactivity, DMDO displays good selectivity for olefins as seen in the selective epoxidation of glycals equipped with a benzylidene acetal protecting group; see: (a) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661–6666. (b) For a review, see: *Handbook of Chemical Glycosylation*; Demchenko, A. V., Ed., Wiley-VCH: Weinheim,2008; pp 436−437.

(23) However, under these oxidation conditions, the 4,6-*O*-benzylidene acetal cleavage in *C*-glucoside **28** gave a mixture of the 4-OH and 6-OH derivatives (**28a**/**28b** 1:1 ratio) accompanied by oxidation products at the C1 position.



(24) Curci, R.; D'Accolti, L.; Fusco, C. *Acc. Chem. Res.* **2006**, *39*, 1−9 and references therein.

TABLE 1. Oxidative Cleavage of 4,6-*O*-Benzylidene Acetals of Carbohydrate Derivatives

Entry	Substrate	Product(s)		Yield (%)	Ratio a:b
					
1	**2**: R = H	**2a**	**2b**	97	71:29
2	**3**: R = Bz	**3a**	**3b**	84	62:38
3	**4**: R = 4-Cl-Bz	**4a**	**4b**	99	67:33
4	**5**: R = Piv	**5a**	**5b**	99	56:44
5	**6**: R = TBS	**6a**	**6b**	94	1:99
6	**7**: R = TBDPS	**7a**	**7b**	97	>1:99
7	**8**: R = Ac	**8a**	**8b**	95	80:20[a]
8	**9**: R = $ClCH_2CO$	**9a**	**9b**	96	94:6
9	**10**: R = Cl_2CHCO	**10a**	**10b**	97	98:2
10	**11** R = Cl_3CCO	-	-	**2** (38%), **2a** (33%)	-
					
11	**1**: R = Ac	**1a**	**1b**	96	80:20
12	**12**: R = Bz	**12a**	**12b**	95	76:24
13	**13**: R = H	**13a**	**13b**	93	71:29
14	**14**: R= $ClCH_2CO$	**14a**	**14b**	99	90:10
15	**15**: R = Ts	**15a**	**15b**	99	11:89
16	**16**: R = Ms	**16a**	**16b**	92	64:36
17	**17**: R= Cl_2CHCO	**17a**	**17b**	93	95:5[a]
18	**18**: R= TBS	**18a**	**18b**	95	3:97[a]
19				80	>99:1[a]
20				76	50:50
21				91	60:40[b]
					
22	**22**: R= $ClCH_2CO$	**22a**	**22b**	99	80:20[a]
23	**23**: R= TBS	**23a**	**23b**	87	10:90[a]
					
24	**24**: R= OAc	**24a**	**24b**	90	64:36[a]
25	**25**: R= TBS	**25a**	**25b**	91	65:35[a]
26				95	87:13
27				92	80:20

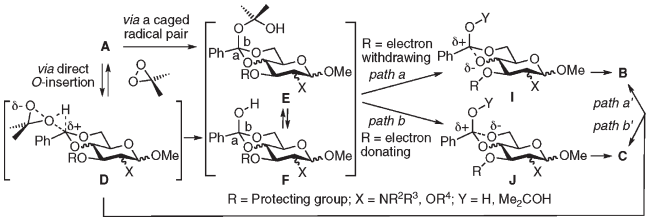
[a]Ratio determined by ^{1}H NMR in the crude product. [b]Inseparable mixture, ratio determined by ^{1}H NMR.

mechanism involving hydrogen-atom abstraction of the benzylidene acetal hydrogen (caged radical pair). Intermediate **D** or **E** would give the corresponding hemiortho ester **F** . Both **E** or **F** could lead, by cleavage of bond *a* or *b*, to the 6-OH and/or 4-OH derivatives. An alternative route could directly provide products **B** or **C** from **D**.[25]

As previously reported,[20] the regiocontrol of the fragmentation may be determined by the relative stability of the partially charged intermediates **I** and **J** (or the analogous polarized intermediates directly from **D**) or the corresponding alkoxides (Scheme 3). With an electron-withdrawing

(25) This would explain why the trapping of the putative hemiortho ester **F** by running the reaction of **1** with DMDO in the presence of an excess of MeOH failed and only led to its slowing down.

SCHEME 3. Putative Intermediates for Regioselective Control in the Oxidative Ring Cleavage by DMDO



protecting group at C3, the secondary intermediate **I** at C4 is more stable, favoring cleavage of the C−O bond *a* and hence the primary benzoate **B** (path a or path a′). If the group at C3 is electron-donating, the primary intermediate **J** at C6 is favored with cleavage of the C−O bond *b* and formation of the secondary benzoate **C** as the major product (path b or path b′).

