Butane 2,3-Bisacetal Protection of Vicinal Diequatorial Diols

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Selective hydroxyl group protection in polyhydroxy molecules continues to be a challenge in synthetic chemistry.[1] For example, methods for selective protection of vicinal diequatorial diols are rare. Ley and coworkers have introduced two very useful protecting groups which exploit multiple anomeric effects to accomplish this task. Diol reaction with 3,3′,4,4′-tetrahydro-6,6′-spirobi-2*H*-pyran (bis-DHP) to give a dispiroacetal (Dispoke)[2] and diol reaction with 1,1,2,2-tetramethoxycyclohexane (TMC) affording a cyclohexane 1,2-diacetal (CDA)[3] have been successfully applied to a variety of carbohydrates and polyhydroxylated molecules. However, bis-DHP is of limited utility for large-scale work due to the synthetic steps required for its preparation.[2b] TMC is readily prepared from cyclohexane-1,2-dione, although this starting material is relatively expensive. An additional practical difficulty is the need for chromatographic purification of both bis-DHP and TMC.[2b,3] In response to the requirements imposed by large-scale synthetic manipulations, reaction of vicinal diequatorial diols with 2,2,3,3-tetramethoxybutane (TMB) to afford butane 2,3-bisacetal (BBA) protection has been examined.

As part of efforts directed toward the synthesis of 3-dehydroquinate (DHQ) synthase inhibitors,[4] the C-3,4 diequatorial hydroxyls of quinic acid needed to be selectively protected. Previous protection of these hydroxyl groups had been achieved in two ways. Knowles and coworkers protected the C-3,4 diequatorial diol unit in 20% yield by direct reaction of methyl quinate with benzyl chloromethyl ether (BOMCl).[5] Formation of multiple products resulted in low yields and required a tedious purification to obtain the desired product. Another approach by Tisnès and co-workers utilized *O*-stannylene derivatives as part of a protection−deprotection sequence also involving the axial C-5 hydroxyl group.[6] Neither of these strategies nor the aforementioned Dispoke or CDA protecting groups seemed amenable to our need for gram-scale quantities of final products and the multistep syntheses required to synthesize these DHQ synthase inhibitors. It occurred to us that TMB would be an inexpensive alternative to TMC while retaining the desired vicinal diequatorial diol protection selectivity.

TMB has apparently not been reported in the literature, although the monoacetal 3,3-dimethoxybutan-2-one[7] and the bisethylene glycol acetal *cis*-1,6-dimethyl-2,5,7,-10-tetraoxabicyclo[4.4.0]decane[8] have been known for some time. Protection of diethyl tartrate diol with monoacetal 3,3-dimethoxybutan-2-one has recently been reported.[9] TMB reagent was prepared by refluxing a methanol solution of trimethyl orthoformate and 2,3-butanedione with a few drops of sulfuric acid followed by purification of the crude product using distillation. The experimental advantages of purification by distillation and the ability to employ an inexpensive starting material became apparent during the preparation of TMB in 50−60% yield on hundred-gram scale.

Selective protection of the C-3,4 vicinal diequatorial hydroxyls of methyl quinate as butane 2,3-bisacetals utilized reaction conditions similar to those employed for CDA protection. A methanolic solution of quinate ester was refluxed with TMB in the presence of trimethyl orthoformate and catalytic (±)-10-camphorsulfonic acid for 12−18 h. The desired BBA-protected methyl quinate was obtained in excellent yield. Fifty grams of quinic acid were then routinely converted into the crystalline BBA-protected methyl quinate as a one-pot procedure in over 80% yield (Table 1, entry 1). The BBA protecting group is compatible with a wide variety of reagents and can be deprotected with aqueous trifluoroacetic acid in methylene chloride.[4]

The scope of BBA protection has been extended beyond quinic acid (Table 1). Reaction of *myo*-inositol with 2 equiv of TMB used the conditions previously described for methyl quinate protection. A pure, crystalline product precipitated out of the solution. This material displayed a simple NMR spectrum which could only be attributed to the highly symmetrical diprotected meso compound (Table 1, entry 2). The yield of meso-diBBA inositol derivative improved with longer reaction times. At relatively short reaction times, low yields of meso-diBBA product were obtained along with a complex mixture of other components. The inositol protection pattern observed for BBA has previously been obtained during reaction of inositol with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TIPSCl).[10] While this silyl protecting group has found some applications in inositol chemistry, the cost of TIPSCl limits its use. BBA provides the same protection pattern in higher yield and at a much lower cost.

