Directed Chiral Synthesis by Way of α-Chloro Boronic Esters

Donald S. Matteson,* Rahul Ray, Richard R. Rocks, and David J. Tsai

Department of Chemistry, Washington State University, Pullman, Washington 99164

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Homologation of (+)-pinanediol boronic esters, $RBO_2C_{10}H_{16}$, with (dichloromethyl)lithium has yielded αS α-chloro boronic esters, $RCHClBO_2C_{10}H_{16}$, in diastereomeric purities ranging from 74% (R = CH_3) to 98% (R = C_6H_5), with typical alkyl groups (*n*-butyl, cyclohexyl) ranging from 83 to 90%. Grignard or lithium reagents replace the α-chloro function by alkyl with inversion. Peroxidic oxidation of the resulting boronic esters proceeds with retention of configuration to yield alcohols of known rotation and absolute configuration. Purification of (+)-pinanediol to 100% enantiomeric excess (ee) was accomplished by way of recrystallization of sodium bis(pinanediol) borate, which on acidification yields a 1:1 mixture of pinanediol and pinanediol boric acid ester, not freed from boron but used directly to make pinanediol boronic esters of 100% ee. The synthetic utility of these processes was demonstrated by highly stereoselective and efficient syntheses of (2*S*,3*S*)-3-phenyl-2-butanol and (2*R*,3*S*)-3-phenyl-2-butanol. The latter synthesis involved construction of the first chiral center from (+)-pinanediol phenylboronate, cleavage of the (+)-pinanediol with boron trichloride and replacement by (−)-pinanediol, and then introduction of the second chiral center.

Introduction

In the preceding article, we have described the efficient homologation of boronic esters with (dichloromethyl)lithium to yield α-chloro boronic esters.[1] The chlorine is readily replaced by the alkyl group of a Grignard reagent or by a variety of other nucleophiles, and the reaction sequence is compatible with typical protected functionality. The resulting boronic esters can be further homologated, allowing the rapid and efficient assembly of highly branched structures, except that without chiral control, hopeless mixtures of diastereomers will result. This paper describes a highly promising solution to this problem and outlines a fundamentally new approach to chiral synthesis that should be applicable to a wide variety of structural types.

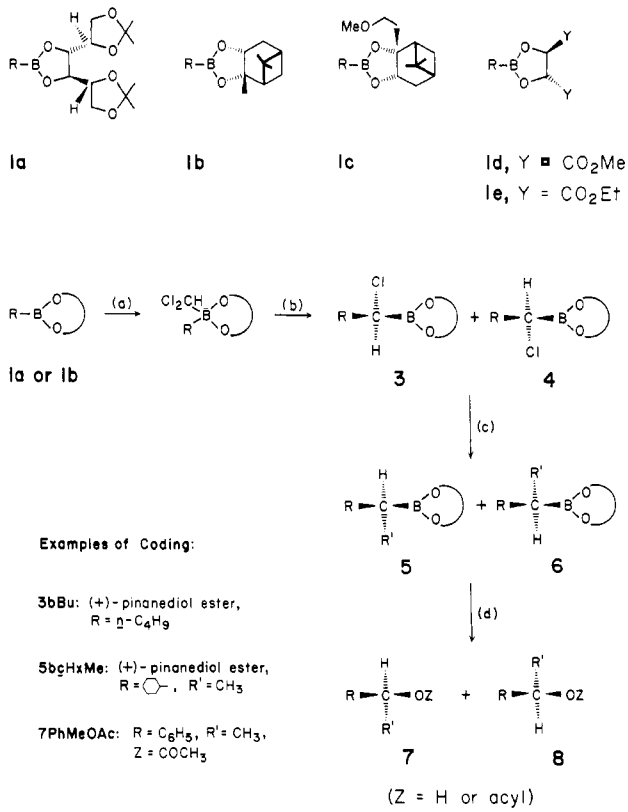
It should be noted that, in the time since our preliminary communication,[2] we have already discovered a significant improvement in the experimental procedure involving zinc chloride catalysis[3] and that any future synthetic applications will naturally incorporate this improvement.

The present work began with a search for useful chiral directing groups with which to esterify boronic acids. Because the rigidity of cyclic structures contributes significantly to control of chirality,[4] and because cyclic boronic esters are more stable toward hydrolysis and generally easier to handle than acyclic boronic esters, our search for directing groups was confined to chiral diols.

Results

Chiral Selectivity. Our approach to determining the chiral selectivity of the homologation process is outlined in Scheme I. Diacetone mannitol[5] butaneboronate (**1a**(Bu)) reacted with (dichloromethyl)lithium in the usual manner[1] to form a mixture of diacetone mannitol (1*S*)- and (1*R*)-1-chloropentane-1-boronates (**3a**(Bu) and **4a**(Bu)). Reaction of an α-halo boronic ester with methyllithium is a boron-assisted nucleophilic displacement,[6] which must proceed with inversion as has been proved experimentally

Scheme I[a]



[a] (a) $LiCHCl_2$, −100 °C; (b) 0–25 °C; (c) R′Li or R′MgBr; (d) $NaBO_3$, acylation of OH by acid anhydride or chloride.

with an analogous α-halo borane system,[7] and therefore **3a**(Bu) must yield **5a**(Bu,Me) and **4a**(Bu) must yield **6a**(Bu,Me). Peroxidic oxidation of boronic esters is required by the mechanism to proceed with retention,[8] as has been demonstrated experimentally,[9] and consequently **5a**(Bu,Me) is converted to (*S*)-2-hexanol (**7**(Bu,Me,H)) and **6a**(Bu,Me) to (*R*)-2-hexanol (**8**(Bu,Me,H)). The absolute configurations and rotations of 2-hexanol and numerous

(1) (a) Matteson, D. S.; Majumdar, D. *Organometallics*, preceding paper in this issue. (b) Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc.* **1980**, *102*, 7588–7590.
(2) Preliminary communication: Matteson, D. S.; Ray, R. *J. Am. Chem. Soc.* **1980**, *102*, 7590–7591.
(3) Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc.* **1983**, *105*, 2077–2078.
(4) Meyers, A. I. *Acc. Chem. Res.* **1978**, *11*, 375–380.
(5) Baer, E.; Fischer, H. O. L. *J. Biol. Chem.* **1939**, *128*, 463–473.
(6) (a) Matteson, D. S.; Mah, R. W. H. *J. Am. Chem. Soc.* **1963**, *85*, 2599–2603. (b) Matteson, D. S. *Acc. Chem. Res.* **1970**, *3*, 186–193.
(7) Midland, M. M.; Zolopa, A. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 248–249.
(8) Kuivila, H. G.; Armour, A. G. *J. Am. Chem. Soc.* **1957**, *79*, 5659–5662.
(9) (a) Kabalka, G. W.; Newton, R. J., Jr.; Jacobus, J. *J. Org. Chem.* **1978**, *43*, 1567–1569. (b) Brown, H. C. "Boranes in Organic Chemistry;" Cornell University Press; Ithaca, NY, 1972; pp 317–409.

