Synthesis of Asymmetrically Deuterated Glycerol and Dibenzylglyceraldehyde via Boronic Esters

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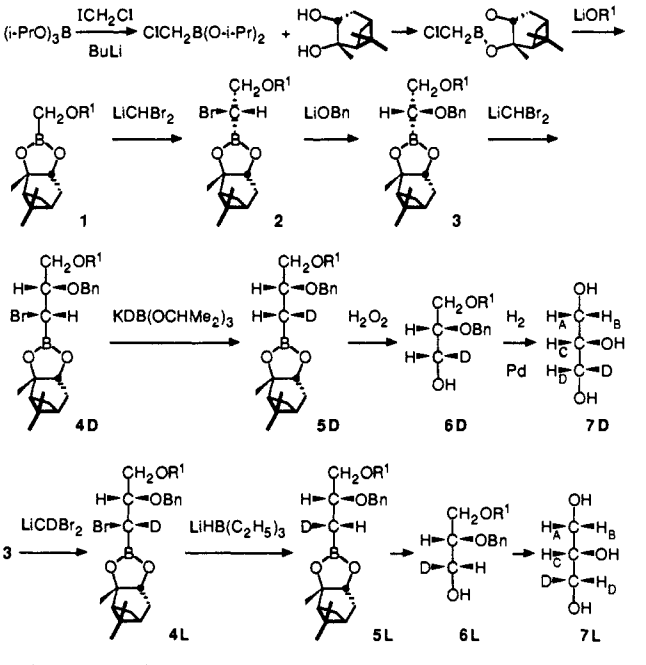
Abstract: (*S*)-Pinanediol [(benzyloxy)methyl]boronate (**1a**) has been converted via an improved procedure to (*S*)-pinanediol (1*R*)-[1,2-bis(benzyloxy)ethyl]boronate (**3a**) (96% de), which with (dibromomethyl)lithium has yielded (*S*)-pinanediol (1*S*,2*S*)-[2,3-benzyloxy)-1-bromopropyl]boronate (**4Da**). Treatment with potassium triisopropoxyborodeuteride has yielded (*S*)-pinanediol (1*R*,2*R*)-[2,3-bis(benzyloxy)propyl]boronate-*1-d* (**5Da**), which on deboronation with hydrogen peroxide and debenzylation has yielded (1*S*,2*S*)-glycerol-*1-d* (**7D**) in ~92–94% de. The opposite diastereomer, (1*R*,2*S*)-glycerol-*1-d* (**7L**), was obtained via **3a** with (dibromomethyl)lithium-*d* and reduction of the resulting (*S*)-pinanediol (1*S*,2*R*)-[2,3-bis(benzyloxy)propyl]boronate-*1-d* (**5La**) with lithium triethylborohydride. Chain extension of (*S*)-pinanediol (*p*-methoxybenzyl)boronate (**1b**) via the alcohols **6b**, benzylation to **8b**, and DDQ cleavage of the methoxybenzyl group to form alcohols **8c** followed by Swern oxidation has led to dibenzyl-(2*R*,3*S*)-glyceraldehyde-*3-d* (**9D**) and dibenzyl-(2*R*,3*R*)-glyceraldehyde-*3-d* (**9L**). Conversion of **8c** to the crystalline trityl ether **8d** reveals that deuterium label placement is in ≥98% absolute configurational excess, and the major diastereomeric contaminant (2–3%) of the glycerol-*d* is in error at C(2).

Asymmetric synthesis with boronic esters[1] provides a particularly simple and direct construction of chirally deuterated molecules.[2] Glycerol (1,2,3-propanetriol) is a ubiquitous metabolic intermediate that is incorporated into glucose and other fundamental biochemical intermediates. The asymmetric labeling of glycerol with deuterium or tritium has provided a wealth of information about mechanisms of biosynthesis.[3-7] Each of four stereoisomers of glycerol labeled with deuterium or tritium in a methylene group has been synthesized via enzymatic routes, and each has presented a separate and rather complex synthetic problem. In general, 1-labeled (2*S*)-glycerol, which corresponds to labeling the CH_2 group [C(6)] of derived glucose, is made from (*Z*)- or (*E*)-phosphoenolpyruvate.[3-5] The synthesis of 1-labeled (2*R*)-glycerol involves hydrogen transfer between a labeled alcohol and isopropylidene-D-glyceraldehyde catalyzed by alcohol dehydrogenase.[6,7]

Results

We have utilized (*S*)-pinanediol[8] haloboronic ester chemistry[1,2,9-11] to achieve a simple chemical synthesis of (1*S*,2*S*)-glycerol-*1-d* (**7D**) and its diastereomer, (1*R*,2*S*)-glycerol-*1-d* (**7L**). We made 0.8-g batches, but these are nowhere near the limits of convenient laboratory operations. We have also made *O*,*O*'-dibenzyl-(2*R*,3*S*)-glyceraldehyde-*3-d* (**9D**) and *O*,*O*'-dibenzyl-(2*R*,3*R*)-glyceraldehyde-*3-d* (**9L**), potentially useful intermediates for the chemical synthesis of other metabolites. A derivative from the route to **9** has provided evidence that the label placement is in ≥98% absolute configurational excess (excess = $x_1 - x_2$, where x_1 and x_2 are the percentages of major and minor isomers). The major diastereomeric impurity, ~2–3%, is the one in error at the central carbon. If the glycerol is viewed as a biochemical precursor to glyceraldehyde, this amounts to 2–3% misplacement of the label at C(1) instead of C(3), but ≥99% chiral purity of the label at C(3).

The route to (*S*)-pinanediol [(arylmethoxy)methyl]boronates (**1**) established previously[9-11] has been improved. Diisopropyl



a, R^1 = benzyl; b, R^1 = *p*-methoxybenzyl; Bn = benzyl

(chloromethyl)boronate (from chloroiodomethane, triisopropyl borate, and butyllithium)[10] was transesterified to (*S*)-pinanediol (chloromethyl)boronate, which with lithium arylmethoxide yielded **1** in multigram quantities.[11]

Procedural errors that can impair the stereoselectivity of chain extension of (*S*)-pinanediol [[(arylmethyl)oxy]methyl]boronates **1** to [(1*S*)-1-bromo-2-[(arylmethyl)oxy]ethyl]boronates **2**[11-13] have

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(10) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687–1689.

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been identified. The generation of (dibromomethyl)lithium from dibromomethane and lithium diisopropylamide (LDA) liberates diisopropylamine, which in the original procedure was removed under vacuum, exposing the borate precursor of **2** to temperatures up to 0 °C for a short period of time. This may have allowed some relatively nonstereoselective rearrangement before the zinc chloride catalyst[9] was introduced. Accordingly, in the improved procedure, the diisopropylamine is left in place and enough extra zinc chloride is added to compensate for converting part of it to amine complex. The use of an insufficient amount of zinc chloride has been found to impair diastereoselection.

In early runs, when **2b** was prepared with an insufficient amount of commercial solution of zinc chloride in diethyl ether and then chromatographed, derivatives contained 20–30% epimer. Although epimerizations[14] of the chloro analogues of **2** are slow, loss of **2a** during chromatography has been noted previously,[11,15] and chromatography of a sample of **2b** of ~85% de (diastereomeric excess) on silica degraded it to ~70% de. Accordingly, **2** were purified only to the point of removing the zinc chloride and then immediately converted to the benzyloxy derivatives **3**. With the added precaution that anhydrous powdered zinc chloride was used rather than the ether solution, **3a** and **3b** were then obtained in at least 92–96% de based on proton NMR analysis.