Reaction of TMB with carbohydrates provided an additional test of the scope of BBA protection. In general, BBA protection was observed to display selectivities similar to those previously observed for CDA and Dispoke protection.[3] TMB reaction with methyl α-D-glucopyranoside gave an inseparable, equimolar mixture of 2,3- and 3,4-regioisomers (Table 1, entry 3). BBA protection of methyl α-D-galactopyranoside gave the desired product along with a small amount of its anomer (Table 1, entry 4). For the methyl pyranosides of D-mannose (Table 1, entry 5), D-lyxose (Table 1, entry 6), L-rhamnose (Table 1, entry 7), and 2-deoxy-D-glucose (Table 1, entry 8) TMB proved to be consistently selective for vicinal diequatorial diol protection.

Overall, the BBA protecting group appears to be a practical alternative to CDA or Dispoke for selective

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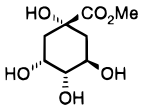
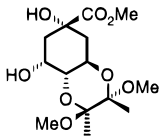
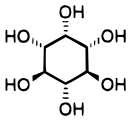
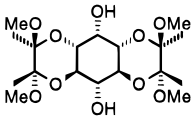
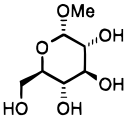
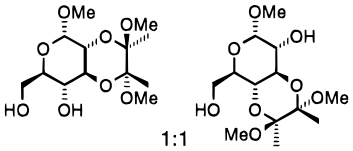
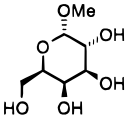
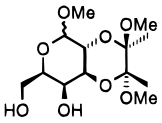
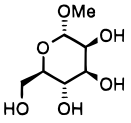
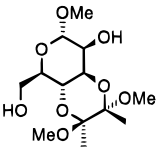
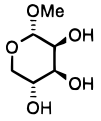
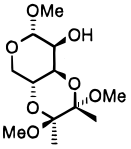
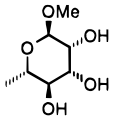
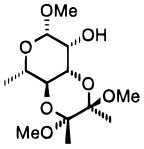
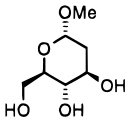
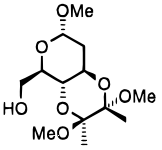
Table 1. Butane 2,3-Bisacetal Protection of Carbocycles and Carbohydrates

Entry	Starting Material	Product	Yield	Literature
1	 Quinic Acid		87	
2	 *myo*-Inositol		79	66[a]
3	 D-Glucose	 1:1	82	80 / 68[b]
4	 D-Galactose	 α/β = 10:1	54	46 / 76[b]
5	 D-Mannose		91	48 / 0[b]
6	 D-Lyxose		83	45 / 62[b]
7	 L-Rhamnose		81	74 / 47[b]
8	 2-Deoxy-D-Glucose		77	

[a] Reference 10. [b] CDA protection/Dispoke protection, see reference 3.

protection of vicinal diequatorial diols. BBA-protected compounds appear to usually be crystalline materials. A useful advantage over other protecting groups is the simple NMR spectrum of the BBA group. Unlike the cyclohexyl resonances that characterize CDA or Dispoke, BBA displays only singlets which are very diagnostic and minimize overlap with other resonances. The rigidity resulting from the formation of the 2,3-dimethoxy-2,3-dimethyl-1,4-dioxane moiety also provides an element for conformational control that can be exploited in subsequent reactions.[4] Finally, the inexpensive, large-scale preparation of TMB and the reagent's convenient purification by distillation makes BBA protection a particularly appealing option for large-scale synthetic manipulations.

