On the Selective Deprotection of Trityl Ethers

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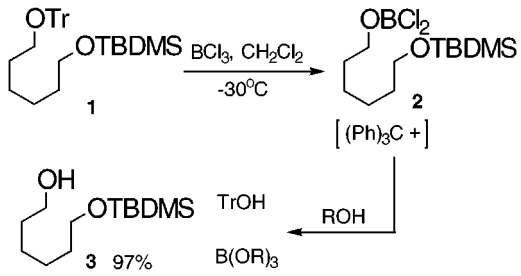
Introduction

The triphenylmethyl (trityl) protecting group has enjoyed widespread use in contemporary organic synthesis since its original applications in classic carbohydrate chemistry.[1] Its lipophilic nature renders it particularly attractive for the protection of polar water soluble alcohols, including monosaccharides. A variety of methods have been employed for its introduction, including trityl triflate,[2] tritylpyridinium fluoroborate,[3] and the commercially available trityl halides.[4] Though the advent of silicon based protecting groups has somewhat marginalized their use, syntheses involving combinations of trityloxy, silyloxy, and other ethers offer the opportunity for highly selective deprotective strategies. The identification of a mild yet expeditious method for removal of the trityloxy protecting group thus formed the basis of our investigation.

Results and Discussion

Prompted by a need to selectively unmask the trityloxy ethers of differentially protected diols,[5] 1,6-hexanediol derivative **1** was prepared as a model substrate. Conventional protocols using formic acid in ether[6] and diethyl aluminum chloride in methylene chloride[7] were investigated. Unsatisfactory results were obtained in both cases, resulting in recovery of diol and a mixture of monodeprotected alcohols. On moving to a boron-based reagent, however, addition of 1.0 equiv of boron trichloride yielded smooth trityloxy deprotection within 10 min at −30 °C (Scheme 1).[8,9] Hydrolytic workup resulted in recovery of near quantitative yields of trityl alcohol and the desired alcohol **3**. ^{11}B NMR analysis confirmed the intermediacy of alkoxyborane **2**, with the replacement of the BCl_3 signal (46.4 ppm) with a peak at 30.7 ppm ($ROBCl_2$), which is in turn converted to $B(OCH_3)_3$ (18.4 ppm) on methanolysis or $B(OH)_3$ (6.8 ppm) on hydrolysis.[10] Subsequent optimization revealed that on a practical scale deprotection is best conducted using dropwise addition of 0.6 equiv of BCl_3 at −30 °C with a concentration of 0.1 M. Encouraged by this finding, a variety of differentially substituted alcohols were prepared and subjected to the deprotection conditions (Table 1). Selective deprotection of primary trityl ethers is achieved in the presence of either primary, secondary, or phenolic *tert*-butyldimethylsilyloxy (TBDMS) groups, the bulkier *tert*-butyldiphenylsilyloxy (TBDPS) group, the triethylsilyl (TES) group, and the commonly used benzyloxy group (entries 1−5).[11] In every case examined complete deprotection was observed within 15 min, isolated yields are typically high (even in the presence of delicate functionality), and stereochemical integrity is maintained (entries 4 and 5). Double deprotections are also rapid (entry 6), yet a consistent and clear preference for detritylation is observed even in the presence of primary TBDMS and *p*-methoxybenzyl (PMB) ethers, making this a desirable orthogonal set (entries 7−10). Numerous applications in synthesis can be envisioned, and key substrates may include saccharides and steroids, where stereochemical integrity cannot be compromised (entries 11 and 12). The ability of preformed dichloroalkoxyboranes to undergo unmasking is noteworthy (entries 13 and 14) and suggests that regioselectivity might even be exercised in the selective deprotection of polyols using this strategy. Unmasking of the trityl group in the presence of appropriate electrophilic functionality may also allow for the design of in situ cyclizations, as demonstrated by the formation of the lactol (entry 15) on treatment with BCl_3 followed by methanolysis.