Preparation of **4Da** or **4Db** from **3** and (dibromomethyl)lithium generated in situ followed the same procedure as the preparations of **2** from **1**, with an additional 1 equiv of zinc chloride to compensate for the additional benzyloxy group. Conversion to **5D** was first done with commercially available lithium triethylborodeuteride in the same manner as the analogous step in the synthesis of an asymmetrically deuterated benzyl boronic ester.[2] However, this reaction produces spontaneously flammable triethylborane. Brown and co-workers have recommended potassium triisopropoxyborohydride for reduction of α-halo boronic esters.[16] We found that formation of potassium triisopropoxyborodeuteride is much slower than formation of the hydride,[17] requiring nearly 1 week to complete as indicated by ^{11}B NMR spectra, but that the reagent is otherwise entirely satisfactory.

For the complementary placement of the deuterium label, we generated (dibromomethyl)lithium-*d* from dideuterodibromomethane and lithium diisopropylamide in the presence of 1,2-bis(arylmethoxy)ethyl boronic ester (**3**) to obtain the deuterated α-bromo boronic esters **4L**. In spite of the possible isotope effect slowing the abstraction of D^+ as well as the use of no excess of the dibromomethane-d_2, the generation of (dibromomethyl)lithium-*d* was efficient. Reduction of **4L** with lithium triethylborohydride readily yielded **5L**.

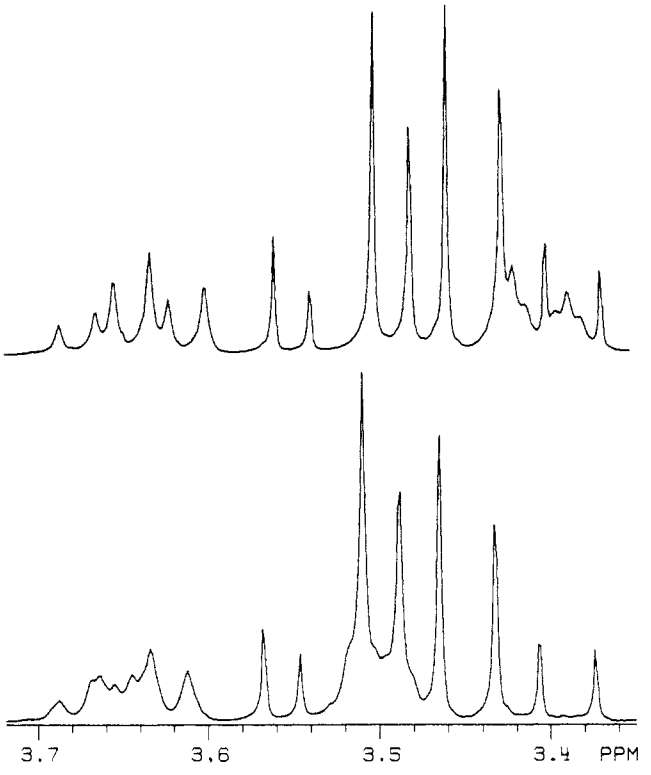
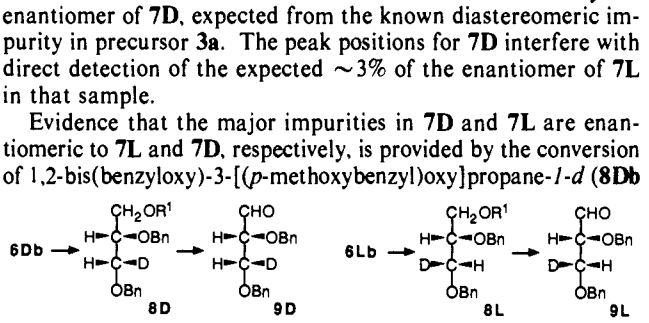


Figure 1. 200-MHz ^1H NMR spectra of (1*S*,2*S*)-glycerol-*1-d* (**7D**) (top curve) and (1*R*,2*S*)-glycerol-*1-d* (**7L**) (bottom curve).

Deboronation of **5Da** or **5La** with hydrogen peroxide to **6Da** or **6La** (the undeuterated form of which is known[18,19]) and debenzylation by catalytic hydrogenation are routine steps. The overall yield of deuterated glycerol from **1** was ~29% or based on use of the deuterium label source, 42–50%.

The ^1H NMR spectra (Figure 1) clearly differentiate (1*S*,2*S*)-glycerol-*1-d* (D isomer **7D**) from (1*R*,2*S*)-glycerol-*1-d* (L isomer **7L**) by the contrasting chemical shifts of the 1-^1H (H_D in the structure diagrams). Though these NMR data do not provide quantitative analysis, the **7L** sample shows weak absorption consistent with ~3–4% diastereomer. This must be mostly the enantiomer of **7D**, expected from the known diastereomeric impurity in precursor **3a**. The peak positions for **7D** interfere with direct detection of the expected ~3% of the enantiomer of **7L** in that sample.

Evidence that the major impurities in **7D** and **7L** are enantiomeric to **7L** and **7D**, respectively, is provided by the conversion of 1,2-bis(benzyloxy)-3-[(*p*-methoxybenzyl)oxy]propane-*1-d* (**8Db** or **8Lb**) to the corresponding alcohol **8Dc** or **8Lc** followed by tritylation[18] to trityl ether **8Dd** or **8Ld**. These show distinct doublets resulting from the diastereotopic 1-^1H absorptions of **8Dd** at δ 3.61 (J = 5.8 Hz) and of **8Ld** at δ 3.63 (J = 4.5 Hz). After recrystallization, which removes the enantiomer but cannot remove the diastereomer that differs only in the position of the label, the minor isomers were not detectable in either case. Based on the



b, R^1 = *p*-methoxybenzyl; c, R^1 = H; d, R^1 = CPh_3

(13) *Chemical Abstracts* indexes acyclic boronic esters as, for example, boronic acid, (chloromethyl)-, bis(1-methylethyl) ester; hence, our semisystematic names such as diisopropyl (chloromethyl)boronate and, by extension (*S*)-pinanediol [(1*S*)-1-bromo-2-(benzyloxy)ethyl]boronate (**2a**). However, the systematic names for cyclic boronic esters abandon both the boronic acid and diol groups as a basis in favor of the heterocycle, and **2a** is indexed as 4,6-methano-1,3,2-benzodioxaborole, 2-[1-bromo-2-(phenylmethoxy)-ethyl]hexahydro-3a,5,5-trimethyl-, [3a*S*-[2(*R**),3aα,4β,6β,7aα]]-, which corresponds to {3a*S*-[2(*R**),3aα,4β,6β,7aα]}-**2**-[1-bromo-2-(phenylmethoxy)ethyl]hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborole. By the Prelog–Cahn–Ingold system the renumbered pinanediol chiral carbons would be 3a*S*,4*S*,6*S*,7a*R*, but *Chemical Abstracts* chooses a single chiral center to specify absolute configuration and defines all the rest in a relative sense by descriptors α and β for rings and by *R** and *S** for open chains. The designation of the side chain chirality as 2(*R**) means that if this were the enantiomer in which index carbon 3a is *R*, the 2-[1-bromo-2-(phenylmethoxy)ethyl] substituent would also be *R*, but in this case carbon 3a is *S*, and therefore the side chain at position 2 is also *S*. Another example is (*S*)-pinanediol (1*S*,2*S*)-[2,3-bis(benzyloxy)-1-bromopropyl]boronate (**4Da**), systematically named {3a*S*-[2(1*R**,2*R**),3aα,4β,6β,7aα]}-2-[1-bromo-2,3-bis-(phenylmethoxy)propyl]hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborole. Systematic names pair enantiomers of a single diastereomer for indexing and obey proper logic for description of chirality as discussed by: Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 3319–3328. However, we find it difficult to keep track of chains of symbols such as 3a*S*-[2-(1*R**,2*R**),3aα,4β,6β,7aα].