Experimental Section

General Chemistry. See ref 11 for general experimental information. Melting points were uncorrected and were determined using a Mel-Temp II melting point apparatus. For NMR spectra in pyridine-d_5, the ^{1}H NMR spectrum was referenced to internal TMS ($\delta = 0.00$ ppm), and the ^{13}C NMR spectrum was

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referenced to pyridine-d_5 with the center of the middle triplet at $\delta = 135.5$ ppm.

2,2,3,3-Tetramethoxybutane. 2,3-Butanedione (68.0 mL, 0.775 mol), trimethyl orthoformate (200 mL, 1.83 mol), and MeOH (100 mL) were treated with sulfuric acid (7 drops). The resulting solution was refluxed 20 h under Ar, during which time the solution turned dark brown. Powdered $NaHCO_3$ (2.2 g) was added to the cool reaction mixture. Concentration under reduced pressure afforded an orange liquid which was diluted with ether and washed with saturated aqueous $NaHCO_3$ (2×). A clear yellow liquid was obtained after concentration. Although this material is impure, it can be used directly for the protection reaction. This material was however routinely distilled to afford a colorless liquid (73 g, 53%): bp 32−33 °C (0.8 mmHg); bp 172−174 °C (760 mmHg); ^{1}H NMR ($CDCl_3$) δ 3.31 (s, 12 H), 1.32 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 103.0, 49.3, 19.0. Anal. Calcd for $C_8H_{18}O_4$: C, 53.91; H, 10.18. Found: C, 54.01; H, 10.08.

Quinic Acid Protection (Entry 1). A suspension of quinic acid (47.5 g, 0.247 mol) and Dowex 50 H^+ (10 g) in MeOH (350 mL) was refluxed under Ar for 15 h. Heating was stopped, and the mixture was filtered to remove the acid catalyst which can be reused directly in subsequent runs. The filter was washed with MeOH (2 × 25 mL). To the combined filtrates were added trimethyl orthoformate (125 mL, 1.14 mol), 2,2,3,3-tetramethoxybutane (44.8 g, 0.251 mol), and (±)-10-camphorsulfonic acid (2.22 g, 0.010 mol). The resulting solution was refluxed under Ar for 22 h. The resulting dark brown solution was treated with powdered $NaHCO_3$ (8.9 g). Concentration afforded an orange suspension which was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was reextracted once with EtOAc and the combined organic layers were dried over $MgSO_4$. Filtration through silica and concentration afforded an orange oil which started to crystallize. Addition of EtOAc/hexane (1:5, v/v) caused complete crystallization into a single block. Recrystallization (EtOAc and hexane) afforded a white solid (63.9 g, 81%). The brown mother liquor was purified by flash chromatography (EtOAc) to afford an additional amount of product (4.9 g, 6%) as a white foamy solid: mp (crystals) 139.8−140.2 °C; ^{1}H NMR ($CDCl_3$) δ 4.31 (ddd, $J = 12$, 10, 5 Hz, 1 H), 4.19 (ddd, $J = 3$, 3, 3 Hz, 1 H), 3.79 (s, 3 H), 3.60 (dd, 10, 3 Hz, 1 H), 3.26 (2 s, 2 × 3 H), 2.19 (ddd, $J = 15$, 3, 3 Hz, 1 H), 2.10 (ddd, $J = 12$, 5, 3 Hz, 1 H), 2.03 (dd, $J = 15$, 3 Hz, 1 H), 1.92 (dd, $J = 12$, 12 Hz, 1 H), 1.34 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.1, 100.2, 99.6, 75.7, 72.6, 69.0, 62.3, 52.8, 47.8, 38.5, 37.3, 17.7, 17.5. Anal. Calcd for $C_{14}H_{24}O_8$: C, 52.49; H, 7.55. Found: C, 52.56; H, 7.52.