If so, with a developing negative charge at O4, path a may be counterbalanced by the presence of acids. We performed the reaction on compound **1** with DMDO in acidic medium,[26] namely, with TsOH (1 equiv). The reaction was slowed down and the regioselectivity was lost and reversed (ratio 4-OH/6-OH of 4:6 compared with a ratio of 8:2, entry 11, Table 1).[27] This is in good agreement with the above rationale. This reasoning would only be valid for an equatorial orientation of the protecting group at C3 (e.g., in the *gluco*, *galacto*, and *manno* series), as in the *altro* series, with an axial orientation at C3, the regiocontrol is lost (see Table 1, entries 24, 25). In all cases, steric effects should also be accounted for in the regiocontrol.

In conclusion, we have shown that DMDO is a valuable reagent for the regioselective oxidative opening of 4,6-*O*-benzylidene acetals of glycopyranosides controlled by the nature of the hydroxyl protecting group at position 3. It gave 6-benzoate-4-hydroxy or 4-hydroxy-6-benzoate derivatives of glycopyranosides in good to high yields.

(26) Adam, W.; Shimizu, M. *Synthesis* **1994**, 560–562.

(27) The addition of a Lewis acid ($FeCl_3 \cdot 6H_2O$ or $CeCl_3 \cdot 7H_2O$) had no effect on the course of the reaction, as was the case in a basic medium ($NaHCO_3$).

Experimental Section

Oxidative Opening of Benzylidene Acetal 10. Methyl 6-*O*-Benzoyl-2-deoxy-3-*O*-(2,2-dichloroacetyl)-2-phtalimido-β-D-glucopyranoside, 10a. Freshly distilled solution of DMDO[16] in acetone (30 mL, ∼0.1 M) was added to benzylidene acetal **10** (317 mg, 0.607 mmol). The reaction mixture was stirred for 96 h at 5 °C, the volatiles were evaporated under reduced pressure, and the crude material was purified by chromatography on silica gel (heptane/EtOAc 9:1 to 7:3) to give the benzoate **10a** (310 mg, 95%) as a white solid. Mp 79.6−82.8 °C (heptane/EtOAc). $[\alpha]^{23}_D$ −13.6 (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 7.3 Hz, 2H, Bz), 7.87−7.79 (m, 2H, NPhth), 7.75−7.68 (m, 2H, NPhth), 7.61 (t, J = 7.3 Hz, 1H, Bz), 7.48 (t, J = 7.3 Hz, 2H, Bz), 5.83−5.76 (m, 2H, H3 + $CHCl_2$), 5.28 (d, $J_{1,2}$ = 8.2 Hz, 1H, H1), 4.90 (dd, $J_{6,6'}$ = 12.2 Hz, $J_{6',5}$ = 3.4 Hz, 1H, H6), 4.56 (dd, $J_{6',6}$ = 12.2 Hz, $J_{6',5}$ = 2.1 Hz, 1H, H6′), 4.30 (dd, $J_{2,3}$ = 11.0 Hz, $J_{2,1}$ = 8.2 Hz, 1H, H2), 3.83 (ddd, $J_{5,4}$ = 9.8 Hz, $J_{5,6}$ = 3.4 Hz, $J_{5,6'}$ = 2.1 Hz, 1H, H5), 3.78 (ddd, $J_{4,5}$ = $J_{4,3}$ = 9.8 Hz, $J_{4,OH}$ = 4.6 Hz, 1H, H4), 3.45 (s, 3H, OMe), 3.10 (d, $J_{OH,4}$ = 4.6 Hz, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7 (C, PhCO), 164.9 (2C, $N(CO)_2$), 164.6 (C, Cl_2CHCO), 134.6 (2CH, NPhth), 133.8 (CH, Bz), 131.7 (2C, NPhth), 130.2 (2CH, Bz), 129.5 (C, Bz), 128.8 (2CH, Bz), 123.8 (2CH, NPhth), 99.3 (CH, C1), 75.9 (CH, C3), 74.5 (CH, C5), 69.6 (CH, C4), 64.0 (CH, $CHCl_2$), 63.5 (CH_2, C6), 57.3 (CH_3, OMe), 54.3 (CH, C2). IR ν (film, cm^{-1}) 3473, 3064, 2945, 2852, 1770, 1712, 1602. MS m/z 560 (MNa^+, 100%). HRMS (ESI) calcd for $C_{24}H_{21}Cl_2NNaO_9$ $[M + Na]^+$ 560.0491, found 560.0494. Anal. Calcd for $C_{24}H_{21}Cl_2NO_9$: C, 53.55; H, 3.93; N, 2.60. Found: C, 53.21; H, 4.05; N, 2.56.

Acknowledgment. This study was financially supported by the ICSN-CNRS and INRA.

Supporting Information Available: Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra for compounds **3a**, **3b**, **4**, **4a**, **4b**, **5**, **5a**, **5b**, **6**, **6b**, **7**, **7b**, **8a**, **9**, **9a**, **10**, **10a**, **12a**, **12b**, **14a**, **17a**, **18**, **18b**, **22a**, **23**, **23b**, **24a**, **25**, **25a**, **25b**, **26a**, **26b**, **27a**, and **27b**. This material is available free of charge via the Internet at http://pubs.acs.org.