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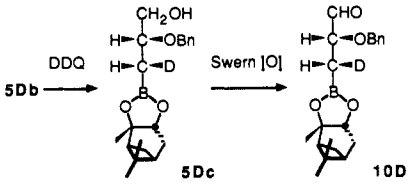
noise level of the spectra, the diastereomeric excess was >98%. Detritylation of **8d** back to **8c** has been demonstrated. This operation provides a formal route to labeled glycerols **7D** and **7L** of >99% diastereomeric and enantiomeric purity, through we have not converted a purified sample of **8c** to **7**.

The *p*-methoxybenzyl compounds (series **b**) also provide a route to asymmetrically deuterated glyceraldehyde derivatives. We converted alcohols **8Dc** and **8Lc** to the corresponding deuterated dibenzyl glyceraldehydes **9D** and **9L** (the unlabeled form of which is known[18,21]). However, in contrast to our successful conversion of tetrabenzylribose to ribose,[11] attempted hydrogenolysis of **9** to glyceraldehyde yielded a mixture containing glycerol. Glyceraldehyde is a gross mixture of hemiacetals and acetals.[20] A commercial sample showed an exceedingly complex ^{1}H NMR spectrum, and correlation of any components of it with our product mixture could not be proved or disproved.

We have also found that dichlorodicyanoquinone (DDQ) oxidative cleavage[22] efficiently converts (*p*-methoxybenzyl)oxy boronic esters **5b** to the corresponding alcohols **5c** and that standard Swern oxidation conditions[23] convert **5c** to aldehyde **10**.



Discussion

Scope. This work establishes that all four stereoisomers of glycerol-*1-d* are readily accessible in high purity via a simple chemical route. Preparations of the 1*R*,2*R* and 1*S*,2*R* enantiomers of **7D** and **7L** would be identical with those of **7D** and **7L** themselves except for the use of the readily available (*R*)-pinanediol as chiral director,[9] and we therefore considered its superfluous to prepare these. The synthetic method would allow tritium labels in place of or in addition to the deuterium labels and could also be used to introduce ^{13}C or ^{14}C at any of the three carbon sites.

The synthetic method could be easily adapted to provide any conceivable combination of C, H, and O labels at specific sites in glycerol. The one exception would be glycerol stereospecifically deuterated at both C(1) and C(3), but asymmetric reduction of dibenzyl glyceraldehyde **9D** or **9L**, for example with isopinocampheyl-9-borabicyclo[3.3.1]nonane-*d*,[24] would fill that gap if the need should arise.

Aldehyde **10** is a potential precursor of other glyceraldehyde derivatives via well-established chemistry. Peroxidic oxidation should convert **10** to 2-*O*-benzylglyceraldehyde, but this compound has been reported as an oil characterized only by conversion to derivatives,[25,26] and this transformation was not attempted. In view of the easy enzymatic conversion of glycerol to glyceraldehyde, we had no incentive to pursue the synthesis of the latter, though the possible utility of **10** as a precursor to glyceraldehyde 3-phosphate[23] or related useful compounds should be readily apparent. The compatibility of the boronic ester group with Swern oxidation conditions observed here also has potential synthetic applications in a broader context.

Diastereomeric Purity. In conventional asymmetric syntheses it is often acceptable to get an isomer ratio of ~10:1 and then purify the major isomer, but the impossibility of purification where the only diastereomeric difference is in the position of a deuterium label underscores the significance of the high initial diastereoselectivity obtainable with boronic ester chemistry. To achieve this high diastereoselectivity, certain experimental details are critical. For verification, it is necessary to make both diastereomers so that the purity can be monitored unambiguously by NMR.

As noted in Results, it is essential that enough zinc chloride be used and that chromatography be avoided in preparations of α-bromo boronic esters. Zinc chloride in diethyl ether has previously not given quite as high diastereoselection as freshly dried powdered zinc chloride.[12] In the present case, it now appears that the quantity was the real problem, but the convenient zinc chloride solution has not been tested again. A large excess of zinc chloride should be avoided, inasmuch as epimerization catalyzed by $ZnCl_2$ + $ZnCl_3^-$ at high concentrations can be very rapid.[14]

The differences between most of the diastereomeric pairs of intermediates in the 200-MHz ^{1}H NMR spectra are subtle enough that the unexpected contamination of the first batch of **2b** with ~20% of its diastereomer was not recognized until both diastereomeric series **5D–7D** and **5L–7L** had been prepared. Benzyl trityl ethers **8Dd** and **8Ld** were the only pair to show a chemical shift difference wide enough for quantitative analysis.

Recrystallization of the 80% **8Dd** removed the isomeric contaminant, which therefore could not have been the diastereomer differing only in the position of the deuterium label at C(1) but must have been the diastereomer which differs at C(2), the enantiomer of **8Ld**, as confirmed by using pure **3b** in repeating the synthesis.

The fact that recrystallization of triethyl ethers **8Dd** and **8Ld** led to material of ≥98% diastereomeric excess indicates the high diastereoselectivity of the introduction of the label in the *p*-methoxybenzyl ether series (**b**). Unfortunately, the deuterated trityl ethers obtained from the dibenzyl ethers **6Da** and **6La** are not clearly distinguishable by 200-MHz ^{1}H NMR as a result of a lack of chemical shift difference between the epimeric $CHDOCPh_3$ groups. Recrystallization of such a trityl ether would still result in purification, but this would not be verifiable until conversion to glycerol-*1-d*, an exercise we did not carry out.

There is no reason to expect that diastereoselectivities differ between the preparations of **6a** and **6b**. It therefore appears that the chiral purity at C(1) of glycerol-*1-d* **7D** or **7L** prepared from **6a** is very high and that most of the observed ~3–4% of diastereomeric impurity is isomeric at C(2). During an enzymatic synthesis of labeled glucose, the deuterium-labeled carbon of the minor isomer would become the aldehyde carbon of the glyceraldehyde intermediate.

^{1}H NMR Interpretation. The 200-MHz spectrum of **7L** (Figure 1) provides direct evidence of high isomeric purity and is consistent with the indirect evidence that the diastereomeric purity should be 96–97% (92–94% de). The H_B peaks in the spectrum of **7D** obscure the H_D peaks of the 3–4% **7L** and its enantiomer presumably present as impurities. At 300 MHz, neither isomer shows sufficient peak separation for semiquantitative analysis.

The availability of both chirally labeled isomers of glycerol **7D** and **7L** allows unambiguous assignment of the chemical shifts and coupling constants. Chemical shifts averaged for all 200- and 300-MHz data, with HDO assumed to be δ 4.700 as the internal reference in D_2O, were as follows: H_A, δ 3.428 ± 0.008 [**7D**, corresponding H_D δ 3.403]; H_B, δ 3.508 ± 0.006 [**7L**, corresponding H_D δ 3.495]; H_C, δ 3.637 ± 0.007. Coupling constants from the 300-MHz data were J_{AB} = 11.70 ± 0.03, J_{AC} = 6.48 ± 0.07, and J_{BC} = 4.36 ± 0.04 Hz, averaged over all appropriate pairs of peaks except H_D's. For **7D**, J_{CD} = 6.4–6.5 Hz; for **7L**, J_{CD} = 4.2–4.3 Hz.