Scheme 1. BCl_3 Mediated Detritylation



Analogous deprotections conducted with boron tribromide resulted in rapid unmasking with marked loss in selectivity, whereas boron trifluoride etherate was less effective, resulting in recovery of substantial amounts of starting material under standard conditions.[12] Commercially available solutions of BCl_3 in methylene chloride, hexanes, heptanes, and xylene were equally effective at inducing the deprotections. The ready availability of these reagents, coupled with the high yields, speed, and selective nature of deprotection, renders this strategy

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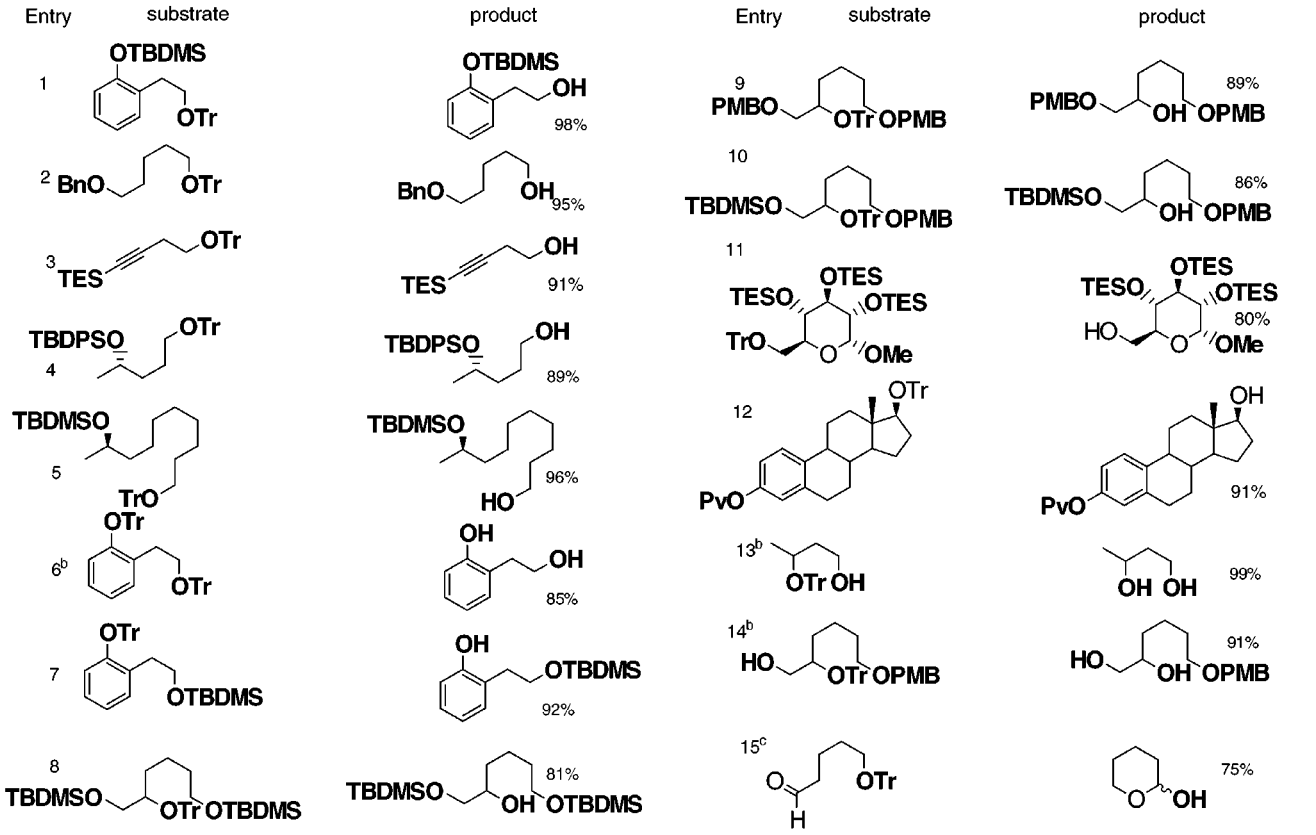
Table 1. Selective Deprotections[a]



[a] BCl_3 (0.6 equiv)/−30 °C/0.1 M CH_2Cl_2/15 min. [b] 0.9 equiv BCl_3 used. [c] BCl_3 (1.0 equiv) then CH_3OH (1.0 equiv).

advantageous for work involving diol and polyol manipulation, particularly where a UV chromophore is desirable in the molecule.

