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Oxidative Cleavage of *p*-Methoxybenzyl Ethers with Methyl(trifluoromethyl)dioxirane

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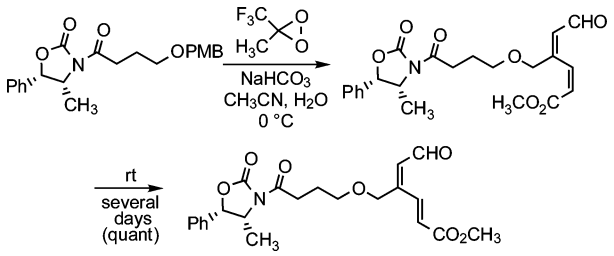
ABSTRACT

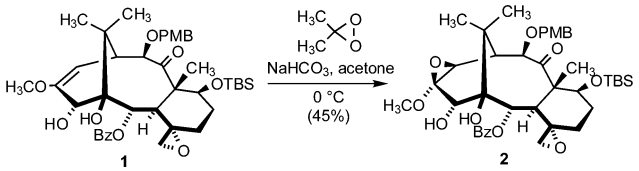


The ability of methyl(trifluoromethyl)dioxirane to cleave *p*-methoxylbenzyl ethers oxidatively in the presence of various additional functional groups has been investigated. These reactions, performed in aqueous acetonitrile, transform a reasonably robust aryl substituent into a dienyl aldehydo ester. The originally generated *E*,*Z*-isomer undergoes slow conversion to the more stable *E*,*E*-form at 20 °C.

The virtue of *p*-methoxybenzyl (PMB) ethers as utilitarian protecting groups has been extensively touted.[1] Most often recognized is their ability to engage in deprotection, frequently involving DDQ under very mild conditions. As part of a program targeting the enhanced oxygenation of extensively substituted taxanes, we have identified the feasibility of effecting the oxidative cleavage of this otherwise quite robust functional group with methyl(trifluoromethyl)dioxirane. To our knowledge, reports of this type of oxidative cleavage have not previously been disclosed.

The discovery of this chemistry began with the early observation that **1**[2,3] but not **3**[3] undergoes epoxidation smoothly when treated with dimethyldioxirane[4] (Scheme 1). Yields of **2** in the vicinity of 50% were routinely realized

Scheme 1



under dilute reaction conditions. The acquisition of HMBS, COSY, and HMQC data convincingly established the product to be the C12−C13 oxirane having an exo-oriented heteroatom.

Comparable reactivity was not observed with the bromine-containing derivative **3**, which was recovered intact following workup. This result can be attributed to steric constraints provided by the bromine substituent, to electronic deactivation of the double bond, or to a combination of these factors. In light of the established 1000-fold greater reactivity of methyl(trifluoromethyl)dioxirane,[5] its use in the context of

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(1) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Georg Thieme Verlag: Stuttgart, 2004; pp 257−269.

(2) Paquette, L. A.; Hofferberth, J. E. *J. Org. Chem.* **2003**, *68*, 2266.

(3) Kreilein, M. M. Ph.D. Dissertation, The Ohio State University, 2005.

(4) (a) Adam, W.; Curci, R.; Edward, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (c) Curci, R. In *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 2, p 1.

(5) Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887.

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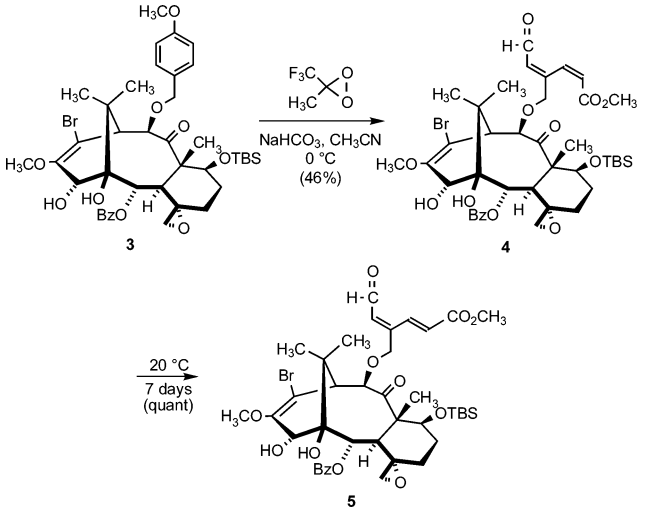
1 and **3** was next probed. Where **1** was concerned, faster reaction was noted, and **2** was similarly produced in 50% yield.