The isotopically induced chemical shift by the geminal deuterium based on the difference $H_A - H_D$ in **7D** is 0.025 ± 0.001 ppm. The difference $H_B - H_D$ in **7L** is 0.013 ± 0.002 ppm. These are in line with isotopic chemical shift differences reported in the early years of NMR measurements,[27] though it is not obvious why the two diastereomers should differ as much as they do.

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Experimental Section

General Data. Reactions involving air-sensitive reagents were run under argon. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl. Zinc chloride was fused, was handled in a glovebox, and was used as a powder (40 mesh). Dimethyl sulfoxide, LDA, potassium deuteride, lithium triethylborohydride, dibromomethane, dibromomethane-d_2, and (*S*)-pinanediol (98% ee) were purchased from Aldrich Chemical Co. If not otherwise noted, techniques were similar to those described previously.[9,11] Instruments used included a Nicolet NT-200 high-field NMR spectrometer, a Bruker 300-MHz NMR spectrometer (University of Idaho), a JEOL FX-90Q NMR spectrometer, a VG Instruments 7070 EHF mass spectrometer,[28] and a Jasco DIP-181 digital polarimeter. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

(*S*)-Pinanediol [(*p*-Methoxybenzyl)oxy]methyl]boronate (1b). A solution of 210 mmol of lithium (*p*-methoxybenzyl)oxide was prepared by addition of 131 mL of 1.6 M butyllithium in hexane to 29.0 g of *p*-methoxybenzyl alcohol in 300 mL of THF at −78 °C. This mixture was stirred during the addition of 12.4 g (175 mmol) of dimethyl sulfoxide,[11] followed by 40.0 g (175 mmol) of (*S*)-pinanediol (chloromethyl)boronate[9,10] at −78 °C, and then allowed to warm to 25 °C and heated to 45–50 °C overnight. The mixture was worked up by addition of saturated aqueous ammonium chloride and ether. The ether phase was washed with water and saturated sodium chloride and then dried over sodium sulfate. The solution was concentrated under reduced pressure, and the residue was flash chromatographed on silica (210–400 mesh, 450–500 g) with 10:1 light petroleum ether/diethyl ether to yield 51.3 g (89%) of pale yellow oil: 90-MHz ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 3 CH_3), 1.15 (d, 1, J = 11 Hz, pinyl C*H*), 1.28 (s, 3, CH_3), 1.40 (s, 3 CH_3), 1.82–2.23 (m, 5, pinyl C*H*), 3.29 (s, 2, OCH_2B), 3.78 (s, 3, CH_3O), 4.34 (dd, 1, J = 1.7 and 8.5 Hz, C*H*OB), 4.44 (s, 2, $ArCH_2O$), 6.85 (d, 2, J = 8.8 Hz, Ar*H*), 7.27 (d, 2, J = 8.8 Hz, ArH_2). Anal. Calcd for $C_{19}H_{27}BO_4$: C, 69.11; H, 8.24; B, 3.27. Found: C, 69.63; H, 8.16; B, 2.93.

(*S*)-Pinanediol [(1*S*)-1-Bromo-2-[(*p*-methoxybenzyl)oxy]ethyl]boronate (2b). A solution of 3.30 g (10 mmol) of **1b** and 5.04 g (29 mmol) of dibromomethane in 20 mL of THF was stirred at −78 °C during the dropwise addition of 7.0 mL (10 mmol) of 1.5 M LDA–THF in cyclohexane, followed by 3.95 g (29 mmol) of fused, powdered zinc chloride. The mixture was allowed to come to room temperature slowly and stirred for 18 h, and then it was worked up by treatment with aqueous ammonium chloride and diethyl ether. The ether solution was filtered through a column of anhydrous magnesium sulfate (15–20 g). The ether solution was concentrated at <40 °C, and the solvent was removed from the residue under vacuum (~10 Torr). For optimum stereoselectivity in the synthetic sequence, the whole operation was done as quickly as possible and the residue was used as such immediately in the next step. For an analytical sample, the ether solution was concentrated, and the residue was chromatographed on silica with 3:1 light petroleum ether/diethyl ether: 2.96 g (70%) of **2b**; 200-MHz ^{1}H NMR ($CDCl_3$) δ 0.84 (s, 3), 1.23 (d, 1, half obscured), 1.29 (s, 3), 1.40 (s, 3), 1.9–2.08 (m, 5), 3.51 (dd, 1, J = 6.7 and 7.7 Hz, C*H*Br), 3.76–3.83 (m, 2, OCH_2CHBr), 3.80 (s, 3, OCH_3), 4.36 (dd, 1, J = 1.8 and 8.6 Hz, C*H*OB), 4.52, (s, 2, $ArCH_2O$), 6.85 (d, 2, J = 8.8 Hz, ArH_2), 7.27 (d, 2, J = 8.8 Hz, ArH_2). Anal. Calcd for $C_{20}H_{28}BBrO_4$: C, 56.77; H, 6.67; B, 2.55; Br, 18.88. Found: C, 56.93; H, 6.85; B, 2.63; Br, 18.86.

(*S*)-Pinanediol [(1*R*)-1-(Benzyloxy)-2-[(*p*-methoxybenzyl)oxy]ethyl]boronate (3b). A solution of the above residue of **2b** in 15 mL of THF was added to a stirred solution of 20 mmol of lithium benzyloxide (from 20 mmol of butyllithium and 2.16 g of benzyl alcohol) in 20 mL of THF at −78 °C. After the usual workup with aqueous ammonium chloride and diethyl ether, **3b** was purified by flash chromatography on silica with 10:1 light petroleum ether/diethyl ether: 2.84 g (63% from **1b**); 200-MHz ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 3, CH_3), 1.23 (d, 1, J = 11 Hz, pinyl C*H*), 1.28 (s, 3, CH_3), 1.39 (s, 3, CH_3), 1.93–2.40 (m, 5, pinyl C*H*), 3.58 (dd, 1, J = 3.2 and 5.3 Hz, C*H*OBn), 3.70–3.75 (m, J = 11.8 Hz, 2, OCH_2CHOBn), 3.80 (s, 3, OCH_3), 4.32 (dd, 1 J = 1.8 and 8.6 Hz, C*H*OB), 4.46 and 4.53 (AB, J = 11.8 Hz, 2, $MeOC_6H_4CH_2O$), 4.65 (s, 2, $PhCH_2O$), 6.85 (d, 2, J = 8.8 Hz, Ar*H*), 7.23–7.36 (m, 7, Ar*H* + C_6H_5); mass spectrum (70 eV) ($C_{19}H_{26}BO_4$ (loss of $MeOC_6H_4CH_2$)) calcd m/e 329.1924, found m/e 329.2205.[28]