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Table I. Diastereoselectivities in the Conversion of (+)-Pinanediol Boronic Esters (1b) to (+)-Pinanediol α-Chloro Boronic Esters (3b and 4b) Measured by Conversion to *sec*-Alkyl Boronic Esters (5b and 6b) and to Optically Active Alcohol Derivatives (7 and 8)

R	3b + 4b, %	R'M	5b + 6b,[a] %	Z of 7 + 8	diastereoselectivity,[b] %
n-C_4H_9	61	CH_3Li	60	COPh	89.3
n-C_4H_9	61	PhMgBr	80	$COCH_3$	90.9
c-C_6H_{11}	67	CH_3Li	69, 66[c]	H	87.6
CH_3	57	PhMgBr	73	$COCH_3$	74.7
Ph	90	CH_3Li[d]	69	$COCH_3$	45.7[d]
Ph		CH_3MgBr	85-87[c]	$COCH_3$	96.8-98.1
CH_2=CH	85	BuMgBr	90[c]	H	good[e]

[a] Based on 3b and 4b except as noted. [b] 100[5b/(5b and 6b)], estimated from rotation of derived 7 and 8, corrected for the use of (+)-pinanediol of 92% ee for all entries except the second example of R = PH, which utilized (+)-pinanediol of 100% ee. [c] Intermediate 3b and 4b not isolated, yield based on 1b. [d] The 3b(Ph) and 4b(Ph) was kept in the original reaction mixture ~1 day before distillation and treatment with CH_3Li. When 3b(Ph) was kept at 0 °C for 2 h and treated in situ with CH_3Li, the diastereoselectivity was 94.8%. [e] 104% based on literature rotation, which is presumed to be erroneous.

related alcohols and derivatives are well established.[10] (*S*)-2-Hexanol was obtained in 36% enantiomeric excess (ee). This modest success was followed by total disappointment when diacetone mannitol phenylboronate (**1a**(Ph)) led to racemic 1-phenylethanol (7(Ph,Me,H) and 8(Ph,Me,H)).

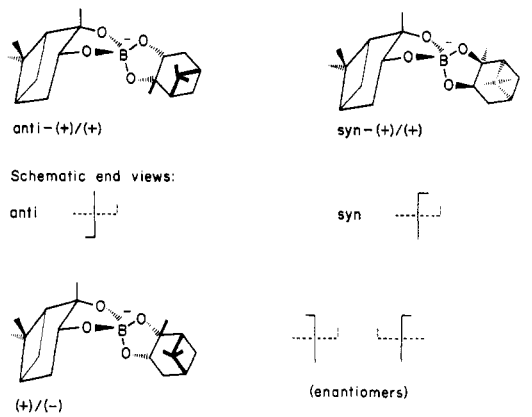
Attempted reaction of nopol methyl ether diol[11] butaneboronate (**1c**(Bu)) with (dichloromethyl)lithium failed, leaving most of the **1c**(Bu) unchanged. Attempted reactions of tartrate esters (**1d**(Bu) and **1e**(Bu)) also failed, with formation of dark, high boiling byproducts and recovery of ~60% of the **1d**(Bu) or **1e**(Bu).

(+)-Pinanediol[11] boronic esters (**1b**) proved to have the right balance of steric factors to allow reasonably efficient homologation and provide generally good chiral control. For example, (+)-pinanediol butaneboronate (**1b**(Bu)), 92% ee, was converted to (*S*)-2-hexyl benzoate (7(Bu,Me,COPh)), 72% ee, corresponding to a diastereomer ratio (**5b**(Bu,Me)/**6b**(Bu,Me)) of 89/11 when the optical purity of the pinanediol is taken into account. Percentages of the major diastereomer measured in this manner are summarized in Table I.

Application of the standard reaction conditions[1] to (+)-pinanediol phenylboronate (**1b**(Ph)) led to a slight preponderance of the "wrong" isomer, (*R*)-1-phenylethyl acetate (8(Ph,Me,Ac)). At this point, it occurred to us that the reactive benzylic α-chloro boronic ester (**3b**(Ph)) might be subject to epimerization by S_N2 attack of the lithium chloride generated in the rearrangement of the intermediate borate complex (**2b**(Ph)) to the product (**3b**(Ph)). We therefore tried shorter times and lower temperatures for the rearrangement of **2b**(Ph) and found 1 h at 0 °C to be sufficient. Exposure to lithium chloride was further minimized by immediate treatment of the **3b**(Ph) in situ with methylmagnesium bromide to form (+)-pinanediol (1*S*)-1-phenylethaneboronate (**5b**(Ph,Me)) in 97–98% diastereomeric purity and high yield. Optically pure (+)-pinanediol (see following section) was used, and the resulting (*S*)-1-phenylethyl acetate (7(Ph,Me,Ac) had 93.7–96.1% ee.

The best conditions found for the preparation of **3b**(Ph) were used to convert (+)-pinanediol vinylboronate (**1b**(Vi)) (92% ee) to the (3*S*)-3-chloro-1-propene-3-boronate (**3b**(Vi)), which with butylmagnesium bromide yielded **5b**(Vi,Bu), which was oxidized to (*S*)-1-hepten-3-ol (7(Vi,Bu,H) having 107% of 92% of the literature rotation, which is presumed to be erroneous.

Scheme II



Failure was encountered in several attempts to homologate (+)-pinanediol (benzyloxy)methaneboronate (**1b**(Ph,CH_2,CH_2)).

Optically Pure Pinanediol Boronates. Oxidation of (+)-pinanediol (2*S*)-hexane-2-boronate (**5b**(Bu,Me)) with sodium perborate in aqueous tetrahydrofuran (THF) resulted in formation of a precipitate of sodium bis[(+)-pinanediol] borate (dihydrate). Because the borate anion incorporates two molecules of pinanediol, different diastereomers arise in the pairing of (+) with (+)-pinanediol and of (+) with (-)-pinanediol. The best commercially available (+)-α-pinene at an affordable price is about 92% ee. Statistical pairing of the (+) and (-) isomers would yield 95.84% (+)/(+), 4% (+)/(-), and only 0.16% (-)/(-) salt, and the pure (+)/(+) isomer should be readily obtainable by recrystallization.

Unfortunately, the situation is complicated by the chirality of the boron atom in the borate, as shown in Scheme II. The (+)/(+) borate can exist in two forms that are geometrical isomers. The (+)/(-) borate consists of a pair of enantiomers at boron.