Inositol Protection (Entry 2). A suspension of *myo*-inositol (0.591 g, 3.28 mmol) in methanol (10 mL), 2,2,3,3-tetramethoxybutane (1.19 g, 6.66 mmol), and trimethyl orthoformate (2.9 mL, 26.50 mmol) was treated with CSA (0.042 g, 0.18 mmol). The resulting mixture was refluxed under Ar. A white precipitate appeared slowly over time. After 135 h at reflux, heating was stopped and the cool reaction mixture was filtered. The precipitate was washed with EtOAc/hexane (1:1, v/v). Drying under vacuum afforded the diprotected product (1.05 g, 79%) as a white solid: mp > 330 °C; ^{1}H NMR (C_5D_5N) δ 4.80 (dd, $J =$ 10, 9 Hz, 2, H), 4.71 (t, $J = 2$ Hz, 1 H), 4.28 (t, $J = 9$ Hz, 1 H), 4.16 (dd, $J = 10$, 2 Hz, 2 H), 3.34 (s, 6 H), 3.24 (s, 6 H), 1.45 (s, 6 H), 1.44 (s, 6 H); ^{13}C NMR (C_5D_5N) δ 100.1, 99.5, 71.0, 70.9, 70.0, 69.5, 47.7, 47.6, 18.1, 18.0; HRMS (FAB) calcd for $C_{18}H_{32}O_{10}$ ($M - H^+$) 407.1917, found 407.1912. Anal. Calcd for $C_{18}H_{32}O_{10}$: C, 52.93; H, 7.90. Found: C, 52.98; H, 7.90.

General Procedure for BBA Protection. A suspension of diol (2−5 mmol, 1 equiv) in a solution of 2,2,3,3-tetramethoxybutane (1−1.2 equiv), trimethyl orthoformate (4 equiv) in methanol (2−5 mL/mmol of diol) was treated with camphorsulfonic acid (0.05 equiv). The mixture was refluxed under Ar for 12−18 h. The cool reaction mixture was then treated with powdered $NaHCO_3$ (ca. 0.5 g) and concentrated under reduced pressure. Purification by flash chromatography or radial chromatography (eluent EtOAc and hexane) provided the protected carbohydrates.

Glucose protection (entry 3): ^{1}H NMR ($CDCl_3$) δ 4.80 (d, $J = 4$ Hz, 1 H), 4.74 (d, $J = 4$ Hz, 1 H), 3.60−4.00 (m, 12 H), 3.43 (s, 3 H), 3.41 (s, 3 H), 3.30 (s, 3 H), 3.29 (s, 3 H), 3.26 (s, 6 H), 3.06 (br, 4 H), 1.34 (s, 3 H), 1.33 (s, 3 H), 1.31 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 99.6, 99.4 (2), 99.3, 99.2, 97.8, 71.7, 69.8, 69.6, 69.5, 69.2, 68.0, 67.4, 65.6, 61.4, 60.7, 55.0, 54.8, 47.8, 47.7 (2), 47.6, 17.5 (2), 17.4 (2); HRMS (FAB) calcd for $C_{13}H_{24}O_8$ ($M - H^+$) 307.1393, found 307.1401. Anal. Calcd for $C_{13}H_{24}O_8 \cdot {}^1/_2H_2O$: C, 49.20; H, 7.94. Found: C, 49.29; H, 7.82.

Galactose protection (entry 4): Mp 88−91 °C; ^{1}H NMR ($CDCl_3$) δ 4.84 (d, $J = 2$ Hz, 1 H), 4.20 (dd, $J = 10$, 3 Hz, 1 H), 4.05−4.10 (m, 1 H), 3.80−4.00 (m, 5 H), 3.43 (s, 3 H), 3.26 (s, 3 H), 3.25 (s, 3 H), 2.77 (br, 2 H), 1.34 (s, 3 H), 1.31 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 100.1, 98.3 (2), 70.1, 69.0, 66.1, 65.0, 62.6, 55.1, 47.9 (2), 17.7, 17.6; HRMS (FAB) calcd for $C_{13}H_{24}O_8$ ($M - H^+$) 307.1393, found 307.1380. Anal. Calcd for $C_{13}H_{24}O_8 \cdot 1/2H_2O$: C, 49.20; H, 7.94. Found: C, 49.37; H, 7.98. Spectral data for the β-anomer: ^{1}H NMR ($CDCl_3$) δ 4.42 (d, $J = 8$ Hz, 1 H), 3.80−4.05 (m, 6 H), 3.74 (dd, $J = 10$, 3 Hz, 1 H), 3.55 (s, 3 H), 3.28 (s, 3 H), 3.27 (s, 3 H), 2.73, (br, 2 H), 1.33 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 101.9, 100.1, 99.7, 74.9, 70.2, 68.0, 66.8, 62.1, 56.7, 48.0, 47.9, 17.6, 17.5.

