Practical One-Pot Di-O-silylation and Regioselective Deprotective Oxidation of 1^0-*O*-Silyl Ether in $1^0,2^0$-Diols†

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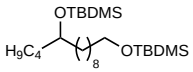
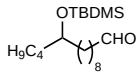
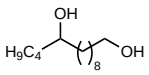
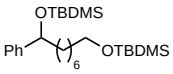
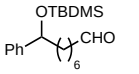
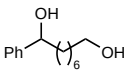
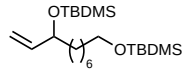
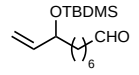
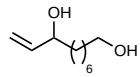
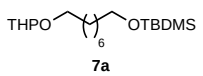
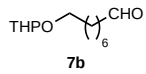
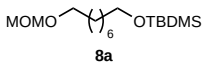
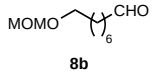
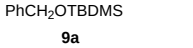
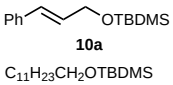
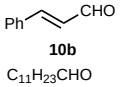
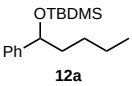
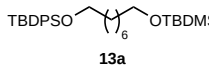
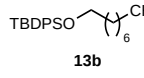
Oxidation of an alcohol to a carbonyl group constitutes a very useful functional group transformation, and the plethora of reagents for this transformation documented in literature directly measures the importance with which this functional group transformation has been addressed.[1] However, only a few reagents are *chemoselective* in oxidizing either a primary alcohol group or a secondary alcohol group exclusively. Though a good number of reagents are available for selective secondary alcohol oxidation,[2] primary alcohol oxidation is rather poorly addressed[3] wherein only $RuCl_2(PPH_3)$,[3b] Cp_2ZrH_2,[3e] and TEMPO[3f] performed the desired transformation with moderate to reasonable selectivity. Additionally, no reagent combination has been reported for simultanious oxidation of primary alcohol while protecting the existing secondary alcohol in a single pot. Our continued interest in developing new oxidation procedures[4] and reagents[5] has prompted us to address this issue wherein we believe judicious choice of the right protective group and oxidation reagent should give a reality to our hypothesis. Thus, the protection−oxidation sequence in a single pot, starting from a $1^0,2^0$-diol (where $1^0,2^0$-diol contains both a primary and a secondary alcohol) (eq 1) will increase the overall efficacy, which is desirable in a long synthetic scheme. Accordingly, we reasoned that if one chooses the trialkylsilyl group as the protective group for a $1^0,2^0$-diol and an oxidation reagent that also incorporates an element that selectively cleaves

Table 1. Disilylation and/or Regioselective Deprotective Oxidation of Diols/Disilyl Ethers

entry	substrate	product	yield[a] (%)
1	 **1a**	 **1b**	70
2	 **2a**	**1b**	64 (82)
3	 **3a**	 **3b**	68
4	 **4a**	**3b**	65 (80)
5	 **5a**	 **5b**	72
6	 **6a**	**5b**	68 (78)
7	 **7a**	 **7b**	72
8	 **8a**	 **8b**	70
9	 **9a**	PhCHO **9b**	72
10	 **10a**	 **10b**	66
11	$C_{11}H_{23}CH_2OTBDMS$ **11a** +  **12a**	$C_{11}H_{23}CHO$ **11b** + **12a**	71 92
12	 **13a**	 **13b**	69

[a] The yields in parentheses are based on recovery of corresponding disilyl ethers.

1^0-*O*-silyl ether,[6] the task could become practical. After a careful study of the literature of chromium-based oxidation reagents and extensive experimentation, we have choosen to utilize freshly prepared quinolinium fluorochromate[7] (QFC) as the selective deprotection−oxidation reagent to serve our needs. To our utmost satisfaction, we were successful in achieving the desired selective deprotective oxidation with QFC (eq 2). The results are presented herein.