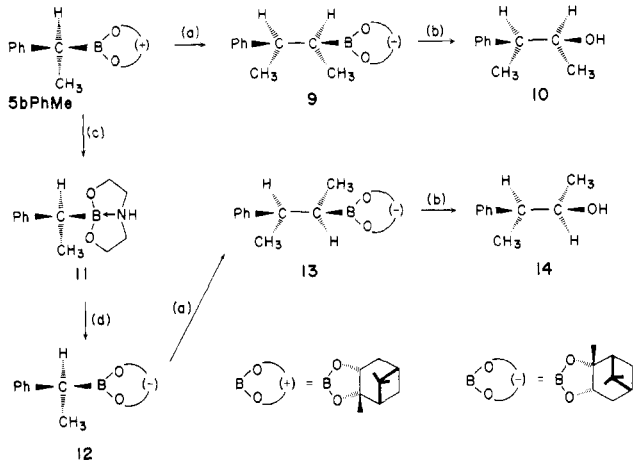
Because of the uncertainty regarding the geometrical isomers of sodium bis[(+)-pinanediol] borate as well as difficulty in freeing it from sodium borate, rotation could not be considered a reliable guide to the enantiomeric purity of the (+)-pinanediol bound in this salt. The rotation of (+)-pinanediol is low[12] and solvent dependent (positive in toluene, negative in methanol), and furthermore, acidification of sodium bis[(+)-pinanediol] borate yielded a 1:1 mixture of (+)-pinanediol and (+)-pinanediol

(10) Jacques, J.; Gros, C.; Bourcier, S. "Absolute Configurations of 6000 Selected Compounds with One Asymmetric Carbon Atom"; Kagan, H. B., Ed.; George Thieme Verlag: Stuttgart, 1977; Vol. 4.

(11) (a) Ray, R.; Matteson, D. S. *J. Indian Chem. Soc.* **1982**, *59*, 119–123. (b) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, *21*, 449–450.

(12) Schmidt, H. *Chem. Ber.* **1960**, *93*, 2485–2490.

Scheme III[a]



[a] (a) $LiCHCl_2$, CH_3MgBr; (b) $NaBO_3$; (c) BCl_3, H_2O, $(HOCH_2CH_2)_2NH$; (d) H^+, (-)-pinanediol.

boric acid, an unusually stable boric acid ester. Fortunately, this mixture behaves much like pinanediol as a reagent for esterifying boronic acids. The only failure we have encountered is that interchange with pinacol boronic esters does not utilize the boric acid bound portion of the pinanediol, evidently because the rate or equilibrium constants for generating free pinanediol and free boronic acid in contact with water are too low.

In view of the foregoing, the enantiomeric excess of the (+)-pinanediol was estimated from the rotation of its phenylboronate ester (**1b**(Ph)). Three crystallizations of the sodium bis(pinanediol) borate were generally sufficient to raise the ee to within experimental error of 100%. When (-)-pinanediol, 82% ee, was used, the first crystallization brought the ee up to 94%.

In more recent work, we have used potassium bis(pinanediol) borate (monohydrate) in place of the sodium salt.[13] On the basis of work with the potassium salt, it appears that the limit of recovery of optically pure pinanediol/pinanediol boric acid is about 65%, as if the remainder is bound in a geometrical isomer that is highly soluble and difficult to crystallize. The potassium salt shows no change in rotation overnight in neutral methanol.

Synthesis of the Diastereomers of 3-Phenyl-2-butanol. This diastereomeric pair was chosen for demonstration of the utility of our new chiral synthesis because Cram had fully characterized these compounds, including assignments of absolute configuration, for use in his classical studies of nonclassical ions.[14]

Conversion of (+)-pinanediol 1-phenylethane-1-boronate (**5b**(Ph,Me)) to *erythro* (2*S*,3*S*)-3-phenyl-2-butanol (**10**) was a straightforward extension of the established homologation sequence (Scheme III). The intermediate α-chloro boronic esters were not isolated but converted in situ to the *sec*-alkyl boronic esters by treatment with methylmagnesium bromide. The overall contained yield of **10** based on (+)-pinanediol phenylboronate (**1b**(Ph)) was 67%, and the diastereomeric purity of **10** was 94% (±1%) on the basis of 90-MHz proton NMR analysis with the aid of $Eu(fod)_3$ shift reagent, which shifts the most upfield doublet of the threo isomer to higher field than that of the erythro isomer. (A more conservative estimate of diastereomeric purity reported previously,[2] 90%, was based largely on 60-MHz NMR and optical rotation data.) The rotations of **10** and its 3-nitrophthalate ester were consistent with the assigned 2*S*,3*S* configuration.[14] Deviations from the reported rotations were within the range expected from the 2*S*,3*R* and 2*R*,3*S* isomer content estimated from the NMR and other data.

Conversion of **5b**(Ph,Me) to (2*R*,3*S*)-3-phenyl-2-butanol (**14**) requires installation of the second chiral center in the opposite sense to the first one. Two approaches were tried. Double inversion is possible in principle, but an attempt to convert **3b**(PhMeCH) to the corresponding α-hydroxy boronic ester and then to the methanesulfonate and finally to displace the methanesulfonate by methylmagnesium bromide failed. The unstable intermediates were not purified, and the cause of the failure is uncertain.

The alternative route was to remove the (+)-pinanediol from **5b**(Ph,Me) and replace it with (-)-pinanediol to form **12**. The difficulty was that pinanediol boronic esters are unusually resistant to hydrolysis or transesterification. Treatment with diethanolamine in ether/2-propanol is known to suffice for the conversion of pinacol boronates to the chelated diethanolamine boronates,[15] but refluxing in butanol was required in order to effect the same transformation of pinanediol benzeneboronate (**1b**(Ph)), and even these conditions failed to affect the more sterically hindered 1-phenylethane-1-boronate (**5b**(Ph,Me)). The higher boiling solvents 1-octanol and ethylene glycol did not help, and heating **5b**(Ph,Me) in neat diethanolamine at 180 °C resulted in apparent deboronation.

Acidic destruction of the (+)-pinanediol, presumably by pinacol rearrangement, was then attempted. There was no apparent degradation of **5b**(Ph,Me) on treatment with 2 M sulfuric acid[15] for a 0.5 h at 100 °C. However, treatment of **5b**(Ph,Me) with liquid boron trichloride initially at -78 °C, followed by addition of dichloromethane and warming to room temperature, resulted in cleavage of the pinanediol. (However, treatment of **5b**(Ph,Me) with 1 M boron trichloride in dichloromethane failed.) Aqueous workup led to the boronic acid, which was not purified but was treated with diethanolamine to yield the crystalline chelate ester **11**, from which the boronic acid is easily regenerated by treatment with 2 M aqueous hydrochloric acid.[15] The boronic acid derived from recrystallized **11** was shown to be optically pure by oxidation to 1-phenylethanol. Treatment with (-)-pinanediol/pinanediol boric acid (100% ee) yielded **12**.

