The Chemistry of L-Ascorbic and D-Isoascorbic Acids. 1. The Preparation of Chiral Butanetriols and -tetrols[1]

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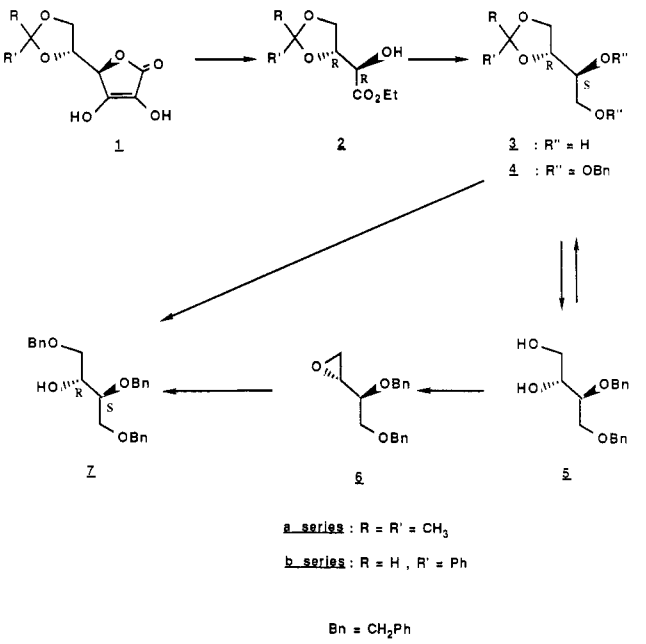
A practical approach to selectively protected chiral threitols and erythritols is described. These functionalized synthons are easily prepared from the title acids.

Recently, we reported the synthesis of 1,2-O-protected L-threitols from L-ascorbic acid.[2] While these and their D-isomers are easily obtained from D- and L-tartaric acids, the same is not true for the chiral erythritols, which are derivable from *meso*-tartaric acid. In this paper we now describe the hitherto unknown, 1,2(*R*)-*O*-isopropylidene- and 1,2(*R*)-*O*-benzylideneerythritols from D-isoascorbic acid.[3] These versatile intermediates were used to prepare other suitably protected triols and tetrols, synthons with unlimited synthetic utility (Scheme I). The present approach circumvents inherent disadvantages encountered in the preparation of related isomeric compounds.[4] The pathways are shorter, the choice of chirality is feasible, and it allows the preferential protection of one hydroxy group at a time, whether primary or secondary,[5] an option not easily afforded by the aforementioned methods[4] or the nucleophilic opening of chiral epoxides.[6]

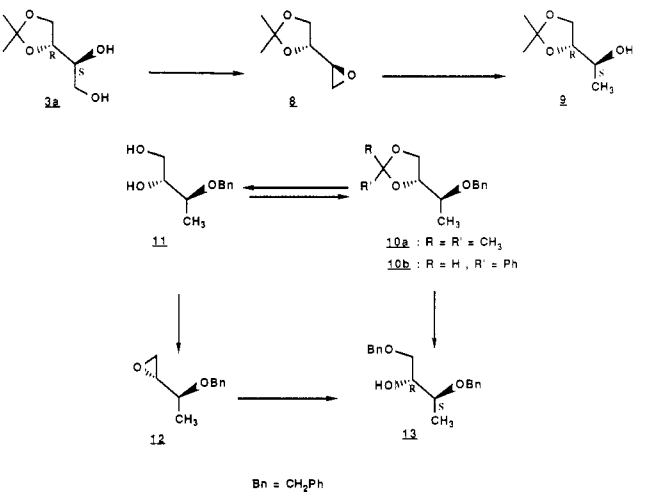
The preparation of (2*R*,3*S*)-1,2-*O*-isopropylidenebutane-1,2,3,4-tetrol (**3a**), a key, chiral derivative of *meso*-erythritol, from D-isoascorbic acid follows analogous procedures reported earlier.[2] Treatment of **3a** with 2 equiv of benzyl bromide in the presence of sodium hydride furnished the dibenzyl derivative **4a**. Acid hydrolysis of the 1,2-*O*-isopropylidene function on **4a** led to (2*R*,3*S*)-3,4-di-*O*-benzylbutane-1,2,3,4-tetrol (**5**), which was converted to the epoxide **6** via the Mitsunobu reaction[7] in 83% yield. Regiospecific ring opening of **6** with sodium benzylate[8] afforded (2*R*,3*S*)-1,3,4-tri-*O*-benzylbutane-1,2,3,4-tetrol (**7**)[9] in good yield.

Regiospecific reductive cleavage of a benzylidene ring[4b,10] offered another route to **7**. This pathway used the pro-

Scheme I



Scheme II



(1) Presented in part at the 194th National Meeting of the American Chemical Society, New Orleans, August 1987, ORGN 279.

(2) Abushanab, E.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1984**, *25*, 3841.

(3) Wu, D. C.-J. Ph.D. Dissertation, University of Rhode Island, 1982. 5,6-*O*-Isopropylidene-D-isoascorbic acid was prepared by the $CuSO_4$–acetone method. Other procedures that have worked well with L-ascorbic acid did not furnish this compound in desirable yields. The 5,6-*O*-benzylidene derivative was obtained as a diastereomeric mixture by using catalytic amounts of trifluoroacetic acid in DMF and benzaldehyde dimethyl acetal. The reported method for 5,6-*O*-benzylidene-L-ascorbic acid[12] was equally inapplicable. The instability of both derivatives precluded obtaining their elemental analyses. Prior to the submission of this manuscript to J. Org. Chem., a report on the uses of L-ascorbic and D-isoascorbic acids appeared: Tanaka, A.; Yamashita, K. *Synthesis* **1987**, 570. Contrary to what was stated by these authors, we were able to prepare 5,6-*O*-isopropylidene-D-isoascorbic acid and found it to be a suitable precursor for the preparation of the title chirons.