(*S*)-Pinanediol [(1*S*,2*S*)-1-Bromo-2-(benzyloxy)-3-[(*p*-methoxybenzyl)oxy]propyl]boronate (4Db). A 2.8-g (6.22-mmol) sample of **3b** with 3.14 g (18.04 mmol) of dibromomethane in 10 mL of THF was treated with 6.53 mmol of LDA in the usual manner at −78 °C, followed by 3.30 g (3.9 equiv) of powdered anhydrous zinc chloride. After being stirred at 20–25 °C for 18 h, the mixture was worked up as before, the solution of **4Db** in ether was again filtered through a pad of anhydrous magnesium sulfate, and the ether layer was concentrated under vacuum. For the synthetic sequence, the residue was used in the next step immediately. For analytical purposes, **4Db** was isolated by chromatography with 3:1 light petroleum ether/diethyl ether: 77%; 200-MHz ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 3, CH_3), 1.27 (s, 3, CH_3), 1.29 (s, 3, CH_3), 1.32 (d, 1, half obscured, pinyl C*H*), 1.84–2.34 (m, 5), 3.49–3.66 (m, 3, $ROCH_2CH(OBn)CHBr$), 3.80 (s, 3, OCH_3), 3.88–3.98 (m, 1, $CH_2CH(OBn)CHBr$), 4.29 (dd, J = 1.8 and 8.7 Hz, 1, C*H*OB), 4.41 and 4.48 (AB, J = 11.8 Hz, 2, $MeOC_6H_4CH_2O$), 4.65 and 4.73 (AB, J = 11.4 Hz, $PhCH_2O$), 6.86 (d, 2, J = 8.8 Hz, Ar*H*), 7.21–7.39 (m, 7, C_6H_5 + Ar*H*). Anal. Calcd for $C_{28}H_{36}BBrO_5$: C, 61.90; H, 6.68; B, 1.99; Br, 14.71. Found: C, 61.20; H, 6.82; B, 2.21; Br, 15.09.

(*S*)-Pinanediol [(1*R*,2*R*)-2-(Benzyloxy)-3-[(*p*-methoxybenzyl)oxy]propyl]boronate-*1-d* (5Db). A solution of **4Db** in 20 mL of THF was stirred at 0 °C during the dropwise addition of potassium triisopropoxyborodeuteride (~1 M; 6.84 mmol) in THF. The mixture was stirred for 5 h. The mixture was treated with water, and the product was extracted with ether and concentrated. Flash chromatography on silica with 10:1 light petroleum ether/diethyl ether yielded 1.64 g of **5Db** (64% from **3**): 200-MHz ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 3, CH_3), 1.10 (d, 1, J = 10.7 Hz, pinyl C*H*), 1.26 (s, 3 CH_3), 1.32 (s, 3, CH_3), 1.82–2.33 (m, 6, pinyl C*H* + C*H*D), 3.43–3.63 (m, 2, $ArCH_2OCH_2$), 3.79 (s, 3, OCH_3), 3.90–3.93 (m, 1, $CH_2CH(OBn)CHD$), 4.48 (s, 3, $MeOC_6H_4CH_2O$), 4.63 (s, 3, $PhCH_2O$), 6.86 (d, 2, J = 8.7, Ar*H*), 7.23–7.36 (m, 7, Ar*H* + C_6H_5); mass spectrum (70 eV) ($C_{21}H_{29}DBO_5$ (loss of $PhCH_2$)) calcd m/e 374.2249, found 374.2211. Anal. Calcd for $C_{28}H_{36}DBO_5$:[29] C, 72.26; H, 8.04; B, 2.32. Found: C, 72.31; H, 8.16; B, 2.33.

(1*S*,2*R*)-2-(Benzyloxy)-3-[(*p*-methoxybenzyl)oxy]propan-1-ol-*1-d* (6Db).[30] A solution of 3.52 g (7.6 mmol) of **5Db** in 100 mL of THF was treated with 0.93 mL of 30% hydrogen peroxide and 2.50 mL of 3 M sodium hydroxide at 0 °C and stirred at 20–25 °C for 2 h. Analysis by TLC showed complete consumption of the **5Db**. The mixture was filtered, extracted with ether, washed with water, and dried over sodium sulfate. After concentration, **6Db** was purified by flash chromatography on silica with 2:1 light petroleum ether/diethyl ether: 2.20–2.30 g (95–100%); 200-MHz ^{1}H NMR ($CDCl_3$) δ 2.23 (d, 1, J = 5.1 Hz, O*H*), 3.55–3.69 (m, 4, $ROCH_2CH(OBn)CHDOH$), 3.79 (s, 3, OCH_3), 4.46 (s, 2, $MeOC_6H_4CH_2O$), 4.59 and 4.70 (AB, J = 11.8 Hz, 2, $PhCH_2O$), 6.86 (d, 2, J = 8.7 Hz, Ar*H*), 7.21–7.35 (m, 7, Ar*H* + C_6H_5; mass spectrum ($C_{18}H_{21}DO_4$) calcd m/e 303.1581, found 303.1531.

(1*S*,2*R*)-1,2-Bis(benzyloxy)-3-[(*p*-methoxybenzyl)oxy]propane-*1-d* (8Db). A 2.0-g (6.6-mmol) sample of **6Db** in 15 mL of anhydrous DMSO was treated with 0.32 g (13.2 mmol) of sodium hydride at 0 °C and the resultant mixture stirred for 0.5 h at 20–25 °C. A 1.49-g (13.2 mmol) portion of benzyl chloride was added, and the mixture was stirred at 50–55 °C overnight. The mixture was diluted with water and the product extracted with ether and concentrated. Flash chromatography with 10:1 light petroleum ether/diethyl ether on silica gel yielded 2.26–2.40 g (84–89%) of **8Db**: 200-MHz ^{1}H NMR ($CDCl_3$) δ 3.56–3.60 (m, 3, $ArOCH_2CH(OBn)CHDOBn$), 3.75–3.83 (m, 1, $CH_2CH(OBn)CHD$), 3.78 (s, 3, OCH_3), 4.46 (s, 2, $MeOC_6H_4CH_2O$), 4.52 (s, 2, $PhCH_2O$), 4.68 (s, 2, $PhCH_2O$), 6.85 (d, J = 8.8 Hz, 2, Ar*H*), 7.20–7.34 (m, 7, Ar*H* + C_6H_5); mass spectrum ($C_{25}H_{27}DO_4$) calcd m/e 393.2050, found 393.1601.[28]

(2*S*,3*S*)-2,3-Bis(benzyloxy)propanol-*3-d* (8DC). A solution of 1.97 g (5.0 mmol) of **8Db** in 30 mL of dichloromethane was stirred with 10 mL of water, and 1.36 g (6.0 mmol) of 2,3-dichloro-5,6-dicyanoquinone was added. After being stirred for 2.5 h at 20–25 °C, the mixture was filtered through a celite pad with the aid of more dichloromethane. The dichloromethane phase was stirred with an equal volume of water for 0.5 h, then washed with saturated sodium chloride, and concentrated. The residue was chromatographed on silica with 2:1 diethyl ether/light petroleum ether to yield 1.23 g (90%) of **8Dc**: 200-MHz ^{1}H NMR ($CDCl_3$) δ 2.23 (br s, 1, O*H*), 3.55–3.75 (m, 4, $HOCH_2CH(OBn)CHDOBn$),

(28) Discrepancies in the mass spectral data reflect random variations between duplicate samples when the measurements were made. Precision has improved (to ±0.002 mu) as the technician has gained experience. Only semiquantitative data are available for some of the peripheral compounds prepared early in the course of this work.

(29) In deuterated compounds, % H calculated as if weight of $H_2O + D_2O$ is interpreted as H_2O by analyst, a very minor correction.

(30) An often unrecognized feature of the Cahn–Ingold–Prelog system is the requirement that subrule 2 (relating to mass number) not be invoked if assignment of priorities can be handled completely by subrule 1 (relating to atomic number). Thus, under subrule 1, CH_2OR (R having a higher atomic number than H) has a higher priority than CHDOH (H and D having the same atomic number, it is necessary to establish priorities on the basis of the branch from the O). We appreciate the discrepancy in our original assignments for compounds 6 and 8, based upon our invoking subrule 2 prematurely, being brought to our attention by editorial staff in Columbus.