In an initial study, 1,10-bis-*O*-(*tert*-butyldimethylsilyl)-tetradecane (Table 1, entry 1) was subjected to QFC oxidation, and we observed a clean deprotective oxidation of 1^0-*O*-silyl ether to aldehyde in 70% yield without effecting the 2^0-*O*-silyl ether. Similarly, treatment of 1,-10-tetradecanediol (Table 1, entry 2) with 2.5 equiv of

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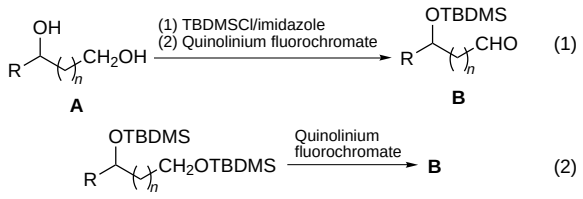

tert-butyldimethylsilyl chloride (TBDMSCl) and imidazole in CH_2Cl_2 for 12 h followed by addition of 3 equiv of freshly prepared[8] QFC for a further 24 h has also resulted in a similar product with identical yield. To prove the generality of these reagent combinations two free diols (Table 1, entries 4 and 6) have been subjected to this one-pot protection−deprotection oxidation sequence with consistant efficacy. Also, few prepared silyl ethers (Table 1, entries 3 and 5) were deprotectively oxidized with QFC. When a mixture of 1^0-*O*-silyl ether and 2^0-*O*-silyl ether (Table 1, entry 11) was exposed to QFC, only the 1^0-*O*-silyl ether was deprotected and oxidized to aldehyde; no trace of 2^0-*O*-silyl ether cleavage or ketone formation was observed. In the case of substrates (Table 1, entries 7 and 8) where acid-sensitive protective groups are present, other than deprotective oxidation, no THP ether cleavage (Table 1, entry 7) and MOM ether cleavage (Table 1, entry 8) were noticed. This stability of acid-labile groups amply shows that QFC is reasonably neutral and silyl deprotection was achieved with fluoride. Incidentally, 2^0-benzylic and allylic ethers are also unaffected (Table 1, entries 3 and 5), whereas 1^0-benzylic and allylic ethers under went smooth deprotection−oxidation (Table 1, entries 9 and 10). Surprisingly, 1^0-*O*-(*tert*-butyldiphenylsilyl) ether resisted the deprotection−oxidation (Table 1, entry 12).

In summary, a new functional group transformation has been developed wherein a series of four transformations, viz., 1^0-*O*-silyl protection, 2^0-*O*-silyl protection, 1^0-*O*-desilylation, and oxidation of a 1^0-alcohol have been achieved in a single vessel. We believe this technique will attract a wide range of synthetic organic chemists, especially those who are in the field of complex natural products synthesis. Efforts are currently underway to prepare new oxidation reagents that can cleave and oxidize other ether protective groups.

Experimental Section

General Methods. Crude products were purified by column chromatography on silica gel of 60−120 mesh. ^{1}H NMR were obtained in $CDCl_3$ at 200 MHz. Chemical shifts are given in ppm with respect to internal TMS, and *J* values are quoted in Hz. Infrared spectra were obtained neat, and only the most significant absorptions in cm^{-1} are indicated. *N*,*N*-Dimethylformamide and dichloromethane were distilled over CaH_2 prior to use. All reactions were carried out under an atmosphere of nitrogen using dry glassware.

Starting Materials. QFC was prepared following the literature procedure.[7] **2a** (Table 1, entry 2) was prepared by addition of BuMgBr onto 10-*O*-(*tert*-butyldimethylsilyl)decan-1-al[9] followed by desilylation using HF−pyridine.[10] **4a** (Table 1, entry 4) was prepared by addition of PhMgBr onto 8-*O*-(*tert*-butyldimethylsilyl)octan-1-al followed by desilylation. **6a** (Table 1, entry 6) was prepared by addition of vinylmagnesium bromide onto 8-*O*-(*tert*-butyldimethylsilyl)octan-1-al followed by desilylation. **7a** (Table 1, entry 7) was prepared from 1,8-octanediol by monotetrahydropyranylation[11] followed by silylation. **8a** (Table 1, entry 8) was prepared from 1,8-octanediol by mono-*O*-silylation followed by MOM protection.[12] **9a**, **10a**, **11a**, and **12a** (Table 1, entries 9−12) were prepared by silylation of commercial alcohols obtained from Aldrich. **1a**, **3a**, and **5a** (Table 1, entries 1, 3, and 5) were prepared from the corresponding diols **2a**, **4a**, and **6a**, respectively. **13a** (Table 1, entry 12) was prepared from commercial 1,8-octanediol by monosilylation with 1 equiv of *tert*-butyldimethylsilyl chloride followed by a second silylation with *tert*-butyldiphenylsilyl chloride.