(4) (a) Hungerbuler, E.; Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 958. (b) Takano, S.; Kurotaki, K.; Sekiguchi, Y.; Satoh, S.; Hirama, M.; Ogasawara, K. *Synthesis* **1986**, 811. (c) MacCoss, M.; Chen, A.; Tolman, R. *Tetrahedron Lett.* **1985**, *26*, 4287.

(5) Although the preparation of a 2,3,4-triprotected butanetetrol was not undertaken, its preparation can be easily achieved from **2a** by silylation followed by ester reduction; see, for example: Larcheveque, M.; Petit, Y. *Tetrahedron Lett.* **1987**, *28*, 1993.

(6) (a) Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* **1983**, *16*, 67. (b) Pfanninger, A. *Synthesis* **1986**, 89.

(7) Mitsunobu, O. *Synthesis* **1981**, 1. A minor modification of this procedure was followed. After the reactants were mixed in benzene, the product was immediately obtained by vacuum distillation (ca. 0.3 mm) at temperatures ranging from 50 to 130 °C depending on the epoxide. Higher boiling epoxides such as **6** could not be obtained since they co-distilled with dihydro-DEAD. This problem was easily solved by running the reaction at 130 °C for 45 min under vacuum followed by filtration of the reaction mixture on silica gel using hexane.

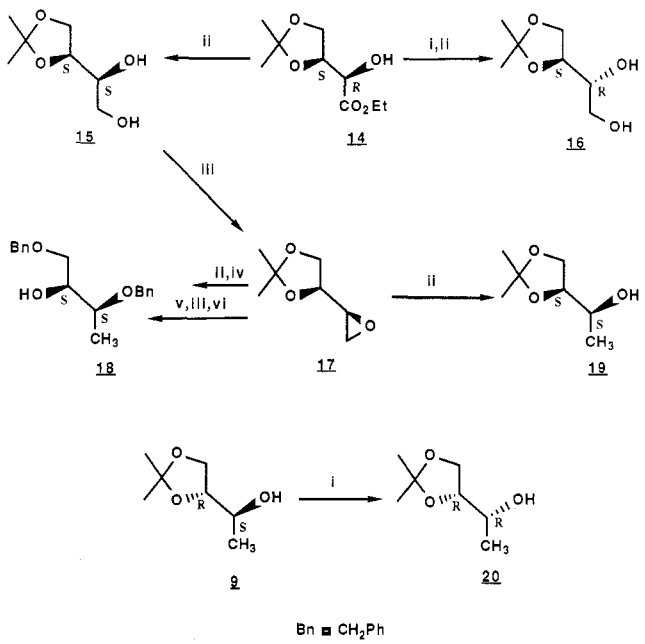
(8) Martin, J. C.; Dvorak, C. A.; Smee, D. F.; Matthews, T. R.; Verheyden, J. P. *J. Med. Chem.* **1983**, *26*, 759.

(9) All four isomers (enantiomers and diastereomers) of **7** have been prepared by a different route; see ref 4c.

(10) (a) Garegg, P. J.; Hultberg, H. *Carbohydr. Res.* **1981**, *93*, C10. (b) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1984**, 201.

0022-3263/88/1953-2598$01.50/0

Scheme III[a]



[a] (i) Ph_3P, DEAD, $PhCO_2H$; (ii) LAH; (iii) Ph_3P, DEAD; (iv) NaH, BnBr; (v) H^+; (vi) $Na^+ {}^-OBn$.

tected tetrol **4b**, which, in turn, was prepared by two different routes. One involved the 1,2-*O*-benzylidene acetal **3b**, which was treated with 2 equiv of benzyl bromide in the presence of sodium hydride to provide **4b** in 75% yield. The other used the 3,4-protected tetrol **5**. Reaction of **5** with benzaldehyde in refluxing benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid gave **4b** in 90% yield. Subsequent treatment of **4b** with sodium cyanoborohydride ($NaCNBH_3$) in anhydrous tetrahydrofuran under acidic conditions led directly to **7**.

The preparation of the triols is depicted in Scheme II. With the exception of the second step, which involves reduction of the epoxide **8** with lithium aluminum hydride (LAH) to provide **9**, the methodology is identical with that described for the syntheses of the tetrols.

Having prepared tetrol **7** and triol **13**, in ca. 50% overall yields, attention was turned to the preparation of other stereoisomers. This was accomplished either by starting with L-ascorbic acid or by inversion of configuration at a specific center. Starting with **15**[2] (Scheme III), which was synthesized from L-ascorbic acid in an identical manner as was **3a** from D-isoascorbic acid, and following the same methodology depicted in scheme II, the 2*S*,3*S*-diastereomers **18** and **19** of **13** and **9**, respectively, were obtained in comparable yields. The other synthetic approach for the preparation of stereoisomers involved inversion of configuration via the Mitsunobu reaction. For example, inversion at C-3 of **9** afforded the 2*R*,3*R*-diastereomer **20**, which is the enantiomer of **19**. Likewise, inversion at C-2 of **14**[2] followed by LAH reduction furnished **16**, the enantiomer of **3a**. The nearly identical but opposite optical rotations of the enantiomers **16** and **20** with their respective counterparts **3a** and **19** serve as evidence for the optical purity and chiral integrity of these compounds.