4.53 (s, 2, PhCH_2O), 4.60 and 4.71 (AB, J = 11.8 Hz, 2, PhCH_2O), 7.29–7.35 (m, 10, C$_6H_5$); mass spectrum ($C_{17}H_{19}DO_3$) calcd m/e 273.1475, found 273.1680.[28]

(2*R*,3*S*)-2,3-Bis(benzyloxy)propanal-*3-d* (9D). A 500-mg (1.83-mmol) sample of **8Dc** was oxidized under Swern conditions.[11,23] Chromatography on silica with 1:1 diethyl ether/light petroleum ether yielded 450 mg (91%) of **9D**: 200-MHz ^{1}H NMR ($CDCl_3$) δ 3.71–3.75 (m, 1, CHD), 3.95 (dd, J = 1.1 and 5.2 Hz, 1, CH$_2$CH(OBn)CHD), 4.52 (s, 2, PhCH_2O), 4.62 and 4.68 (AB, J = 11.8 Hz, 2, PhCH_2O), 7.25–7.43 (m, 10, C$_6H_5$), 9.69 (d, J = 1.1 Hz, 1, CH=O); mass spectrum ($C_{17}H_{17}DO_3$) calcd m/e 271.1318, found 271.1387.

(*S*)-Pinanediol [(1*S*,2*S*)-2-(Benzyloxy)-1-chloro-3-[(*p*-methoxybenzyl)oxy]propyl]boronate-*1-d* (Cl Analogue of 4Lb). A 10.0-g (22.2-mmol) sample of **3** with 4.3 mL of dichloromethane-d_2 (99.6 atom % D) in 100 mL of THF was treated with 28.8 mmol of LDA at −78 °C according to the procedure described for preparation of **4Db**. Chromatography yielded 3.81 g (34%) of the Cl analogue of **4Lb**: 200-MHz ^{1}H NMR ($CDCl_3$) δ 0.81 (s, 3), 1.26 (d, half obscured, 1), 1.27 (s, 3), 1.32 (s, 3), 1.84–2.08 (m, 5), 3.51–3.67 (m, 2, ROCH_2CH), 3.79 (s, 3, OCH_3), 3.91–4.01 (m, 1, CH$_2$CH(OBn)CDCl), 4.31 (dd, J = 1.1 and 8.7 Hz, 1, CHOB), 4.44 (s, 2, MeOC$_6H_4$CH_2O), 4.69 (s, 2, PhCH_2O), 6.86 (d, J = 8.7 Hz, 2, ArH_2), 7.21–7.37 (m, 7, ArH_2 + C$_6H_5$); mass spectrum ($C_{21}H_{28}DBClO_5$) calcd m/e 408.1859, found 408.1839.

(*S*)-Pinanediol [(1*S*,2*S*)-2-(Benzyloxy)-1-bromo-3-[(*p*-methoxybenzyl)oxy]propyl]boronate-*1-d* (4Lb). A 10.0-g (22.2-mmol) sample of **3** with 4.70 g (26.75 mmol) of dibromomethane-d_2 (99.6 atom % D) in 100 mL of THF was treated with 28.8 mmol of LDA at −78 °C, followed by 11.81 g (86.59 mmol, 3.9 equiv) of dry powdered anhydrous zinc chloride. After being stirred at 20–25 °C for 18 h, the mixture was worked up as before, the solution of **4Lb** in ether was again filtered through a pad of anhydrous magnesium sulfate, and the ether layer was concentrated under vacuum. The residue, free of ether, was used in the next step immediately.

(*S*)-Pinanediol [(1*S*,2*R*)-2-(Benzyloxy)-3-[(*p*-methoxybenzyl)oxy]propyl]boronate-*1-d* (5Lb). The procedure was the same as for the preparation of **5Db** except that **4Lb** was used in place of **4Db** and lithium triethylborohydride (45 mmol, 2 equiv) was used in place of the KIPBD. (*Caution*: Spontaneously flammable triethylborane is a byproduct. A fire occurred when air instead of argon was admitted to the flask after concentration on the rotary evaporator.) The workup as before yielded 5.27 g of **5Lb** (63.4% overall from **3**): 200-MHz ^{1}H NMR ($CDCl_3$) same as **5Db** except that the pinanediol doublet was at δ 1.08 and the multiplets at δ 1.82–2.40, 3.42–3.66, and 3.87–3.96 were somewhat altered and more widely split; mass spectrum ($C_{28}H_{36}DBO_5$) calcd m/e 465.2797, found 465.2780.

(1*R*,2*R*)-2-(Benzyloxy)-3-[(*p*-methoxybenzyl)oxy]propanol-*1-d* (6Lb). The procedure was the same as that used for preparation of **6Db** except that **5Lb** was used in place of **5Db**: 95–100% isolated; 200-MHz ^{1}H NMR ($CDCl_3$) was the same as **6Db** except that the CH_2CH-(OBn)CHD multiplet was shifted to δ 3.56–3.73; mass spectrum ($C_{18}H_{21}DO_4$) calcd m/e 303.1581, found 303.1541.

(1*R*,2*R*)-1,2-Bis(benzyloxy)-3-[(*p*-methoxybenzyl)oxy]propane-*1-d* (8Lb). The procedure was the same as that used for preparation of **8Db** except that **6Lb** was used in place of **6Db**: 89%; 200-MHz ^{1}H NMR was the same as **8Db** except that the multiplet arising from ROCH_2CH-(OBn)CHDOBn was shifted to δ 3.57–3.66; mass spectrum ($C_{25}H_{27}DO_4$) calcd m/e 393.2050, found 393.2137.

(2*S*,3*R*)-2,3-Bis(benzyloxy)propanol-*3-d* (8Lc). Oxidation of **8Lb** with DDQ was carried out under the same conditions used to convert **8Db** to **8Dc**: 89%; 200-MHz ^{1}H NMR of **8Lc** was the same as **8Dc** except that the multiplet assigned to HOCH_2CH(OBn)CHDOBn was shifted to δ 3.57–3.81; mass spectrum ($C_{17}H_{19}DO_3$) calcd m/e 273.1475, found 273.1228.[28]

(2*R*,3*R*)-2,3-Bis(benzyloxy)propanal-*3-d* (9L). Oxidation of **8Lc** was carried out under the same Swern conditions used for conversion of **8Dc** to **9D**: 200-MHz ^{1}H NMR of **9L** was the same as **9D** except that the multiplet assigned to BnOCHD was shifted to δ 3.73–3.83 and the doublet of doublets corresponding to BnOCHD(CH(OBn)CHO was at δ 3.96 with J = 1.1 Hz and the altered value 4.0 Hz; mass spectrum ($C_{17}H_{17}DO_3$) calcd m/e 271.1318, found 271.1453.[28]

(1*S*,2*S*)-Glycerol-*1-d* (7D). A solution of 2.7 g of dibenzyl ether **6Da** in 10 mL of 95% ethanol was hydrogenated with 150 mg of 10% palladium on charcoal for 18 h at 1 atm. Filtration and concentration yielded 0.88 g (96%) of (1*S*,2*S*)-glycerol-*1-d* (**7D**): $[\alpha]^{21}_{546}$ −0.27° (c 2, H_2O); average of 200- and 300-MHz ^{1}H NMR (D_2O, HDO = δ 4.700 as internal standard) δ 3.403 (d of unresolved t's, $J \sim$ 1.4 Hz, J = 6.4–6.5 Hz, H_D), 3.428 ± 0.008 (dd, 1, J = 6.48 ± 0.07 Hz, J = 11.70 ± 0.03 Hz, H_A), 3.508 ± 0.006 (dd, 1, J = 4.36 ± 0.04 Hz, J = 11.70 ± 0.03 Hz, H_B), 3.637 ± 0.007 (m, 1, J = 6.48 ± 0.07 Hz, J = 4.36 ± 0.04 Hz, H_C); mass spectrum ($C_3H_7DO_3$) calcd m/e 93.0536, found 93.0552.