Homologation of (-)-pinanediol (1*S*)-1-phenylethane-1-boronate (**12**) to the (2*R*,3*R*)-3-phenylbutane-2-boronate (**13**) and oxidation to (2*R*,3*S*)-3-phenyl-2-butanol (**14**) proved straightforward. On the basis of 90-MHz NMR analysis, the threo content of **14** was 96% (±1%). The rotations of **14** and its 3-nitrophthalate were consistent with the assigned 2*R*,3*S* configuration,[14] allowing for the presence of some 2*S*,3*S* and 2*R*,3*R* isomer.

Discussion

It is not obvious why the chiral preference is that observed in the rearrangement of (+)-pinanediol borates (**2b**) to αS α-chloro boronic esters (**3b**), let alone why the selectivity should be so high, though pinene derivatives do have a history of being excellent chiral directing groups.[16,17]

(13) Sadhu, K. M. Ph.D. Thesis, Washington State University, 1983, pp 14–15. The potassium salt may be recrystallized by dissolving in the minimum amount of hot 50% aqueous ethanol and precipitating with acetone. Details are still evolving and will be published in a future article.

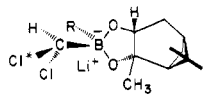
(14) (a) Cram, D. J. *J. Am. Chem. Soc.* **1949**, *71*, 3863–3870. (b) Cram, D. J. *Ibid.* **1952**, *74*, 2149–2151.

(15) Matteson, D. S.; Arne, K. H. *Organometallics* **1982**, *1*, 280–288.

(16) (a) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 486–487. (b) Brown, H. C. "Hydroboration"; W. A. Benjamin: New York, 1962; pp 205–208. (c) Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1977**, *99*, 5211–5213.

(17) The absolute configuration of α-pinene has been established: Brewster, J. H. *J. Am. Chem. Soc.* **1959**, *81*, 5483–5493.

The five-membered dioxaborolane ring must have a chiral twist imposed by the pinanyl group. The possibility having the fewer axial substituents in the pinanyl ring is illustrated by structure **15**. The same chiral twist would clearly be the favored one in the case of diacetone mannitol boronic esters (**1a**), which also yield αS α-chloro boronic esters (**3a**).[18]



15

Whether the favored conformation of **2b** is **15** or the alternative having the CH_3 group axial, the chlorine that is displaced from the prochiral $CHCl_2$ group preferentially is the one that is starred in **15**, and the remaining chlorine must be pointed toward the side of the structure that appears to be cluttered with more substituents. The lithium cation may play a significant role in the transition state, perhaps linking the departing chloride and one or both of the oxygen atoms by electrostatic interactions.

It is assumed that the chlorine is displaced with inversion in the normal manner[6,7] and that the $CHCl_2$ group has been added to the (+)-pinanediol boronic ester (**1b**) exclusively from the side illustrated in **15**, which is by far the less sterically hindered based on inspection of models. When (+)-pinanediol dichloromethaneboronate (**1b**-(Cl_2CH)) is treated with a Grignard or lithium reagent, stereochemically different (and less useful) results follow,[19] supporting the idea that **2b** is essentially a single diastereomer at boron (**15**).

It may be noted that the chiral selectivity of this process, in which the chiral selection occurs at the point of displacing one of the two chlorines from the prochiral $CHCl_2$ group, is much greater than in the homologation of a (+)-pinanediol boronic ester with [chloro(trimethylsilyl)-methyl]lithium, where the chiral selection occurs at the point of adding the lithium reagent to the boronic ester.[20]

The dramatic improvement in yields and diastereoselectivities recently achieved by the use of zinc chloride catalysis of the rearrangement of **2** to **3** render the uncatalyzed process described in the present paper obsolete,[3] except perhaps where R = phenyl, vinyl, or other group of similarly high migratory aptitude. Even where R = Ph, a number of attempts to purify **3b**(Ph) failed until a stable, crystalline sample was obtained from a preparation in the presence of zinc chloride.[21] The observed rates of epimerization of **3b**(Bu) and **3b**($PhCH_2$) are sufficient to account for essentially all of the observed lack of stereospecificity in the uncatalyzed rearrangements.[21] The preparations described in the present article may be updated merely by adding 0.5–0.9 mol of zinc chloride to the cold **2b**.[3]

We conclude that the homologation of pinanediol boronic esters (**1b**) with (dichloromethyl)lithium to form α-chloro boronic esters (**3b**) provides a new and potentially broadly useful method of directed chiral synthesis. Adjacent chiral centers can be assembled with a high degree of stereoselectivity, independently of any already existing chirality. Both enantiomers of pinanediol are readily accessible in optically pure form, and one may be cleaved from boron and replaced by the other, which places the absolute configuration of each chiral center under the control of the chemist.

Experimental Section

General Data. The preceding paper describes the general handling of organometallic reagents and anhydrous solvents with strict exclusion of air and water.[1a] Proton NMR spectra were measured with a Varian EM360 at 60 MHz, a Brucker WH 90 at 90 MHz, or a Nicolet NT 200 at 200 MHz and are referred to internal tetramethylsilane. Optical rotations given as "$[\alpha]^{20}_D$" were measured with a venerable Rudolph visual polarimeter accurate to ±0.02°. Rotations described as "$[\alpha]^{23}_{546}$" were measured at room temperature with a Jasco DIP-181 automatic polarimeter with digital readout to 0.001°; "$[\alpha]^{24.8}_{546}$" indicates a thermostated cell. Melting points were determined in open capillaries with a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were by Galbraith Laboratories, Knoxville, TN.

Pinanediol. Details of the large-scale preparation of this compound have been published elsewhere.[11a] More recent work has suggested that addition of 5–10 mL of triethylamine/mol at the start of the reflux guards against over oxidation without requiring fine tuning of the reflux rate.[22] (+)-α-Pinene, 92% ee, and (−)-α-pinene, 82% ee, were purchased from Aldrich Chemical Company.

Boronic Acids. Benzeneboronic acid and butaneboronic acid were purchased (Aldrich Chemical Co.), and others were synthesized from Grignard reagents by the usual procedure.[23]

Pinanediol Boronic Esters. A solution of pinanediol (which may contain up to 50% pinanediol boric acid if derived from a borate salt) and 1.1 nominal equivalent of the moist boronic acid in ether was stirred 4–21 h at 20–25 °C (though there was no evidence that the reactions are not rapid) and then diluted with an equal volume of petroleum ether. The organic phase was washed with water, dried over magnesium sulfate, and concentrated, and the residue of boronic ester was distilled under vacuum.