Experimental Methods[13]

Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (300 MHz) or solvent as the internal standard for ^{13}C (75 MHz). Reactions were performed in glassware which had been oven dried (140 °C/12 h) and then flame-dried prior to use, under an atmosphere of nitrogen. Methylene chloride was distilled from P_2O_5. All reagents and solvents were commercial grade (Aldrich) and purified according to established convention. Chromatography (SGC) was performed on E. Merck 60H silica gel. Analytical TLC was performed on glass-backed 0.25 mm plates, with anisaldehyde and phosphomolybdic acid for visualization. Substrates were prepared from commercially available diols using standard methods.[5,14−16] Product identity was confirmed with authentic (entry 1,[15] 2,[17] 8,[18] 15[19]) or commercial (entry 3, 6, 13) material.

General Protection Procedure. 4-(1,1,1-Triethylsilyl)-3-butynyl Trityl Ether. Triphenylmethyl chloride (0.831 g, 2.98 mmol), DMAP (33 mg, 0.271 mmol), 4-(1,1,1-triethylsilyl)-3-butyn-1-ol (500 mg, 2.71 mmol), and triethylamine (0.75 mL, 5.42 mmol) were dissolved in dry DMF (8 mL). The mixture was stirred at 40 °C for 12 h. The solution was poured onto HCl (1%, 10 mL) and the resulting mixture extracted with ethyl acetate (4 × 10 mL). The combined organic extracts were washed with water (2 × 10 mL), $NaHCO_3$ solution (saturated, 1 × 10 mL), and brine (1 × 10 mL) and then concentrated in vacuo. The residual oil was purified by SGC (9:1 hexane:diethyl ether), affording 4-(1,1,1-triethylsilyl)-3-butynyl trityl ether as a white cyrstalline solid (1.02 g, 88%): mp 66 °C; ^1H NMR 7.50 (d, 3H J = 7.2 Hz), 7.34−7.22 (m, 12H), 3.21 (t, 2H, J = 6.8 Hz), 2.55 (t, 2H, J = 6.8 Hz), 1.01 (t, 9H, J = 8.1 Hz), 0.66−0.58 (m, 6H); ^{13}C NMR 143.9, 128.6, 127.6, 126.8, 105.5, 86.4, 82.7, 61.7, 21.5, 7.6, 4.6. Anal. Calcd for $C_{29}H_{34}OSi$: C, 81.64; H, 8.03. Found: C, 81.23; H, 8.02.

General Deprotection Procedure. 3-Pivaloylestradiol. To a solution of 3-pivaloyl-17-trityloxyestradiol (82 mg, 0.137 mmol) in CH_2Cl_2 (5.0 mL) at −30 °C was added BCl_3 (68 μL, 0.068 mmol, 1.0 M in CH_2Cl_2,) dropwise via syringe. After 30 min at −30 °C, the reaction was quenched by the addition of anhydrous MeOH. The solution was poured onto a $NaHCO_3$ solution (saturated, 5 mL), stirred for 5 min, and then extracted with CH_2Cl_2 (5 × 5 mL). The organic phase was washed with brine (2 × 5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residual oil was purified by SGC (1:1, hexane:diethyl ether), affording 3-pivaloylestradiol as white crystals (44 mg, 91%): mp 181−183 °C; ^1H NMR 7.28 (d, 1H, J = 8.7 Hz), 7.01 (dd, 1H, J = 2.4 Hz, 8.7 Hz), 6.77 (s, 1H), 3.71 (t, 1H, J = 8.3 Hz), 2.85 (t, 2H, J = 4.1 Hz), 2.35−1.17 (m, 23H), 0.77 (s, 3H); ^{13}C NMR 177.1, 148.6, 137.9, 137.5, 126.1, 121.2, 118.3, 81.7, 50.0, 44.1, 43.2, 39.0, 38.5, 36.7, 30.5, 29.5 27.2, 27.0, 26.1, 23.1, 11.1; $[\alpha]_D$ = 42.3 (c = 0.5, $CHCl_3$). Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H; 9.05. Found: C, 77.10; H; 9.01.

The following were similarly produced.