(1R,2*S*)-Glycerol-*1-d* (7L). This compound was prepared from dibenzyl ether **6La** in the same manner as **7D** from **6Da**: 96%; $[\alpha]^{21}_{546}$ −0.86° (c 2, H_2O); ^{1}H NMR of **7L** had the same δ and J values as **7D** except δ 3.403 was absent, and it was replaced by δ 3.495 (d of broad peaks, 1, J = 4.2–4.3 Hz, H_D); mass spectrum ($C_3H_7DO_3$) calcd m/e 93.0536, found 93.0519.

(1*S*,2*S*)-1,2-Bis(benzyloxy)-3-(triphenylmethoxy)propane-*1-d* (8Dd). A solution of 300 mg (1.02 mmol) of dibenzyl ether **8Dc** in 1 mL of anhydrous pyridine and 2 mL of THF was treated with 375 mg (1.34 mmol) of chlorotriphenylmethane and stirred at 80 °C for 18 h. The mixture was cooled, quenched with ice-cold water, and extracted with dichloromethane. The organic phase was washed with saturated sodium chloride, dried over sodium sulfate, and concentrated and the pyridine removed by codistillation with toluene to leave a yellow solid that was chromatographed with 4:1 light petroleum ether/diethyl ether to give a colorless solid (0.460 g, 89%) that was recrystallized from pentane: mp 84 °C (lit.[18] mp 84–84.5 °C); $[\alpha]^{21}_{546}$ +9.14° (c 0.7, $CHCl_3$) [lit.[18] (not deuterated) $[\alpha]^{21}_D$ +9.2° (c 1, $CHCl_3$)]; 200-MHz ^{1}H NMR ($CDCl_3$) δ 3.27 (d, 2, J = 5.1 Hz, CH_2OCPh$_3$), 3.61 (d, 1, J = 5.8 Hz, CHD), 3.76 (dt, overlapped into a quartet, 1, J = 5.1 and 5.8 Hz, HDCCHOCH$_2$Ph), 4.51 (s, 2, PhCH_2), 4.65 and 4.73 (AB, J = 11.4 Hz, 2, PhCH_2), 7.17–7.47 (m, 25, C$_6H_5$).

(1*R*,2*R*)-1,2-Bis(benzyloxy)-3-(triphenylmethoxy)propane (8Ld). The dibenzyl ether **8Lc** was treated in the same manner as **8Dc** (0.400g, 77%) and was recrystallized from pentane: mp 84 °C; $[\alpha]^{21}_{546}$ +10.72° (c 0.55, $CHCl_3$); 200-MHz ^{1}H NMR ($CDCl_3$) δ 3.27 (d, 2, J = 5.0 Hz, CH_2OCPh$_3$), 3.63 (d, 1, J = 4.5 Hz, CHD), 3.76 (dt, overlapped into a quartet, 1, J = 5.0 and 4.5 Hz, HDCCHOCH$_2$Ph), 4.51 (s, 2, PhCH_2), 4.62 and 4.70 (AB, J = 11.5 Hz, 2, PhCH_2), 7.17–7.47 (m, 25, ArH).

(*S*)-Pinanediol (1*R*)-[1,2-Bis(benzyloxy)ethyl]boronate (3a). (*S*)-Pinanediol [(benzyloxy)methyl]boronate (**1a**)[11] was used in place of **1b** in the same procedure used for the preparation of **3b**, except that only 1.9 equiv of zinc chloride was used for the preparation of **2a**.

(*S*)-Pinanediol (1*S*,2*S*)-[2,3-Bis(benzyloxy)-1-bromopropyl]boronate (4Da). The same procedure used for the preparation of **4Db** was used, but with **3Da** in place of **3Db**.

(*S*)-Pinanediol [(1*R*,2*R*)-2,3-Bis(benzyloxy)propyl]boronate-*1-d* (5Da). The procedure was the same as for the preparation of **5Db** from **4Db**: overall yield from **3a**, 56% of **5Da**; 200-MHz ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 3, CH_3), 1.10 (d, 1, J = 10.7 Hz, pinyl CH), 1.26 (s, 3, CH_3), 1.32 (s, 3, CH_3), 1.82–2.33 (m, 6, pinyl CH + CHDB), 3.55 (m, 2, J = 4.8 Hz, J = 6.0 Hz, BnOCH_2), 3.94 (m, 1, J = 4.8, J = 6.0 Hz, CH$_2$CH(OBn)CHD), 4.22 (dd, 1, J = 1.8 Hz, J = 8.6 Hz, pinyl CHOB), 4.49 and 4.55 (AB, J = 12.3 Hz, 2, PhCH_2), 4.55 (s, 2, PhCH_2), 7.24–7.39 (m, 10, C$_6H_5$). Anal. Calcd for $C_{27}H_{34}DBO_4$: C, 74.48; H, 8.13; B, 2.48. Found: C, 74.59; H, 8.27; B, 2.62.

(1*S*,2*R*)-2,3-Bis(benzyloxy)propanol-*1-d* (6Da). The procedure was the same as for preparation of **6Db** from **5Db** except **5Da** was used: 98% isolated; 200-MHz ^{1}H NMR ($CDCl_3$) δ 3.60 (m, 2, OCH_2CH(OBn)-CHDO), 3.64 (br, 1, CH(OBn)CHDO), 3.66 (m, 1, OCH$_2$CH(OBn)-CHDO), 4.51 (s, 2, PhCH_2), 4.59 and 4.69 (AB, J = 11.8 Hz, 2, PhCH_2), 7.23–7.35 (m, 10, C$_6H_5$). Anal. Calcd for $C_{17}H_{19}DO_3$: C, 74.70; H, 7.42. Found: C, 74.69; H, 7.57.

(*S*)-Pinanediol [(1*S*,2*S*)-1-Bromo-2,3-bis(benzyloxy)propyl]boronate-*1-d* (4La). The procedure was the same as for the preparation of **4Lb** except that **3La** was used instead of **3Lb**.

(*S*)-Pinanediol [(1*S*,2*R*)-2,3-bis(benzyloxy)propyl]boronate-*1-d* (5La) was prepared according to the same procedure as **5Lb** except that **4La** was used instead of **4Lb**. The overall yield from **3a** was 61%: 200-MHz ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 3, CH_3), 1.10 (d, 1, J = 10.7 Hz, pinyl CH), 1.26 (s, 3, CH_3), 1.32 (s, 3, CH_3), 1.82–2.33 (m, 6, pinyl CH + CHDB), 3.55 (m, 2, J = 4.8 Hz, J = 5.8 Hz, BnOCH_2), 3.94 (m, 1, J = 4.8, J = 5.8 Hz, J = 7.8 Hz, CH$_2$CH(OBn)CHD), 4.22 (dd, 1, J = 1.8 Hz, J = 8.6 Hz, pinyl CHOB), 4.52 and 4.59 (AB, J = 12.3 Hz, 2, PhCH_2), 4.65 (s, 2, PhCH_2), 7.23–7.35 (m, 10, C$_6H_5$). Anal. Calcd for $C_{27}H_{34}BDO_4$: C, 74.48; H, 8.13; B, 2.48. Found: C, 74.50; H, 8.10; B, 2.67.