Thus, starting with D-isoascorbic acid, one can obtain, in good yields, triols and tetrols having the 2*R*,3*S*-configuration. Inversion at C-3 via the Mitsunobu reaction provides their 2*R*,3*R*-diastereomers. On the other hand, beginning with L-ascorbic acid and using identical synthetic methodology furnish those triols and tetrols possessing the 2*S*,3*S*- and 2*S*,3*R*-configurations. Finally, it is worth mentioning that a second inversion at C-2 in either series, e.g., **13** or **18**, would afford their diastereomeric counterparts and offers a method of obtaining all four triols or tetrols from one source. Applications of these chiral threitols and erythritols will be described in forthcoming publications.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on Varian EM-390 and FT-80a spectrometers, respectively. The chemical shifts are expressed in parts per million with respect to tetramethylsilane. Silica gel (Merck, grade 60, 230–400 mesh, 60A) suitable for column chromatography was purchased from Aldrich. Thin-layer chromatography was run on precoated (0.2 mm) silica gel 60 F-254 plates manufactured by EM Laboratories, Inc., and short-wave ultraviolet light (254 nm) was used to detect the UV-absorbing spots. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

Ethyl (2*R*,3*R*)-3,4-*O*-Isopropylidene-2,3,4-trihydroxybutanoate (2a). A mechanically stirred suspension of 200 g (1.14 mol) of D-isoascorbic acid in acetone (4.5 L) was treated with 300 g of anhydrous $CuSO_4$. After the reaction was stirred at room temperature for 24 h, a second 300-g portion of $CuSO_4$ was added, and stirring was continued for an additional 24 h. The reaction was then filtered and concentrated, giving a near-quantitative yield of 3,4-*O*-isopropylidene-D-isoascorbic acid (**1a**). The isopropylidene derivative was then dissolved in water (1.2 L) containing 312 g of K_2CO_3. This solution was chilled in an ice bath and stirred while 30% H_2O_2 (249 mL) was slowly added. During the addition the temperature was maintained below 20 °C. The solution was stirred overnight and then concentrated in vacuo. The moist solid was extracted with boiling absolute EtOH (6 × 500 mL). After filtration and evaporation, the salt was dried under vacuum to provide 236 g of material. Treatment of a mechanically stirred suspension of the salt with EtI (241 g) in CH_3CN (1.5 L) at reflux for 24 h gave, after concentration and removal of the inorganic salt, 198 g of crude ester. Distillation under reduced pressure gave pure (NMR and TLC) **2a**: 188.3 g (84%, 81% from D-isoascorbic acid); bp 70–110 °C (0.10 mmHg). A second distillation, bp 72 °C (0.0075 mmHg), gave analytically pure ester: $[\alpha]_D$ −29.14° (*c* 1.565, MeOH); ^1H NMR ($CDCl_3$) δ 1.35 (m, 9), 3.90–4.50 (m, 7).

Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found: C, 52.89; H, 8.02.

Ethyl (2*R*,3*R*)-3,4-*O*-Benzylidene-2,3,4-trihydroxybutanoate (2b). To a stirred solution of D-isoascorbic acid (100 g, 0.568 mol) in DMF (100 mL) were added benzaldehyde dimethyl acetal (100 g, 0.657 mol) and trifluoroacetic acid (5.0 g). After being stirred for 120 h at room temperature, the reaction was concentrated in vacuo (50 mL of distillate collected), and the resultant viscous yellow liquid, **1b**, was dissolved in water (600 mL) containing K_2CO_3 (140 g) and was oxidized with 30% hydrogen peroxide (126 mL, 1.14 mol) at ice bath temperature. After being stirred at room temperature overnight, the solution was concentrated in vacuo, yielding a moist viscous salt, which was extracted with boiling absolute ethanol (5 × 300 mL). Evaporation of the solvent gave a viscous yellow solid (173.0 g), which was mixed with CH_3CN (500 mL) containing EtI (133.0 g, 0.852 mol), and the mixture was then stirred and heated to reflux for 20 h. The reaction was then concentrated and filtered and the product dissolved in CH_2Cl_2. This solution was washed several times with a 10% Na_2CO_3 solution and then dried over $MgSO_4$. After filtration and concentration, the product was purified by silica gel column chromatography and eluting with hexane–ethyl acetate (9:1, v/v). This procedure produced analytically pure **2b** (94.2 g) in 65.8% yield (from D-isoascorbic acid): ^1H NMR ($CDCl_3$) δ 1.20 (m, 3), 3.70–4.60 (m, 7), 5.63 and 5.90 (s, 1), 7.27 (m, 5).

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.77; H, 6.15.

(2*R*,3*S*)-1,2-*O*-Isopropylidenebutane-1,2,3,4-tetrol (3a). To a cooled, mechanically stirred suspension of powdered LAH (26.2 g, 0.69 mol) in anhydrous tetrahydrofuran (THF, 500 mL) was added dropwise a solution of **2a** (106.7 g, 0.52 mol) in anhydrous THF (200 mL). After addition was complete the reaction was

stirred for 1 h and then heated at reflux for 1 h. The excess LAH was decomposed by sequential addition of water (25 mL), a 15% NaOH solution (25 mL), and water (70 mL). The mixture was filtered, and the solids were extracted (Soxhlet) with $CHCl_3$ for 24 h. The combined THF and $CHCl_3$ solutions were dried over anhydrous $MgSO_4$ and then concentrated to furnish 80.7 g (95.3%) of **3a**. Analytically pure **3a** was obtained by distillation under reduced pressure: bp 103–107 °C (0.01 mmHg); $[\alpha]^{25}_D$ +7.82° (*c* 4.18, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3), 1.40 (s, 3), 3.40–3.80 (m, 3), 3.80–4.15 (m, 3), 4.30 (s, 2, D_2O exchangeable).