With the focus now turned to **3**,[3] the dominant pathway for its consumption involved oxidative cleavage of the *p*-methoxybenzyl group to deliver the *E*,*Z*-configured aldehydo ester **4** (Scheme 2). The isolated yield of **4** was 46%

Scheme 2



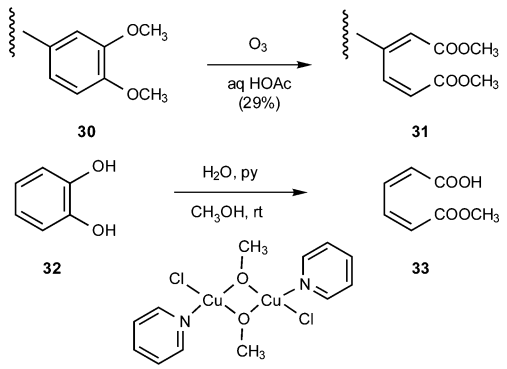
at 50% conversion. During the course of standing at room temperature for one week, **4** underwent almost complete conversion to its thermodynamically more stable *E*,*E* isomer **5**. Under electrospray high-resolution mass spectral conditions, both **4** and **5** (calcd for $C_{41}H_{55}BrO_{12}SiNa^+$ *m*/*z* 869.2538 and 871.2518) exhibit closely corresponding ions, e.g., *m*/*z* = 869.2511 and 871.2571. The 500 MHz ^{1}H NMR spectra of the product pair recorded on C_6D_6 solutions reveal several distinctive features of interest. For example, the signals for the olefinic protons of the side chain of compound **4** (δ 6.36 and 5.89, 12 Hz) differ significantly from those of **5** (δ 8.08 and 6.56, 16 Hz). The combination of DQF-COSY, NOESY, HMQC, and Grad-HMBC studies involving **5** provided information fully diagnostic of its global structural taxane-based features.

Products **4** and **5** are recognized to be more highly functionalized than their precursor **3**. In light of the apparent tolerance of the reaction conditions to a variety of functional groups, a general procedure was devised to gain some appreciation of the scope of this transformation (Table 1). The structural features of PMB ethers **6**−**13** were considered to be sufficiently diverse for our purposes. As matters worked out, the free hydroxyl in **6**, the ester and amide groups resident in **7** and **13**, and the ketone and ether functionalities found in **9**, **10**, and **12** tolerate the oxidative ring-cleavage conditions well. The bromine substituent in **8** similarly plays no adverse role.

Most protocols involving epoxidation with the fluorinated dioxirane rely on the addition of a mixture of Oxone and sodium bicarbonate to a solution containing the reactant and trifluoroacetone.[6] The adoption of this procedure, referred to as method B in Table 1, was compared in selected examples with modifications involving changes in the timing of reagent addition. The efficacies associated with these changes proved not to be dramatically different. Notwithstanding, our preference is to use method C (see for example the oxidation of **9**). In contrast, the sensitivity of **14**−**21** to chromatographic purification was clearly contributory in part to the reduced yields observed for the oxidative ring cleavage. The utilization of Florisil or deactivated silica gel (6% H_2O w/w) was often more tolerant of the sensitive functionality contained in **14**−**21**.

As in the **4** → **5** example, storage of **14**−**21** at room temperature in a solvent-free state for the duration of 7−10 days resulted in quantitative *E*,*Z* → *E*,*E* isomerization (^{1}H NMR analysis). The apparent generality of this previously unencountered reaction should prove of interest to those planning to involve methyl(trifluoromethyl)dioxirane as a reagent in complex molecule total synthesis settings. Important new applications of this chemistry may also evolve in the future. To a limited extent, the oxidative cleavage of *p*-methoxybenzyl ethers holds similarity to the ozonolytic ring fission of the veratryl group (**30**) (Scheme 3). As utilized

Scheme 3



by Woodward in his strychnine synthesis,[7] this otherwise stable aryl group can be oxidatively cleaved to **31** in a completely selective manner for the purpose of unmasking functionality amenable to further chemical change. The four-electron ring opening of catechol (**32**) to *cis*,*cis*-muconic acid monomethyl ester (**33**) under anaerobic conditions has also been recognized for some time.[8,9] As in the latter case, aldehydo esters **14**−**29** hold the distinction of possessing distinguishable functional groups. A limitation of the oxida-