(+)-Pinanediol Butaneboronate (1b(Bu)). This compound was prepared by the general procedure from butaneboronic acid: 76%; bp 68–70 °C (0.1 torr); 60-MHz NMR (CCl_4) δ 0.8–2.5 (m, 24, pinanyl with CH_3's at δ 0.85, 1.30, 1.33 + *n*-butyl), 4.25 (dd, 1, CHOB). Anal. Calcd for $C_{14}H_{25}BO_2$: C, 71.50; H, 10.29; B, 4.60. Found: C, 71.30; H, 10.30; B, 4.30.

(+)-Pinanediol Benzeneboronate (1b(Ph)). When prepared by the general procedure from 92% ee (+)-pinanediol and benzeneboronic acid, this compound was a viscous oil: 88% bp 98–100 °C (0.05 torr). Anal. Calcd for $C_{16}H_{21}BO_2$: C, 75.02; H, 8.27; B, 4.22. Found: C, 75.08; H, 8.45; B, 4.09. A sample prepared from optically pure pinanediol boric acid was chromatographed on silica with 3% ether in petroleum ether and sublimed at 0.01 torr: mp 74.5–75.5 °C; $[\alpha]^{25.0}_{546}$ +22.7°, $[\alpha]^{25.0}_{365}$ +56.0° (*c* 2.1, toluene); $[\alpha]^{25.0}_{589}$ +17.8°, $[\alpha]^{25.0}_{546}$ +21.0°, $[\alpha]^{25.0}_{365}$ +52.0° (*c* 4.5, benzene); $[\alpha]^{25.0}_{589}$ +18.1°, $[\alpha]^{25.0}_{546}$ +21.4° (*c* 9.4, benzene); 200-MHz ^1H NMR ($CDCl_3$) δ 0.89 (s, 3, CH_3), 1.22 (d, 1), 1.31 (s, 3, CH_3), 1.49 (s, 3, CH_3), 1.95 (m, 2), 2.20 (m, 2), 2.42 (m, 1), 4.45 (dd, 1, OCH), 7.40 (m, 3, Ar*H*), 7.82 (m, 2, Ar*H*). The 50.3-MHz ^{13}C NMR spectrum was consistent with the assigned structure.

(+)-Pinanediol Cyclohexaneboronate (1b(c-Hx)). This compound was prepared from cyclohexaneboronic acid by the general procedure: 96%; bp 93 °C (0.1 torr); 60-MHz NMR (CCl_4) δ 0.8–2.5 (m, 26, pinanyl with CH_3's at δ 0.87, 1.33, 1.36 + cyclohexyl), 4.23 (dd, 1, OCH). Anal. Calcd for $C_{16}H_{27}BO_2$: C, 73.29; H, 10.38; B, 4.12. Found: C, 73.02; H, 10.33; B, 3.96.

(+)-Pinanediol Methaneboronate (1b(Me)). A solution of 10 g of pinanediol and 4 g of methaneboronic anhydride–pyridine complex[24] in 150 mL of benzene was refluxed 24 h. (No evidence that the reaction is not rapid at room temperature was obtained.) The solution was washed with 1 M hydrochloric acid and then

(18) In addition to the homologation of **1a**(Bu) described in detail in this paper, we have homologated **1a**(Ph,CH_2) and obtained $PhCH_2CHOHCH_3$ having a similar absolute configuration and enantiomeric excess.

(19) Tsai, D. J. S.; Jesthi, P. K.; Matteson, D. S., submitted for publication.

(20) Tsai, D. J. S.; Matteson, D. S. *Organometallics* **1983**, *2*, 236–241.

(21) Matteson, D. S.; Erdik, E. *Organometallics* **1983**, *2*, 1083–1088.

(22) Sadhu, K. M., unpublished observation.

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with water, dried over magnesium sulfate, and distilled: bp 37–41 °C (0.25 torr); 8.7 g (77%); 60-MHz NMR (CCl_4) δ 0.20 (s, 3, BCH_3), 0.8–2.5 (m, with CH_3's at δ 0.85, 1.30, 1.33 + pinanyl), 4.23 (dd, 1, OCH). Anal. Calcd for $C_{11}H_{19}BO_2$: C, 68.08; H, 9.87; B, 5.57. Found: C, 67.88; H, 9.76; B, 5.32.

Sodium Bis[(+)-pinanediol] Borate. A solution of 45.2 g (0.26 mol) of (+)-pinanediol (91.85% ee) in 500 mL of THF was added to a solution of 12.9 g (0.034 mol, 1:2 atom/pinanediol) of sodium borate decahydrate and 3 g (0.075 mol) of sodium hydroxide in 100 mL of water. After the solution was stirred overnight, the two liquid phases were separated, the THF phase was washed once with 50 mL of saturated sodium chloride, and the THF phase was concentrated under vacuum to ~200 mL and kept at 0 °C to complete crystallization. The solid was collected and was recrystallized by dissolving in 150 mL of hot ethanol and initiating crystallization with 5 mL of 2-propanol. The collected sodium bis[(+)-pinanediol] borate dihydrate was dried in air; 30.4 g (56%). Anal. Calcd for $C_{20}H_{38}BNaO_6$: C, 58.83; H, 9.38; B, 2.65; Na, 5.63. Found: C, 59.10; H, 9.09; B, 2.22; Na, 5.64.

Optically Pure (+)-Pinanediol/Pinanediol Borate. A 30-g portion of sodium (+)-pinanediol borate dihydrate suspended in 300 mL of THF at 0 °C was treated with 50 mL of cold 1 M hydrochloric acid. After 1 h at 0–10 °C, the solution was extracted with five 100-mL portions of petroleum ether, the organic phase was dried over magnesium sulfate, and the product was distilled: 22.1 g; bp 90 °C (0.25 mm) (lit.[11] bp 110–116 °C (0.3–1.0 torr)). From the 60-MHz NMR spectrum, this material appeared to be pure pinanediol. However, subsequent investigation has indicated that acid treatment of pinanediol borate salts leaves a substantial portion of the pinanediol boric acid,[25] which has similar physical properties and which converts boronic acids to pinanediol boronic esters under the same conditions as pinanediol itself does. The optical purity was checked by esterification with benzeneboronic acid to form (+)-pinanediol benzeneboronate (**1b**(Ph)), which was distilled, $[\alpha]^{21}_D$ +17.8° (*c* 8, benzene). From the rotation of the α-pinene used in the original preparation, $[\alpha]^{22}_D$ +47.1°, the rotation of (+)-pinanediol benzeneboronate (**1b**(Ph)) from the original pinanediol, $[\alpha]^{22}_D$ +16.1°, and the rotation of pure (+)-α-pinene,[26] $[\alpha]^{22}_D$ +51.28°, the computed optical purity of the purified (+)-pinanediol/pinanediol borate was 101.5%, (±2%). (See preparation of **1b**(Ph) for more accurate rotation data.)