Anal. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.57; H, 8.64.

(2*R*,3*S*)-1,2-*O*-Benzylidenebutane-1,2,3,4-tetrol (3b). To a stirred suspension of powdered LAH (3.16 g, 83.4 mmol) in freshly distilled, dry THF (200 mL) was added dropwise a solution of **2b** (24.9 g, 98.8 mmol) in dry THF (35 mL). After being stirred 18 h at room temperature, the reaction was heated at reflux for 1 h, then cooled, and treated with water (3 mL), a 15% NaOH solution (3 mL), and water (10 mL), respectively. The gelatinous mixture was vigorously shaken with $CHCl_3$ (1.0 L) and then slowly vacuum filtered. The solid was extracted (Soxhlet) with $CHCl_3$ for 40 h, and the combined chloroform extracts were dried over $MgSO_4$. Evaporation of the solvent gave a viscous orange liquid, which was heated at 60 °C in vacuo to remove the small amount of benzaldehyde which was present. Upon cooling **3b** solidified: 16.7 g (80.3%). Analytically pure **3b** was obtained by recrystallization from an Et_2O/hexane mixture: mp 55–62 °C; ^{1}H NMR ($CDCl_3$) δ 3.40–4.20 (m, 8), 5.67 and 5.77 (s, 1), 7.31 (m, 5).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.73; H, 6.76.

(2*R*,3*S*)-3,4-Di-*O*-benzyl-1,2-*O*-isopropylidenebutane-1,2,3,4-tetrol (4a). To a mechanically stirred suspension of NaH (25.55 g, 1.065 mol; previously washed three times with petroleum ether) in dry DMF (1.4 L) was added dropwise a solution of **3a** (75.0 g, 0.463 mol) in DMF (400 mL). The reaction was stirred for 25 min, and then benzyl bromide (171.1 g, 1.0 mol) was added dropwise. The reaction was stirred for 1 h before concentration under reduced pressure. Excess NaH was decomposed by addition of water. The product was extracted with $CHCl_3$ and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave 146.0 (92%) of pure (NMR) **4a**. An analytical sample of **4a** was obtained by chromatography on a silica gel column, eluting with hexane–ethyl acetate (9:1, v/v): $[\alpha]_D$ +16.77° (*c* 1.795, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 3), 1.30 (s, 3), 3.30–3.70 (m, 3), 3.70–4.25 (m, 3), 4.35 (s, 2), 4.52 (q_{AB}, 2, J = 12 Hz), 7.11 (s, 10).

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.84; H, 7.77.

(2*R*,3*S*)-3,4-Di-*O*-benzyl-1,2-*O*-benzylidenebutane-1,2,3,4-tetrol (4b). Method A. Compound **5** (81.1 g, 0.268 mol) dissolved in benzene (500 mL) was treated at reflux temperature with freshly distilled benzaldehyde (35.0 g) and *p*-toluenesulfonic acid (2.25 g). The water which formed was collected in a Barrett receiver. After 20 h at reflux, the solvent was evaporated and the product dissolved in hexane (250 mL) containing a small amount of ether. After washing with dilute Na_2CO_3 solution, the organic phase was dried over anhydrous $MgSO_4$ and then concentrated. Pure **4b** was obtained by silica gel column chromatography (elution with hexane–ethyl acetate, 9:1, v/v) followed by vacuum distillation of the residual benzaldehyde at 0.30 mmHg: 93.4 g (89.2%). ^{1}H NMR ($CDCl_3$) δ 3.40–3.85 (m, 3), 3.85–4.35 (m, 3), 4.43 (s, 2), 4.64 (q_{AB}, 2, J = 12 Hz), 5.63 and 5.81 (s, 1), 7.20 (m, 15).

Anal. Calcd for $C_{25}H_{26}O_4$: C, 76.90; H, 6.71. Found: C, 76.71; H, 6.70.

Method B. To a stirred suspension of NaH (1.32 g, 54.7 mmol; previously washed three times with petroleum ether) in dry DMF (50 mL) was added dropwise a solution of **3b** (5.0 g, 23.8 mmol) in dry DMF (20 mL). After complete addition, stirring was continued at room temperature for 20 min, and then benzyl bromide (8.80 g, 51.4 mmol) was added dropwise while the reaction was cooled in an ice bath. After being stirred at room temperature overnight, the reaction was concentrated in vacuo and carefully mixed with water (100 mL). The aqueous mixture was extracted with CH_2Cl_2, and the organic layer was dried over anhydrous $MgSO_4$. The remaining DMF (indicated by NMR) was removed by evaporation at 90 °C under reduced pressure, giving 8.2 g of crude **4b**. Analytically pure **4b** was obtained by silica gel column chromatography and eluting with hexane–ethyl acetate (9:1, v/v): 6.94 g (74.7%). The product was identical with that obtained from method A.

(2*S*,3*R*)-1,2-Di-*O*-benzylbutane-1,2,3,4-tetrol (5). Compound **4a** (100 g, 0.29 mol) was dissolved in 95% EtOH (400 mL) to which water (50 mL), concentrated HCl (2 mL), and acid-activated Amberlite CG-120 resin (60 g) were added. The reaction was stirred at room temperature and was monitored by TLC until the disappearance of **4a**. After filtration of the resin, the remaining acid was neutralized with a saturated Na_2CO_3 solution, the reaction was concentrated, and the product was extracted with CH_2Cl_2 and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave 81.5 g (92.3%) of **5**. Analytically pure **5** was obtained by silica gel column chromatography using hexane–ethyl acetate (9:1, v/v) and then absolute EtOH as eluent. The product was isolated in the EtOH fraction: $[\alpha]_D$ +4.21° (*c* 1.46, EtOH); ^{1}H NMR ($CDCl_3$) δ 3.55 (m, 8), 4.35 (s, 2), 4.47 (q_{AB}, 2, J = 12 Hz), 7.13 (s, 10).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.61; H, 7.42.