2-(2-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxyphenoyl)-1-ethanol: colorless oil;[15] ^1H NMR 7.16 (td, 1H, J = 2.0, 7.5 Hz), 7.03 (dd, 1H, J = 2.0, 8.0 Hz) 6.93 (dd, 1H, J = 1.0, 8.0 Hz) 6.83 (td, 1H, J = 1.5, 7.0 Hz) 3.94 (t, 2H, J = 5.0 Hz), 2.90 (t, 2H,

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J = 5.5 Hz), 0.93 (s, 9H), 0.10 (s, 6H); ^{13}C NMR 155.8, 130.7, 128.2, 126.9, 120.0, 116.9, 65.8, 35.7, 25.8, 18.3, −5.7. Anal. Calcd for $C_{14}H_{24}O_2Si$: Found: C, 66.25; H; 9.32. Required: C, 66.61; H; 9.58.

(4*S*)-4-{[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy}pentan-1-ol: colorless oil; ^{1}H NMR 7.7 (m, 6H), 7.4 (m, 9H), 3.91 (m, 1H), 3.57 (m, 2H), 1.51 (m, 4H), 1.1 (m, 12H); ^{13}C NMR 135.9, 135.8, 134.6, 134.3, 129.6, 129.5, 127.5, 127.4, 69.3, 63.0, 35.5, 28.2, 27.0, 22.9, 19.2; IR (neat) 3368; $[\alpha]_D = -50.1$ (c = 0.051, MeOH). Anal. Calcd for $C_{21}H_{30}O_2Si$: C, 73.65; H; 8.83. Found: C, 73.79; H; 8.64.

(9*R*)-9-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}decan-1-ol: colorless oil; ^{1}H NMR 3.75 (m, 1H), 3.62 (t, 2H, J = 6.6 Hz), 1.6−1.2 (m, 14H), 1.10 (d, 3H, J = 6 Hz), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR 68.7, 63.0, 39.7, 32.8, 29.6, 29.6, 29.4, 26.0, 25.8, 25.7, 23.8, 18.2, −4.4; IR (neat) 3339 (br) cm^{-1}; MS (*m*/*e*) 287 (M^+); $[\alpha]_D = +1.26$ (c = 0.5, $CHCl_3$). Anal. Calcd for $C_{16}H_{36}O_2Si$: C, 66.60; H; 12.58. Found: C, 66.88; H; 12.46.

1,6-Bis{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-2-hexanol: colorless oil; ^{1}H NMR 3.66−3.56 (m, 4H), 3.38 (dd, 1H, J = 8.1 Hz, 10.5 Hz), 2.45 (d, 1H, J = 2.4 Hz), 1.58−1.32 (m, 6H), 0.89 (s, 9H) 0.88 (s, 9H), 0.06 (s, 6H), 0.04 (s, 6H); ^{13}C NMR 72.0, 67.4, 63.3, 33.1, 32.8, 26.2, 26.1, 22.2, 18.6, 18.6, −4.95, −5.02, −5.08. Anal. Calcd for $C_{18}H_{42}O_3Si_2$. Found: C, 59.63; H; 11.95. Required: C, 59.61; H; 11.67.

1,6-Bis[(4-methoxybenzyl)oxy]-2-hexanol: colorless oil; ^{1}H NMR 7.26 (d, 4H, J = 8.4 Hz), 6.88 (d, 2H, J = 8.7 Hz), 6.87 (d, 2H, J = 8.7 Hz), 4.47 (s, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.49−3.40 (m, 4H), 3.28 (dd, 1H, J = 7.9 Hz, 9.1 Hz), 1.68−1.34 (m, 6H); ^{13}C NMR 159.1, 158.9, 130.6, 130.0, 129.3, 129.2, 113.8, 113.7, 74.3, 73.0, 72.6, 70.3, 70.0, 55.3, 33.0, 29.8, 22.3. Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H; 8.07. Found: C, 70.34; H; 8.05.

1-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}-6-[(4-methoxybenzyl)oxy]-2-hexanol: colorless oil; ^{1}H NMR 7.25 (d, 2H, J = 8.7 Hz), 6.87 (d, 2H, J = 8.7 Hz), 4.48 (s, 2H), 3.80 (s, 3H), 3.60 (t, 2H, J = 6.3 Hz), 3.47 (dd, 2H, J = 3.3 Hz, J = 9.6 Hz), 3.28 (dd, 1H, J = 8.1 Hz, 9.6 Hz); ^{13}C NMR 159.3, 130.2, 129.5, 114.0, 74.5, 73.2, 70.6, 63.3, 55.5, 33.2, 33.1, 26.3, 26.2, 22.1, 18.7, −4.9. Anal. Calcd for $C_{20}H_{36}O_4Si$: C, 65.17; H; 9.75. Found: C, 64.98; H; 9.84.