Optimized Disilylation and Selective Desilylation−Oxidation Procedure. To a solution of 1,10-tetradecanediol (**2a**, 0.55 g, 2.41 mmol) in dry CH_2Cl_2 (8 mL) were added imidazole (0.41 g, 5.94 mmol) and TBDMSCl (0.91 g, 6.01 mmol). The reaction mixture was stirred at room temperature for 12 h (monitored by TLC, 25% EtOAc in hexane) followed the addition of QFC (1.81 g, 7.22 mmol) and dry DMF[13] (0.2 mL) and the resulting mixture stirred for a further 12 h. The reaction mixture was diluted with *n*-hexane (20 mL) and filtered through a small pad of silica gel. Evaporation of the volatiles followed by flash chromatography using silica gel (5% EtOAc in hexane as the eluent) furnished 0.53 g of pure 10-*O*-(*tert*-butyldimethylsilyl)tetradecan-1-al (**1b**) (64%, R_f 0.5), and 0.22 g of 1,10-bis-*O*-(*tert*-butyldimethylsilyl)tetradecane (**1a**) (20%, R_f 0.8) was recovered.

Optimized Selective Deprotection−Oxidation Procedure. To 1,10-bis-*O*-(*tert*-butyldimethylsilyl)tetradecane (**1a**, 0.65 g, 1.41 mmol) in dry CH_2Cl_2 (8 mL) were added QFC (1.05 g, 4.22 mmol) and DMF (0.2 mL) and the resulting mixture stirred at ambient temperature for 15 h. Usual workup (*vide supra*) furnished 0.34 g of the desired 10-*O*-(*tert*-butyldimethylsilyl)tetradecan-1-al (**1b**) (70%).

10-*O*-(*tert*-butyldimethylsilyl)tetradecan-1-al (1b): ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 6H), 0.91 (br s, 12H), 1.20−170 (br m, 16H), 2.41 (t, 2H, $J = 5$ Hz), 3.60 (t, 2H, $J = 3$ Hz), 9.78 (s, 1H); IR (film) 1720 cm^{-1}; MS 314 (M^+, 5), 255 (75), 199 (20).

8-*O*-(*tert*-butyldimethylsilyl)-8-phenyloctan-1-al (3b): ^{1}H NMR ($CDCl_3$) δ 0.20 (s, 6H), 1.10 (s, 9H), 1.41−1.90 (br m, 10H), 2.55 (t, 2H, $J = 5$ Hz), 4.78 (t, 2H, $J = 4$ Hz), 7.30−7.50 (m, 5H), 9.90 (s, 1H); IR (film) 1725 cm^{-1}. Anal. Calcd for $C_{20}H_{34}O_2Si$: C, 71.80; H, 10.24. Found: C, 71.90; H, 10.30.

8-*O*-(*tert*-butyldimethylsilyl)-9-decen-1-al (5b): ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 6H), 0.91 (s, 9H), 1.20−1.81 (m, 10H), 2.39 (t, 2H, $J = 6$ Hz), 3.85−4.10 (m, 1H), 4.91−5.15 (m, 2H), 5.61−5.85 (m, 1H), 9.75 (s, 1H); IR (film) 1735 cm^{-1}. Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.55; H, 11.34. Found: C, 67.70; H, 11.40.

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(8) Once prepared, the Quinolinium fluorochromate (stored in a plastic container in the dark) is active for 2 weeks.

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(13) The amount of DMF addition is critical, since more DMF generally resulted in partial formation of alcohol along with desired aldehyde.