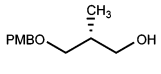
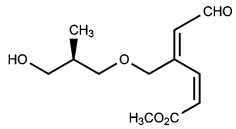
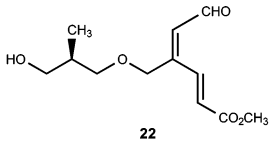
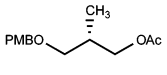
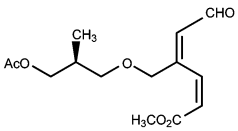
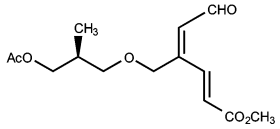
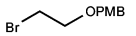
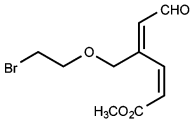
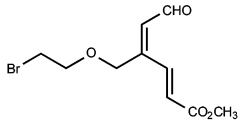
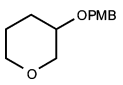
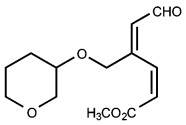
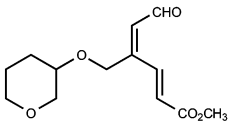
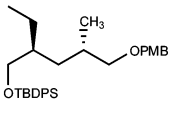
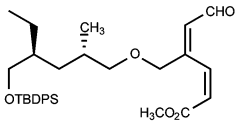
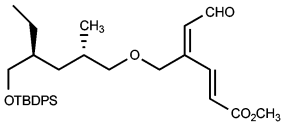
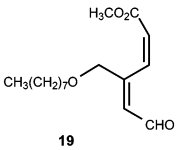
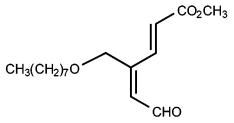
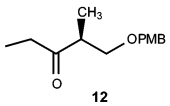
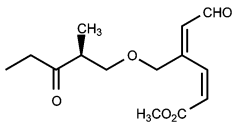
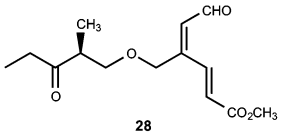
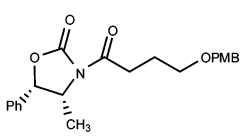
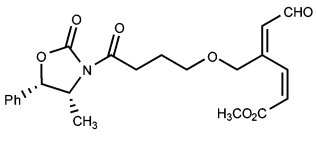
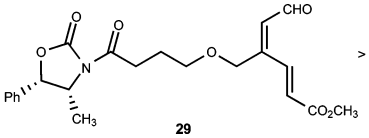
(6) Takahata, H.; Banba, Y.; Sasatani, H.; Nemoto, H.; Kato, A.; Adachi, I. *Tetrahedron* **2004**, *60*, 8199.

(7) (a) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749. (b) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *Tetrahedron* **1963**, *19*, 247.

(8) (a) Rogic, M. M.; Demmin, M. M.; Hammond, W. B. *J. Am. Chem. Soc.* **1976**, *98*, 7441. (b) Demmin, M. M.; Rogic, M. M. *J. Org. Chem.* **1980**, *45*, 4210.

(9) The oxidation of catechol to the muconic acids is also known: McKague, A. B. *Synth. Commun.* **1999**, *29*, 1463.

Table 1. Results of Oxidative Cleavage and Thermal Equilibration

substrate	product	method[a]	yield/conv.[b]	purif.[c]	isomer	yield
 **6**	 **14**	A	22% / 71%	Silica	 **22**	> 97%
		C	32% / 48%	Deact. Silica		
 **7**	 **15**	B	29% / 95%	Silica	 **23**	> 97%
		C	29% / 59%	Silica		
		C	36% / 50%	Deact. Silica		
 **8**	 **16**	B	16% / 68%	Silica	 **24**	> 97%
		B	22% / 58%	Florisil		
		C	39% / 49%	Deact. Silica		
 **9**	 **17**	B	35% / 12 %	Florisil	 **25**	> 97%
		C	14% / 68%	Silica		
		C	21% / 52%	Deact. Silica		
 **10**	 **18**	C	31% / 43%	Deact. Silica	 **26**	> 97%
$CH_3(CH_2)_7OPMB$ **11**	 **19**	C	40% / 46%	Deact. Silica	 **27**	> 97%
		C	38% / 41%	Deact. Silica		
 **12**	 **20**	B	36% / 38%	Florisil	 **28**	> 97%
		C	41% / 26%	Deact. Silica		
 **13**	 **21**	C	46% / 59%	Deact. Silica	 **29**	> 97%
		C	48% / 72%	Deact. Silica		

[a] Method A: Trifluoroacetone added to Oxone and $NaHCO_3$. Method B: A mixture of Oxone and $NaHCO_3$ added to trifluoroacetone. Method C: Oxone added to a mixture of $NaHCO_3$ and trifluoroacetone. [b] The yields are based on percent conversion. [c] The deactivated silica gel was prepared by addition of 6% H_2O on a w/w basis and agitating the silica gel for several hours to guarantee homogeneity.

tions reported here is the low efficiency with which the oxidized counterpart is produced at the present time.

Supporting Information Available: General experimental details and characterization data for all compounds including their recorded ^1H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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