Sodium (−)-Pinanediol Borate (Dihydrate). The procedure described for the (+)-enantiomer was used, starting with (−)-pinanediol of 82% ee. After the first recrystallization from ethanol/2-propanol, the derived (−)-pinanediol benzeneboronate had $[\alpha]^{23}_D$ −16.6° (94.4% ee). After two more recrystallizations, the rotation of the derived benzeneboronate was $[\alpha]^{16}_D$ −17.6° (*c* 8, benzene).

General Procedure for Homologation of Boronic Esters to α-Chloro Boronic Esters. The procedure described in the preceding paper[1a] was used to generate 10 mmol of (dichloromethyl)lithium in 20 mL of THF, and 10 mmol of the boronic ester in 10 mL of THF was injected into the cold mixture. The mixture was allowed to warm to 20–25 °C and stirred 12–20 h, except that (+)-pinanediol (α*S*)-α-chlorobenzylboronate (**3b**(Ph)) was allowed to warm only to 0 °C and kept 1 h at 0 °C before use. Except as noted, the α-chloro boronic esters were not isolated, but the solutions just described were used directly in the next step.

General Procedure for Reaction of α-Chloro Boronic Esters with Grignard or Lithium Reagents. A solution of α-chloro boronic ester (~0.3 M) in THF was cooled to −78 °C, and the equivalent amount of Grignard or lithium reagent was injected into the stirred mixture from a syringe. The mixture was allowed to warm to 20–25 °C and stirred 10–20 h. When lithium reagents were used, the lithium chloride was precipitated by addition of dichloromethane and the filtered solution was distilled under vacuum. When Grignard reagents were used, 10 mL of aqueous 1.2 M hydrochloric acid was added and the product was extracted with ether three portions), dried over magnesium sulfate, and distilled.

General Procedure for the Alkaline Peroxide Oxidation of Boronic Esters. A mixture of the boronic ester (2 mmol), sodium perborate (3 mmol), and sodium hydroxide (2.5 mmol) in 10 mL of water and 15 mL of THF was refluxed under argon for 15 h, cooled to 25 °C, saturated with sodium chloride, extracted with three portions of ether, dried over magnesium sulfate, and distilled under vacuum.

(+)-Pinanediol (*S*)-1-Phenylethane-1-boronate (5b-(Ph_2Me)). Optically pure (+)-pinanediol benzeneboronate (20–30 mmol) was converted to (+)-pinanediol (α*S*)-α-chlorobenzylboronate (**3b**(Ph)) in THF solution by the general procedure, and after the solution had been kept 1 h at 0 °C, it was cooled to −78 °C and treated with an equivalent amount of methyllithium/lithium bromide in ether or methylmagnesium bromide in ether. Reaction time and workup according to the general procedure yielded 85–87% (+)-pinanediol 1-phenylethane-1-boronate: bp 115 °C (0.1 torr); 200-MHz NMR ($CDCl_3$) δ 0.89 (s, 3), 0.94 (d, 1), 1.25 (s, 3), 1.37 (s, 3), 1.39 (d, *J* = 8 Hz, 3, $BCHCH_3$), 1.80 (m, 2), 2.05 (m, 2), 2.30 (m, 1), 2.50 (q, 1, $BCHCH_3$), 4.25 (dd, 1, BOCH), 7.15 (m, 1, Ar*H*), 7.25 (m + s, 4, Ar*H*). The 50.3-MHz ^{13}C NMR spectrum consisted of a pattern characteristic of pinanediol boronic esters, plus a peak at δ 17 ($BCHCH_3$) and a broad peak at δ 25 ($BCHCH_3$), and aromatic C's at δ 125, 128, 128.5, and 145. From the residual peak of pinanediol benzeneboronate (**1b**(Ph)) at δ 135, the content of unchanged **1b**(Ph) was estimated to be 1.7%. This sample, shown to be of 98% diastereomeric purity, had $[\alpha]^{21}_{589}$ +42.4° and $[\alpha]^{21}_{546}$ +50.52°. A sample that had been prepared from (+)-pinanediol of 92% ee was analyzed. Anal. Calcd for $C_{18}H_{25}BO_2$: C, 76.07; H, 8.87; B, 3.80. Found: C, 75.78; H, 9.00; B, 3.54.

Conversion of (+)-Pinanediol (*S*)-1-Phenylethane-1-boronate (5b(Ph,Me)) to (*S*)-1-Phenylethanol (7(Ph,Me,H)) and Its Acetate (7(Ph,Me,Ac)). The general peroxide oxidation procedure was used to convert a portion of the **5b**(Ph,Me) to (*S*)-1-phenylethanol (7(Ph,Me,H)): bp 109–111 °C (30 torr); slight impurity (~2% of 1 H, s) evident at δ 1.65 in the 200-MHz NMR spectrum, not removed by TLC and bulb-to-bulb distillation; $[\alpha]^{20}_{589}$ −45.7° (*c* 4.2, toluene) (lit.[27] −50.6°), ee 90.3%; $[\alpha]^{20}_{546}$ −54.2°. The alcohol was acetylated with acetic anhydride in pyridine to yield (*S*)-1-phenylethyl acetate: bp 113 °C (30 torr); 97%; 200-MHz NMR spectrum showed no impurity, $[\alpha]^{23}_{589}$ −119.7° (*c* 4.2, benzene) (lit.[27] −124.5°), ee 96.1%; $[\alpha]^{23}_{546}$ −144.3°. From a different sample of boronic ester, the acetate had $[\alpha]^{23}_D$ −116.7° (*c* 2.7, benzene), ee 93.7%.

(+)-Pinanediol (1*S*,2*S*)-1-Chloro-2-phenylpropane-1-boronate (3b(PhMeCH)). Homologation of (+)-pinanediol (*S*)-phenylethane-1-boronate (**5b**(Ph,Me) (from pinanediol of 92% ee) with (dichloromethyl)lithium was carried out according to the general procedure. The THF solution of the product was diluted with pentane to precipitate lithium chloride, filtered, and distilled to yield **3b**(PhMeCH): bp 135–138 °C (0.1 torr); 75%; 60-MHz NMR (CCl_4) δ 0.8–2.5 (m, pinanyl pattern, CH_3's at δ 0.78, 1.08, 1.25), 1.50 (d, *J* = 7 Hz, $CHCH_3$), 3.0–3.5 (m, 2, $CHCHCH_3$), 4.20 (dd, 1, BOCH), 7.31 (s, 5, C_6H_5). Anal. Calcd for $C_{19}H_{26}BClO_2$: C, 68.60; H, 7.88; B, 3.25; Cl, 10.66. Found: C, 68.77; H, 8.02; B, 3.08; Cl, 10.41.