6-[(4-Methoxybenzyl)oxy]-1,2-hexanediol: colorless oil; ^{1}H NMR 7.25 (d, 2H, J = 8.8 Hz), 6.87 (d, 2H, J = 8.8 Hz), 4.48 (s, 2H), 3.80 (s, 3H), 3.64 (t, 2H, J = 6.1 Hz), 3.47 (dd, 2H, J = 2.8 Hz, 9.6 Hz), 3.29 (dd, 1H, J = 7.8 Hz, 9.6 Hz); ^{13}C NMR 159.4, 130.1, 129.6, 114.0, 74.5, 73.2, 70.5, 63.0, 55.5, 33.0, 32.9, 22.0; HRMS calcd for $C_{14}H_{22}O_4$ (M^+) 254.1518, found 254.1518.

(2*S*,3*S*,4*R*,5*S*)-6-Methoxy-3,4,5-tris[(1,1,1-triethylsilyl)-oxy]tetrahydro-2*H*-2-pyranyl}methanol: colorless oil; ^{1}H NMR 4.61 (d, 1H, J = 3.9 Hz), 3.82−3.40 (m, 6H), 3.31 (s, 3H), 0.99−0.92 (m, 27H), 0.74−0.59 (m, 18H); ^{13}C NMR 100.0, 75.1, 74.3, 72.5, 72.0, 62.1, 54.7, 7.3, 7.1, 6.9, 5.6, 5.4, 5.2; $[\alpha]_D = 49.4$ (c = 0.8, $CHCl_3$). Anal. Calcd for $C_{25}H_{56}O_6Si_3$: C, 55.92; H; 10.51. Found: C, 56.14; H; 10.34.

5-(Trityloxy)pentanal. Pyridinium chlorochromate (6.50 g, 30.16 mmol) was added slowly to a solution of 5-(trityloxy)-1-pentanol[16] (9.53 g, 27.42 mmol) and sodium acetate (2.24 g, 27.42 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred at 30 °C for 12 h. The mixture was diluted with diethyl ether (150 mL), filtered through a plug of silica gel, and then concentrated in vacuo. SGC of the residue (19:1 hexane:ethyl acetate) gave 5-(trityloxy)pentanal (98%, 9.25 g) as a colorless oil; ^{1}H NMR 9.74 (s, 1H), 7.22−7.44 (m, 15H), 3.08 (t, 2H, J = 6.00 Hz), 2.40 (t, 2H), 1.67−1.74 (m, 4H); ^{13}C NMR 202.6, 144.3, 128.6, 127.7, 126.9, 62.9, 43.6, 29.4, 28.3, 19.0; IR (neat) 1744 cm^{-1}. Anal. Calcd for $C_{24}H_{24}O_2$: C, 83.69; H; 7.02. Found: C, 83.42; H; 6.94.

Tetrahydro-2*H*-2-pyranol. Boron trichloride (4.04 mL, 4.04 mmol, 1 M, CH_2Cl_2) was added to a solution of 5-(trityloxy)pentanal (1.55 g, 4.49 mmol) in CH_2Cl_2 (30 mL) at −78 °C. The mixture was stirred at −30 °C for 45 min and quenched by the addition of dry MeOH. The mixture was then poured onto a $NaHCO_3$ solution (saturated, 10 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL) and concentrated in vacuo. The residual oil was purified by gradient chromatography using deactivated (Et_3N) silica gel (7:3 through to 1:9 hexane:ethyl acetate) to afford tetrahydro-2*H*-2-pyranol (330 mg, 75%) as a colorless oil, spectroscopically identical with an authentic sample:[19] ^{1}H NMR 4.87 (s, 1H), 3.98 (m, 1H), 3.53 (m, 1H), 2.94 (s, 1 H), 1.83 (m, 2H), 1.51 (m, 4H); ^{13}C NMR 20.0, 24.9, 31.7, 63.6, 94.1.

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