Mannose protection (entry 5): ^{1}H NMR ($CDCl_3$) δ 4.75 (s, 1 H), 4.11 (dd, $J = 10$, 10 Hz, 1 H), 4.00 (dd, $J = 10$, 3 Hz, 1 H), 3.93 (s, 1 H), 3.70−3.85 (m, 3 H), 3.37 (s, 3 H), 3.28 (s, 3 H), 3.26 (s, 3 H), 3.07 (s, 1 H), 2.49 (br, 1 H), 1.32 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 101.0, 100.2, 99.7, 70.5, 69.5, 68.0, 62.7, 61.1, 54.8, 48.0, 47.8, 17.7, 17.6; HRMS (FAB) calcd for $C_{13}H_{24}O_8$ ($M - H^+$) 307.1393, found 307.1404. Anal. Calcd for $C_{13}H_{24}O_8$: C, 50.64; H, 7.85. Found: C, 50.41; H, 7.90.

Lyxose protection (entry 6): mp 63−64 °C; ^{1}H NMR ($CDCl_3$) δ 4.68 (s, 1 H), 4.05−4.25 (m, 1 H), 3.90−3.95 (m, 2 H), 3.55−3.70 (m, 2 H), 3.37 (s, 3 H), 3.27 (s, 3 H), 3.26 (s, 3 H), 2.82 (br, 1 H), 1.33 (s, 3 H), 1.28 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 101.1, 100.4, 99.6, 69.5, 68.6, 62.7, 60.4, 54.8, 47.9, 47.8, 17.6 (2); HRMS (FAB) calcd for $C_{12}H_{22}O_7$ ($M - H^+$) 277.1287, found 277.1296. Anal. Calcd for $C_{12}H_{22}O_7$: C, 51.79; H, 7.97. Found: C, 51.50; H, 7.84.

Rhamnose protection (entry 7): mp 144−147 °C; ^{1}H NMR ($CDCl_3$) δ 4.67 (s, 1 H), 3.90−4.00 (m, 2 H), 3.65−3.85 (m, 2 H), 3.36 (s, 3 H), 3.27 (s, 3 H), 3.24 (s, 3 H), 2.53 (br, 1 H), 1.32 (s, 3 H), 1.29 (s, 3 H), 1.28 (d, $J = 6$ Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 100.8, 100.1, 99.7, 69.7, 68.3, 68.2, 66.3, 54.6, 48.0, 47.6, 17.7, 17.6, 16.5; HRMS (FAB) calcd for $C_{13}H_{24}O_7$ ($M - H^+$) 291.1444, found 291.1435. Anal. Calcd for $C_{13}H_{24}O_7$: C, 53.41; H, 8.27. Found: C, 53.33; H, 8.25.

2-Deoxy glucose protection (entry 8): ^{1}H NMR ($CDCl_3$) δ 4.84 (d, $J = 3$ Hz, 1 H), 4.12 (ddd, $J = 13$, 10, 5 Hz, 1 H), 3.70−3.85 (m, 3 H), 3.62 (dd, $J = 10$, 10 Hz, 1 H), 3.32 (s, 3 H), 3.28 (s, 3 H), 3.27 (s, 3 H), 2.37 (br, 1 H), 1.99 (dd, $J = 13$, 5 Hz, 1 H), 1.77 (ddd, $J = 13$, 13, 3 Hz, 1 H), 1.29 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 99.6, 99.5, 98.6, 69.9, 68.2, 64.6, 61.1, 53.4, 47.8, 47.6, 34.4, 17.6, 17.5. Anal. Calcd for $C_{13}H_{24}O_7$: C, 53.41; H, 8.27. Found: C, 53.23; H, 8.22.

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