(+)-Pinanediol (2*S*,3*R*)-3-Phenylbutane-2-boronate (9). Homologation of (+)-pinanediol (*S*)-1-phenylethane-1-boronate (**5b**(Ph,Me)) (from pinanediol of 100% ee) with (dichloromethyl)lithium was carried out according to the general procedure and was followed by treatment with methylmagnesium bromide according to the general procedure. Bulb-to-bulb distillation at 0.1 torr, bath 130–135 °C, yielded 94% **9**: 60-MHz NMR (CCl_4) δ 0.8–2.5 (m, CH_3's at δ 0.88, 1.33, 1.37), 0.75 (d, *J* = 7 Hz, $BCHCH_3$), 1.25 (d superimposed on pinanyl pattern, $PhCHCH_3$), 2.70 (m, $PhCHCH_3$), 4.27 (dd, BOCH), 7.30 (s, C_6H_5). Anal. Calcd for $C_{20}H_{29}BO_2$: C, 76.93; H, 9.36; B, 3.46. Found: C, 76.93; H, 9.41; B, 3.40.

(2*S*,3*S*)-3-Phenyl-2-butanol (10). Peroxide oxidation of (+)-pinanediol (2*S*,3*R*)-3-phenylbutane-2-boronate (**9**) was carried out by the general procedure. The yield of (2*S*,3*S*)-3-phenyl-2-butanol (**10**) after bulb-to-bulb distillation at 75–80 °C (2 torr) was 88%: 60-MHz NMR (CCl_4) δ 1.06 (d, 3, $CHCH_3$), 1.33 (d,

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3, $CHCH_3'$), 2.0 (br s, 1, OH), 2.7 (m, 1, PhCH), 3.90 (quintet, 1, CHOH), 7.37 (s, 5, C_6H_5). Addition of ~50 mg of the shift reagent $Eu(fod)_3$ separated one of the methyl doublets of the 2R*,3S* isomer (threo isomer)[14] upfield. From the NMR spectrum at 90 MHz, the erythro/threo ratio was estimated to be 94/6. The small rotation of **10** has been reported for the neat liquid,[14] $[\alpha]^{25}_D$ −0.69°. For our sample in a 1-cm cuvette, α_D was −2.1°. The 3-nitrophthalate of **10** was prepared, crystallized once: mp 138–139 °C (lit.[14] mp 144–145 °C); $[\alpha]^{20}_D$ +31.3° (c 3.5, ethanol) (lit.[14] $[\alpha]^{25}_D$ +34.6°).

Diethanolamine (*S*)-1-Phenylethane-1-boronate (11). An ~8-mL sample of boron trichloride was condensed at −78 °C, and a solution of 4.21 g of (+)-pinanediol (*S*)-1-phenylethane-1-boronate (**5b**(Ph,Me)) in 20 mL of dichloromethane was added. The dark solution was allowed to warm slowly to room temperature (~2 h), and the residual boron trichloride was evaporated in a stream of argon. Moist ether (~5 mL) was added in small portions (exothermic reaction), followed by water (~10 mL). Extraction with dichloromethane, washing with aqueous sodium bicarbonate, and concentration yielded the boronic acid as an oil, which was dissolved in 10 mL of ether and treated with 1.56 g of diethanolamine in 3 mL of 2-propanol. The diethanolamine ester (**11**) precipitated immediately, and a second crop was obtained from the mother liquors. Recrystallization by precipitation from chloroform with benzene yielded 2.45 g (72%) of the diethanolamine ester (**11**): mp 200–201 °C (lit.[28] for racemate 204 °C); 60-MHz NMR (Me_2SO-d_6) δ 1.21 (d, 3, $CHCH_3$), 1.96 (q, 1, $PhCHCH_3$), 3.3 (s, water), 2.75 (m, overlapped with Me_2SO peak, NCH_2), 3.75 (m, 4, OCH_2), 6.2 (br s, 1, NH), 7.23 (m, 5, C_6H_5).

(−)-Pinanediol (*S*)-1-Phenylethane-1-boronate (12). A 1.97-g sample of diethanolamine (*S*)-1-phenylethane-1-boronate (**11**) suspended in 30 mL of ether was stirred under argon with 5 mL of 2 M hydrochloric acid, and the ether solution was separated and treated with 1.55 g of (−)-pinanediol (ee 100%, benzeneboronate ester $[\alpha]^{19}_D$ −17.6°). After 4 h the solution was dried over magnesium sulfate and the product (**12**) was distilled bulb-to-bulb at 80–85 °C (0.05 torr) and then chromatographed on silica with 10% ether in petroleum ether: 2.0 g (79%); 60-MHz NMR (CCl_4) δ 0.8–2.5 (m, 19), 4.25 (dd, 1, BOCH), 7.25 (s, 5, C_6H_5). Anal. Calcd for $C_{18}H_{25}BO_2$: C, 76.07; H, 8.87; B, 3.80. Found: C, 76.21; H, 8.91; B, 3.70.

(−)-Pinanediol (2*R*,3*R*)-3-Phenylbutane-2-boronate (13). (−)-Pinanediol (*S*)-1-phenylethane-1-boronate (**12**) was homologated with (dichloromethyl)lithium by the general procedure, and the solution of α-chloro boronic ester was treated with methylmagnesium bromide according to the general procedure. Distillation yielded 91% of the product **13**: bp 115–117 °C (0.025 torr); 60-MHz NMR (CCl_4) δ 0.7–2.5 (m, pinanyl pattern CH_3's at δ 0.77, 1.13, 1.23), 1.12 (d, $CHCH_3$), 1.27 (d, $CHCH_3'$), 2.72 (m, $PhCHCH_3$), 4.05 (dd, 1, BOCH), 7.26 (s, 5, C_6H_5). Anal. Calcd for $C_{20}H_{29}BO_2$: C, 76.93; H, 9.35; B, 3.46. Found: C, 77.16; H, 9.42; B, 3.52.

(2*R*,3*S*)-3-Phenyl-2-butanol (14). The peroxidic oxidation of (−)-pinanediol (2*R*,3*R*)-3-phenylbutane-2-boronate (**13**) was carried out according to the general procedure, and the product **14** was isolated by bulb-to-bulb distillation at 85–90 °C (4 torr): 93%; 60-MHz NMR ($CDCl_3$) δ 1.19 (d, J = 7 Hz, 3, $CHCH_3$), 1.27 (d, J = 7 Hz, 3, $CHCH_3'$), 1.83 (br s, 1, OH), 2.70 (quintet, 1, PhCH), 3.88 (quintet, 1, CHOH), 7.38 (s, 5, C_6H_5). Addition of ~50 mg of the shift reagent $Eu(fod)_3$ revealed one of the CH_3 doublets of the 2*S*,3*S* isomer (erythro) between the two CH_3 doublets of the major 2*R*,3*S* product. From the 90-MHz spectrum the threo/erythro ratio was estimated to be 96/4. The 3-nitrophthalate ester was prepared and purified by way of extraction into aqueous sodium bicarbonate and regeneration with acid, but the material failed to crystallize. The 60-MHz NMR spectrum was in accord with the assigned structure. The rotation of the oil was measured, $[\alpha]^{22}_D$ −30.0° (c 2, ethanol) (lit.[14] $[\alpha]^{25}_D$ −34.2°).