(2*R*,3*S*)-1,2-Epoxy-3,4-bis(benzyloxy)butane (6). Triphenylphosphine (TPP, 28.25 g, 0.108 mol) and the dibenzyl diol **5** (28.1 g, 0.093 mol) were dissolved in benzene (300 mL) in a single-necked 1-L round-bottom flask. The solution was concentrated to ca. 150 mL under diminished pressure and then cooled. To the cooled solution was added, dropwise, diisopropyl azodicarboxylate (DIAD, 23.0 g, 0.11 mol), and when the addition was complete the mixture was allowed to stir for 30 min. Next, the remaining benzene was removed under diminished pressure, and the resulting solution was heated and stirred at 125–130 °C (0.03 mmHg) for 1.5 h. Silica gel was then added to the hot solution to form a slurry. The slurry was mixed with chloroform and dried on a Buchi rotary evaporator. This material was added to the top of a silica gel column and the column eluted with hexane–ethyl acetate (9:1, v/v). The fractions containing the product were pooled, and the solvent was removed to furnish **6** (21.8 g, 83%) as a liquid: $[\alpha]_D$ +4.87° (*c* 1.54, ethanol); ^{1}H NMR ($CDCl_3$) δ 2.66 (d, 2), 3.03 (m, 1), 3.46 (m, 1), 3.60 (d, 2), 4.50 (s, 2), 4.60 (s, 2), 7.23 (s, 10).

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.04; H, 7.09. Found: C, 75.91; H, 7.27.

(2*R*,3*S*)-1,3,4-Tri-*O*-benzylbutane-1,2,3,4-tetrol (7). Method A: Opening of 6 with Sodium Benzyl Oxide. To a stirred suspension of NaH (15.9 g, 0.331 mol; washed with hexane) in dry DMF (100 mL) was added, dropwise, a solution of benzyl alcohol (35.75 g, 0.331 mol) in DMF (50 mL). When the addition was complete, the mixture was allowed to stir for 15 min at room temperature, and then a solution of **6** (18.8 g, 0.066 mol) in DMF (35 mL) was added. The reaction mixture was heated at 100 °C for 1.5 h. After cooling, the reaction mixture was poured into a separatory funnel and water (100 mL) was added. This mixture was extracted with ethyl ether (3 × 150 mL). The ether extracts were combined, washed with water (2 × 50 mL), and dried over anhydrous $MgSO_4$. The ether was removed under diminished pressure, and the resulting residue was purified on a silica gel column by using hexane–ethyl acetate (9:1, v/v) as the eluent. Workup provided **7** (21.36 g) in 82% yield: $[\alpha]_D$ +11.42° (*c* 2.45, MeOH); ^{1}H NMR ($CDCl_3$) δ 2.65 (d, 1, D_2O exchangeable), 3.66 (m, 5), 3.93 (m, 1), 4.42 (s, 2), 4.50 (s, 2), 4.60 (q_{AB}, 2, J = 12 Hz), 7.25 (s, 15).

Anal. Calcd for $C_{25}H_{28}O_4$: C, 76.50; H, 7.19. Found: C, 76.27; H, 7.37.

Method B: Reductive Opening of 4b with Sodium Cyanoborohydride. Sodium cyanoborohydride (29.2 g, 0.465 mol) and powdered molecular sieves (10 g) were placed in a flame-dried, three-necked, round-bottom flask and kept under a dry nitrogen atmosphere. [**Note**: Consistent yields are dependent on keeping all reagents and glassware extremely dry.] To this mixture was added a solution of **4b** (20.0 g, 0.465 mol) in freshly distilled THF (300 mL). Dry hydrogen chloride gas was bubbled into the reaction mixture for 45 min while the temperature was maintained at 0 °C. The reaction was allowed to stir for 1.5 h. Next, water (40 mL) and 12 N HCl (100 mL) were added, and the reaction mixture was allowed to stand overnight to decompose unreacted sodium cyanoborohydride. After the mixture was allowed to stand,

an additional amount of water (150 mL) was added to the reaction, and the molecular sieves were separated by centrifugation. The solution was extracted with ethyl ether (3 × 150 mL). The ether layer was washed with a saturated sodium bicarbonate solution (3 × 100 mL) and water (2 × 100 mL) and dried over anhydrous $MgSO_4$. The ether was removed under diminished pressure, and the resulting residue was purified by flash chromatography. The silica gel column was eluted with hexane–ethyl acetate (9:1, v/v). The fractions containing the product were pooled and evaporated to provide pure **7** (15.7 g, 78%) as a colorless liquid. This product was identical in all respects with that obtained from method A.

(2*R*,3*S*)-3,4-Epoxy-1,2-*O*-isopropylidenebutane-1,2-diol (8). Diethyl azodicarboxylate (DEAD, 2.58 g, 0.014 mol) was added dropwise to a stirred solution of **3a** (2.17 g, 0.013 mol) and TPP (3.73 g, 0.014 mol) in dry benzene (20 mL). An exothermic reaction was observed. After the mixture cooled to room temperature, the benzene was removed under diminished pressure, and the remaining residue was distilled at 42 °C (0.7 mmHg) to give 1.53 g (79.5%) of pure **8**: $[\alpha]_D$ +8.67° (*c* 2.215, EtOH); ^1H NMR ($CDCl_3$) δ 1.33 (s, 3), 1.4 (s, 3), 2.5–2.68 (m, 1), 2.8 (dd, 1, J = 4.5 Hz), 2.88–3.07 (m, 1), 3.68–4.23 (m, 3).

Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.21; H, 8.62.

(2*R*,3*S*)-1,2-*O*-Isopropylidenebutane-1,2,3-triol (9). To a magnetically stirred suspension of LAH (3.18 g, 0.08 mol) in anhydrous ethyl ether (50 mL) under gentle reflux was added dropwise a solution of **8** (10.35 g, 0.07 mol) in anhydrous ethyl ether (20 mL). After the addition was complete, the reaction mixture was stirred at room temperature for 2 h and then heated at reflux for 1 h. After the usual workup, pure **9** (8.65 g, 82.5%) was obtained. An analytical sample of **9** was obtained by distillation under reduced pressure: bp 53 °C (0.03 mmHg); $[\alpha]_D$ +17.73° (*c* 1.455, EtOH); ^1H NMR ($CDCl_3$) δ 1.17 (d, 3, J = 6 Hz), 1.36 (s, 3), 1.45 (s, 3), 2.45 (br s, 1, D_2O exchangeable), 3.5–4.2 (m, 4).

Anal. Calcd for $C_7H_{14}O_3$: C, 57.52; H, 9.65. Found: C, 57.41; H, 9.51.

(2*R*,3*S*)-3-*O*-Benzyl-1,2-*O*-isopropylidenebutane-1,2,3-triol (10a). Compound **9** (33.4 g, 0.22 mol) in dry DMF (30 mL) was added dropwise to a cold (10 °C), mechanically stirred suspension of NaH (8.3 g, 0.346 mol; previously washed three times with petroleum ether). After the mixture was stirred at 10 °C for 2 h, a solution of benzyl bromide (43.14 g, 0.252 mol) in dry DMF (20 mL) was added over a 20-min period, and the resulting mixture was stirred for 2 h. Next, water (6.5 mL) was carefully added to the reaction flask, the mixture was stirred, and then the mixture was poured into water (1.5 L). The product was extracted with ethyl ether (4 × 150 mL). The ether extracts were combined, washed with water (5 × 100 mL), and dried over anhydrous $MgSO_4$. Removal of the ether under diminished pressure gave **10a** (43.5 g, 81%). Analytically pure **10a** was obtained by silica gel chromatography using hexane–ethyl acetate (9:1, v/v) as eluent: $[\alpha]_D$ +43.4° (*c* 4.605, EtOH); ^1H NMR ($CDCl_3$) δ 1.08 (d, 3, J = 6 Hz), 1.32 (s, 3), 1.38 (s, 3), 3.23–4.23 (m, 4), 4.52 (q_{AB}, 2, J = 12 Hz), 7.28 (br s, 5).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.14; H, 8.42.

(2*R*,3*S*)-3-*O*-Benzylbutane-1,2,3-triol (11). Activated Amberlite IR-120 resin (32.9 g; the resin was activated by being stirred with 137 mL of concentrated hydrochloric acid for 4 h) and water (43.5 mL) were added to a solution of **10a** (39.15 g, 0.165 mol) in ethanol (392 mL). The reaction mixture was stirred at room temperature for 20 h and then filtered, and the filtrate was concentrated under diminished pressure to obtain an oily material. This material was dissolved in ether (100 mL) and dried over anhydrous $MgSO_4$. Removal of the excess solvent furnished **11** (28.18 g, 86.7%). An analytical sample was obtained by chromatography on silica gel: $[\alpha]_D$ +31.94° (*c* 4.48, EtOH); ^1H NMR ($CDCl_3$) δ 1.17 (d, 3, J = 6 Hz), 3.32–3.9 (m, 6, partially exchangeable with D_2O), 4.44 (q_{AB}, 2, J = 12 Hz), 7.25 (br s, 5).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.33; H, 8.22. Found: C, 67.13; H, 8.43.

(2*R*,3*S*)-3-*O*-Benzyl-1,2-*O*-benzylidenebutane-1,2,3-triol (10b). To a solution of **11** (17.7 g, 0.09 mol) in dry benzene (500 mL) was added freshly distilled benzaldehyde (14.1 g, 0.133 mol) and a catalytic amount of *p*-toluenesulfonic acid (0.68 g). The reaction mixture was heated at reflux for 24 h, and the water generated was collected by a Dean–Stark apparatus. After this time, the reaction was allowed to cool to room temperature and then washed sequentially with a 10% aqueous sodium bisulfite solution (10 × 125 mL), 10% aqueous bicarbonate (2 × 100 mL), and water (2 × 100 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered and then the excess benzene removed under diminished pressure to afford **10b** (23.1 g, 90.1%). An analytical sample was provided by silica gel chromatography using hexane–ethyl acetate (9:1, v/v) as eluent: ^1H NMR ($CDCl_3$) δ 1.23 and 1.25 (2 d, 3, J = 6 Hz), 3.35–4.77 (m, 4), 5.7 and 5.82 (2 s, 1), 7.0–7.53 (m, 10).

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.04; H, 7.09. Found: C, 75.81; H, 7.39.