(1*R*,2*R*)-2,3-Bis(benzyloxy)propanol-*1-d* (6La) was prepared by the same procedure as **6Lb** except that **5La** was used instead of **5Lb**: 100% isolated; 200-MHz ^{1}H NMR ($CDCl_3$) δ 3.59 (m, 2, OCH_2CH(OBn)-CHDO), 3.64 (m, 1, OCH$_2$CH(OBn)CHDO), 3.67 (br, 1, CH(OBn)-CHDO), 4.51 (s, 2, PhCH_2), 4.57 and 4.67 (AB, J = 11.8 Hz, 2, PhCH_2), 7.23–7.35 (m, 10, C$_6H_5$). Anal. Calcd for $C_{17}H_{19}DO_3$: C, 74.70; H, 7.42. Found: C, 74.58; H, 7.39.

Potassium triisopropoxyborohydride-*d* (KIPBD) was prepared according the procedure for the corresponding hydride[17] except that potassium deuteride was used instead of potassium hydride and longer refluxing was required. Following the reaction, ^{11}B NMR indicated >95% completion by the end of 5 days; 64-MHz ^{11}B NMR δ 6.06 [lit.[17] (^{1}H analogue) δ 6.1].

(S)-Pinanediol [(1R,2R)-2-(Benzyloxy)-3-hydroxypropyl]boronate-1-d (5Dc). A solution of 0.6 g (1.3 mmol) of **5Db** in 10 mL of dichloromethane was stirred with 2.5 mL of water, and 0.36 g (1.56 mmol) of 2,3-dichloro-5,6-dicyanoquinone was added. After being stirred for 2.5 h at 20-25 °C, the mixture was filtered through a celite pad with the aid of more dichloromethane. The dichloromethane phase was stirred with an equal volume of water for 0.5 h, then washed with water and saturated sodium chloride, and then concentrated. The residue was chromatographed on silica with 2:1 diethyl ether/light petroleum ether to yield 0.493 g (90%) of **5Dc**: 200-MHz ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 3, CH_3), 1.10 (d, 1, J = 10.7 Hz, pinyl CH), 1.26 (s, 3, CH_3), 1.32 (s, 3, CH_3), 1.82-2.33 (m, 6, pinyl CH + CHDB), 3.58-3.83 (m, 3, HOCH_2CH(OBn)CHD), 4.27 (dd, 1, J = 1.9 Hz, J = 8.0 Hz, pinyl CHOB), 4.64 (s, 2, PhCH_2), 7.23-7.35 (m, 5, C_6H_5). Anal. Calcd for $C_{20}H_{28}DBO_4$: C, 69.58; H, 8.50; B, 3.13. Found: C, 69.34; H, 8.72; B, 2.78.

(S)-Pinanediol [(1R,2R)-2-(Benzyloxy)-3-oxopropyl]boronate-1-d (10D). A 190-mg (0.55-mmol) sample of **5Dc** was oxidized under Swern conditions (oxalyl chloride, triethylamine, dimethyl sulfoxide).[23] Flash chromatography on silica with 1:1 diethyl ether/light petroleum ether yielded 170 mg (91%) of **10D**: 200-MHz ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 3, CH_3), 1.10 (d, 1, J = 10.7 Hz, pinyl CH), 1.26 (s, 3, CH_3), 1.32 (s, 3, CH_3), 1.82-2.33 (m, 6, pinyl CH + CHDB), 4.05 (dd, 1, J = 1.7 Hz, J = 7.4 Hz, CH(OBn)), 4.29 (dd, 1, J = 1.8 Hz, J = 8.6 Hz, pinyl CHOB), 4.64 (s, 2, PhCH_2), 7.23-7.35 (m, 5, C_6H_5), 9.67 (d, 1, J = 1.7 Hz, CHO). Anal. Calcd for $C_{20}H_{26}DBO_4$: C, 69.98; H, 7.96; B, 3.15. Found: C, 69.63; H, 8.50; B, 2.70.

Detritylation of (1S,2R)-1,2-Bis(benzyloxy)-3-(triphenylmethoxy)-propane-1-d (8Dd). A solution of 120 mg (0.2 mmol) of **8Dd** in 15 mL of methanol, 5 mL of ether, and 0.5 mL of water was stirred with 0.5 g of Amberlyst 15 sulfonic acid resin overnight at 35-40 °C.[31] Flash chromatography on silica with 1:1 ether/light petroleum ether yielded 50 mg (92%) of **8Dc**, confirmed by ^{1}H NMR. An alternative detritylation of **8Ld** was discovered accidentally. A solution of **8Ld** ($[\alpha]^{21}_{546}$ +10.72° (c 0.554, $CHCl_3$ + 0.6% EtOH)) was kept 1 week at ~20 °C. The rotation changed to α^{21}_{546} -0.059°, α^{21}_{577} -0.048°, calculated $[\alpha]^{21}_{546}$ -20.1°, $[\alpha]^{21}_{577}$ -16.3° if the **8Ld** is assumed completely detritylated to **8Lc** [lit.[19] $[\alpha]^{25}_{D}$ -17.2° (c 1, $CHCl_3$)]. This material had the same TLC retention time as **8Lc**, plus a mobile component assumed to be unchanged **8Ld**.

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Atropisomers of 1,4-Benzodiazepines. Synthesis and Resolution of a Diazepam-Related 1,4-Benzodiazepine

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Abstract: The resolution of 7-chloro-1,3-dihydro-1-(1,1-dimethylethyl)-5-phenyl-2H-1,4-benzodiazepin-2-one (**7**), the N^1-*tert*-butyl analogue of diazepam, is described. Compound **7** does not contain an asymmetric center but exists as a mixture of conformational isomers. The resolution of **7** was effected by resolving the 4,5-dihydro form of **7**, compound **8**, which now contains two elements of asymmetry. The resulting enantiomers **9** and **10** were then oxidized to reintroduce the 4,5 double bond, which removed the center of asymmetry and led to the enantiomers of **7**, compounds **11** and **12**. The absolute configurations of compounds **10** and **12** were determined by single-crystal X-ray analysis. The interaction of the two enantiomers **11** and **12** with the benzodiazepine receptor in a binding assay showed that the active conformer has the R (3-methylene group exo) configuration. Attempts to resolve the 2′-chloro and 2′-fluoro analogues of **7** were not successful. On the basis of molecular mechanics calculations, the barrier to inversion of **22** (the 2′-chloro analogue) was determined to be less than that found for compound **7**. Compounds **11** and **12** represent the first examples of optically active 1,4-benzodiazepines whose asymmetry is due only to conformational elements.

Since the introduction of the first 1,4-benzodiazepine, chlordiazepoxide (**1**), in 1960, the 1,4-benzodiazepines[1] have become the drugs of choice for the treatment of anxiety, sleep disorders, status epilepticus, and other convulsive disorders. In addition, they are also used as muscle relaxants, for alleviation of panic attacks, and as induction agents in anesthesiology. The discovery[2,3] in 1977 of specific, high-affinity receptors in mammalian brain tissue for 1,4-benzodiazepines has led to a useful screening procedure for identifying compounds that interact with the receptor. Many of these compounds are non-benzodiazepines[4] and in vivo manifest pharmacological effects similar to those of the benzodiazepines.

Many reports[5] have appeared that attempt to correlate structure with binding affinity at the benzodiazepine receptor from both

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