(2*R*,3*S*)-3-(Benzyloxy)-1,2-epoxybutane (12). This compound was obtained according to the procedure described for the preparation of **8**. Treatment of **11** (6.11 g, 0.031 mol) in dry benzene (59 mL) with TPP (9.40 g, 0.035 mol) and DEAD (6.57 g, 0.036 mol) gave pure **12** (4.05 g, 73%): bp 97 °C (0.05 mmHg); $[\alpha]_D$ +4.54° (*c* 1.565, EtOH); ^1H NMR ($CDCl_3$) δ 1.08 (d, J = 6 Hz, 3, CH_3), 2.52–3.0 (m, 3), 3.15–3.55 (m, 1), 4.52 (s, 2), 7.27 (br s, 5).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.98; H, 8.11.

(2*R*,3*S*)-1,3-Di-*O*-benzylbutane-1,2,3-triol (13). Method A: Opening of the Epoxide 12 with Sodium Benzyl Oxide. Benzyl alcohol (31 mL), **12** (8 g, 0.045 mol), and *tert*-butyl alcohol (119 mL) were added successively to a stirred solution of sodium hydroxide (3.62 g, 0.091 mol) in water (3.6 mL) at room temperature. The reaction mixture was stirred vigorously for 3 h at 91 °C. The reaction mixture was then diluted with water (60 mL) and extracted with ethyl ether (3 × 50 mL). The ether extract was washed with a saturated sodium chloride solution (2 × 30 mL) and dried over anhydrous $MgSO_4$. The ether and excess benzyl alcohol were removed under diminished pressure to furnish **13** (10.95 g, 85.3%). An analytical sample was obtained by chromatography on silica gel using hexane–ethyl acetate (9:1, v/v) as eluent: $[\alpha]_D$ +26.5° (*c* 0.91, EtOH); ^1H NMR ($CDCl_3$) δ 1.18 (d, 3, J = 6 Hz), 2.65 (br d, 1, J = 2 Hz, D_2O exchangeable), 3.36–3.92 (m, 4), 4.27–4.67 (m 4), 7.23 (br s, 10).

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.43; H, 7.59.

Method B: Sodium Cyanoborohydride ($NaCNBH_3$) Reduction of the Benzylidene 10b. The title compound was prepared according to the procedure described for the preparation of **7**. A suspension of **10b** (12.05 g, 0.043 mol) and 19.8 g (0.299 mol) of $NaCNBH_3$ in dry THF (450 mL) containing powdered 4A molecular sieves (24 g, activated at 400 °C for 6 h) was cooled to 0 °C. Hydrogen chloride gas (dried through concentrated H_2SO_4) was bubbled through the reaction mixture for 3 h. After the reaction mixture was stirred for an additional 1.5 h at 0 °C, it was worked up in the usual manner to afford 8.68 g (71.5%) of oily material. This material was a mixture of **13** and (2*R*,3*S*)-2,3-di-*O*-benzylbutane-1,2,3-triol in a 13:2 ratio, respectively, as confirmed by ^{13}C NMR. Chromatography provided pure **13**, which was identical, in all respects, with the material obtained from method A.

(2*R*,3*R*)-1,2-*O*-Isopropylidenebutane-1,2,3,4-tetrol (16). Benzoic acid (2.44 g, 20 mmol), TPP (5.3 g, 20 mmol), and compound **14**[2] were dissolved in dry THF (100 mL). To this solution was added dropwise a solution of DIAD (4.2 g, 20 mmol) in THF (20 mL). After the mixture was stirred 12 h at room temperture, the solvent was removed under diminished pressure and the residue taken up in ethyl ether. The solid which precipitated was removed by filtration, the filtrate and washings were concentrated, and the resulting oil was chromatographed on a silica gel column. The column was eluted with hexane followed by hexane–ethyl acetate (95:5, v/v). The fractions containing UV positive material were pooled and furnished the intermediate ethyl (2*S*,3*S*)-2-*O*-benzoyl-3,4-*O*-isopropylidene-2,3,4-trihydroxybutanoate (2.2 g, 72%): $[\alpha]^{25}_D$ −13.61° (*c* 4.88, EtOH); ^1H NMR ($CDCl_3$) δ 1.18–1.55 (m, 9), 4.02–4.7 (m, 5), 5.3 (d, 1, J = 6 Hz), 7.26–7.62 (m, 3), 8.02 (dd, 2, J = 2 and 6 Hz).

To a cooled, stirred suspension of powdered LAH (45 mg, 1.18 mmol) in anhydrous ethyl ether (10 mL) was added dropwise a solution of the benzoate (241 mg, 0.78 mmol) in anhydrous ethyl

ether (5 mL). After the addition was complete, the reaction mixture was stirred at room temperature for 1 h and then heated at reflux for 3 h. The excess LAH was decomposed by sequential addition of water (0.1 mL), a 15% NaOH solution (0.1 mL), and water (0.2 mL). After filtration, the ethereal layer was dried over anhydrous sodium sulfate and concentrated to a light, yellow oil. The oil was distilled to provide **16** (120 mg, 90%): bp 110–120 °C (0.3 mmHg); $[\alpha]^{25}_D$ −7.61° (*c* 6.51, EtOH). The ^{1}H NMR spectrum was identical with that of **3a**.

(2*S*,3*S*)-3,4-Epoxy-1,2-*O*-isopropylidenebutane-1,2-diol (17). This compound was prepared in 89% yield from **15**[2] by using the same procedure described for **8**: $[\alpha]_D$ −3.23° (*c* 4.025, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3, CH_3), 1.41 (s, 3, CH_3), 2.56–2.80 (m, 2), 2.86–3.03 (m, 1), 3.72–4.1 (m, 3). This compound was identical with an authentic sample prepared earlier (see ref 2).

(2*S*,3*S*)-1,3-*O*-Dibenzylbutane-1,2,3-triol (18). The procedure followed was identical with that described for the preparation of **13** by method A: $[\alpha]_D$ +22.6° (*c* 2.55, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.17 (d, 3, *J* = 6 Hz), (d, 1, *J* = 3 Hz), 3.4–3.8 (m, 4), 4.5 (q_{AB}, 2, *J* = 12 Hz), 4.5 (s, 2), 7.25 (s, 10).

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.75. Found: C, 75.38; H, 7.70.

(2*S*,3*S*)-1,2-*O*-Isopropylidenebutane-1,2,3-triol (19). This compound was prepared in 91% yield by the same procedure described for **9** and was identical with an authentic sample prepared earlier (see ref 2): $[\alpha]_D$ −11.31 (*c* 3.06, EtOH). The ^{1}H NMR spectrum of **19** was identical with that of **20**.

(2*R*,3*R*)-1,2-*O*-Isopropylidenebutane-1,2,3-triol (20). Compound **9** (14.6 g, 0.1 mol), TPP (39.74 g, 0.15 mol), and benzoic acid were dissolved in dry benzene (200 mL). A solution of DIAD (31.3 g, 0.15 mol) in dry benzene (50 mL) was added dropwise at room temperature. After 20 h, the precipitate was filtered off, and the residue obtained after evaporation was mixed with silica gel (75 g, 60–230 mesh). This mixture was placed on top of a silica gel column and eluted with hexane followed by hexane–ethyl acetate (95:5, v/v) to furnish a crude mixture (22.2 g) of the benzoate and benzoic acid.[11] This mixture was dissolved in methanol (125 mL) and sodium hydroxide (0.144 mol) in water (25 mL) and was stirred at room temperature overnight. Evaporation of the methanol followed by extraction of the residue with ether provided **20** (10.75 g, 74%): $[\alpha]_D$ +11.35° (*c* 2.03, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.13 (d, 3, *J* = 6 Hz), 1.37 (s, 3), 1.42 (s, 3), 2.75 (br s, 1), 3.45–4.2 (m, 4).

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Registry No. **1a**, 50271-42-6; **1b**, 114184-95-1; **2a**, 114184-94-0; **2b**, 114184-96-2; **3a**, 114184-97-3; **3b**, 114184-98-4; **4a**, 114184-99-5; **4b**, 114185-01-2; **5**, 114185-00-1; **6**, 114185-02-3; **7**, 101703-83-7; **8**, 74134-78-4; **9**, 74183-61-2; **10a**, 87604-49-7; **10b**, 114185-03-4; **11**, 87604-55-5; **12**, 114185-04-5; **13**, 114185-05-6; **14**, 114185-07-8; **15**, 91274-05-4; **16**, 114185-09-0; **17**, 93367-10-3; **18**, 114185-10-3; **20**, 74183-62-3; **20** (3-*O*-benzoyl derivative), 114185-11-4; D-isoascorbic acid, 89-65-6; (2*R*,3*S*)-2,3-di-*O*-benzylbutane-1,2,3-triol, 114185-06-7; ethyl (2*S*,3*S*)-2-*O*-benzoyl-3,4-*O*-isopropylidene-2,3,4-trihydroxybutanoate, 114185-08-9.

(11) A small amount of this mixture was purified by silica gel chromatography to give (2*R*,3*R*)-3-*O*-benzoyl-1,2-*O*-isopropylidenebutane-1,2,3-triol: $[\alpha]^{25}_D$ −8.95° (*c* 2.95, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.33 (d, 3, *J* = 6 Hz), 1.37 (s, 3), 1.45 (s, 3), 3.65–4.43 (m, 3), 5.05–5.36 (m, 1), 7.23–7.68 (m, 3), 7.92–8.22 (m, 2). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.19; H, 7.25. Found: C, 67.01; H, 7.16.

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Symmetrical Alkoxysilyl Ethers. A New Class of Alcohol-Protecting Groups. Preparation of *tert*-Butoxydiphenylsilyl Ethers

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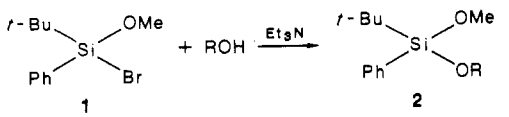
The preparation and evaluation of a new class of alcohol-protecting groups, the alkoxydiphenylsilyl ethers, are described. In particular, *tert*-butoxydiphenylsilyl ethers, which can be formed from primary, secondary, or tertiary alcohols and *tert*-butoxydiphenylsilyl chloride, offer the useful synthetic properties of acid stability and high fluoride reactivity. Opportunities for selective silyl group cleavage are highlighted.

Introduction

Silicon-based methodology for the protection of alcohols has made a major contribution in organic synthesis.[1] The ability to modulate selectivity and reactivity by varying the steric and electronic requirements of the substituents on silicon has been demonstrated by such reagents as *tert*-butyldimethylsilyl chloride[2] and *tert*-butyldiphenylsilyl chloride.[3] This latter compound, for example, can discriminate a primary from a secondary or tertiary alcohol; such discrimination is a consequence of the more demanding steric environment of the *tert*-butyldiphenylsilyl substituent. A consequence of this fact is that, once formed, such silyl ethers are correspondingly more resistant to hydrolysis or fluorolysis.

Scheme I. Preparation of *tert*-Butylmethoxyphenylsilyl Ethers



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With the intent of breaking this steric nexus, we have shown that silyl ethers substituted with a further electron-withdrawing substituent, like an oxygen atom, are readily attacked by fluoride ion. Hence, we prepared the

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