(+)-Pinanediol (*S*)-1-Chloropentane-1-boronate (3b(Bu)). (+)-Pinanediol butaneboronate (ee 92%) was homologated with (dichloromethyl)lithium according to the general procedure. On distillation a forerun of unconverted **1b**(Bu) was obtained, followed by the α-chloro boronic ester **3b**(Bu): bp 100 °C (0.1 torr); 61%; 60-MHz NMR (CCl_4) δ 0.8–2.5 (m, pinanyl with CH_3's at δ 0.90, 1.36, 1.43 + n-C_4H_9), 3.40 (t, 1, CH_2CHClB), 4.40 (dd, 1, BOCH). Anal. Calcd for $C_{15}H_{26}BClO_2$: C, 63.29; H, 9.21; B, 3.80. Found: C, 63.38; H, 9.16; B, 3.46.

(+)-Pinanediol (*S*)-Hexane-2-boronate (5b(Bu,Me)). (+)-Pinanediol (*S*)-1-chloropentane-1-boronate (**3b**(Bu)) was treated with methyllithium according to the general procedure. On distillation a forerun that appeared to be pinanediol methaneboronate (NMR evidence) was obtained, followed by the product **5b**(Bu,Me): bp 99–100 °C (0.5 torr); 60-MHz NMR (CCl_4) δ 0.8–2.5 (m, pinanyl with CH_3's at δ 0.87, 1.31, 1.35 + 2-hexyl with CH_3 at δ 0.93, J = 4 Hz), 4.30 (dd, BOCH). Anal. Calcd for $C_{16}H_{29}BO_2$: C, 72.73; H, 11.06; B, 4.09. Found: C, 72.53; H, 11.23; B, 4.04.

(*S*)-2-Hexanol (7(Bu,Me,H). Peroxidic oxidation of (+)-pinanediol (*S*)-hexane-2-boronate (**5b**(Bu,Me)), from pinanediol of 92% ee, carried out according to the general procedure yielded (*S*)-2-hexanol: 88%, bp 97–100 °C (100 torr); $[\alpha]^{21}_D$ +8.6° (c 11, ethanol) (lit.[29] $[\alpha]^{20}_D$ +10.9°). Treatment with benzoyl chloride in pyridine yielded the benzoate ester; bp 150–155 °C (20 torr) [lit.[30] bp 144 °C (19 torr)]; $[\alpha]^{21}_D$ +29.6° (c 4.5, ethanol) (lit.[30] $[\alpha]_D$ + 40.98°).

(+)-Pinanediol (*R*)-1-Phenylpentane-1-boronate (5b-(Bu,Ph)). (+)-Pinanediol (*S*)-1-chloropentane-1-boronate (**3b**-(Bu)) was treated with phenylmagnesium bromide according to the general procedure, which yielded 80% **5b**(Bu,Ph): bp 125–128 °C (0.1 torr); 60-MHz NMR (CCl_4) δ 0.8–2.4 (m, pinanyl with CH_3's at δ 0.82, 1.27, 1.31 + aliphatic), 4.23 (dd, 1, BOCH), 7.25 (m, 5, C_6H_5). Anal. Calcd for $C_{21}H_{31}BO_2$: C, 77.30; H, 9.58; B, 3.31. Found: C, 77.35; H, 9.68; B, 3.31.

(*R*)-1-Phenyl-1-pentanol Acetate (7(Bu,Ph,Ac)). Peroxidic oxidation of (+)-pinandiol (*R*)-1-phenylpentane-1-boronate (**5b**-(Bu,Ph)) from pinanediol of 92% ee, by the general procedure yielded 87% of the alcohol, which was acetylated to the acetate **7**(Bu,Ph,Ac): bp 83 °C (2 torr) [lit.[31] bp 140 °C (20 torr)]; $[\alpha]^{20}_D$ +60.1° (c 4, benzene) (lit.[31] $[\alpha]_D$ +80.05°).

(+)-Pinanediol (*S*)-Chloro(cyclohexyl)methaneboronate (3b(c-Hx)). (+)-Pinanediol cyclohexaneboronate (**1b**(c-Hx)) (ee 92%) was homologated with dichloromethyl)lithium by the general procedure to yield the α-chloro boronic ester (**3b**(c-Hx)): bp 135 °C (0.1 torr); 67%, 60-MHz NMR (CCl_4) δ 0.8–2.5 (m, pinanyl with CH_3's at δ 0.87, 1.32, 1.39 + cyclohexyl), 3.17 (d, 1, CHClB), 4.37 (dd, 1, BOCH).

(+)-Pinanediol (*S*)-1-Cyclohexylethane-1-boronate (5b-(c-HxMe)). Treatment of (+)-pinanediol (*S*)-chloro(cyclohexyl)methaneboronate (**3b**(c-Hx)) with methyllithium/lithium bromide according to the general procedure yielded 69% **5b**(c-HxMe): bp 110–112 °C (0.1 torr); 60-MHz NMR (CCl_4) δ 0.8–2.4 (m with CH_3's at δ 0.87, 0.89 (d) with J = 4, 1.30, 1.34 Hz), 4.20 (dd, 1, BOCH). Anal. Calcd for $C_{18}H_{31}BO_2$: C, 74.48; H, 10.77; B, 3.73. Found: C, 74.24; H, 10.73; B, 3.96.

(*S*)-1-Cyclohexylethanol (7(c-Hx,Me,H)). (+)-Pinanediol cyclohexaneboronate (**2b**(c-Hx)) (ee 92%) was homologated with (dichloromethyl)lithium, and the solution of the α-chloro boronic ester (**1b**(c-Hx)) was treated with methyllithium according to the general procedures to yield 66% (+)-pinanediol (*S*)-1-cyclohexylethane-1-boronate (**5b**(c-Hx,Me)), which was oxidized in the usual way to (*S*)-1-cyclohexylethanol (**7**(c-Hx,Me,OH): 78%; bp 120 °C (60 torr) [lit.[32] bp 82–83 °C (12 torr)]; appeared pure by NMR [(CCl_4) δ 1.0–2.0 (m, cyclohexyl), 1.12 (d, CH_3), 3.0 (s, OH), 3.50 (m, CHOH)] and TLC $[\alpha]^{22}_D$ +3.92° (neat) (lit.[32] $[\alpha]_D$ +5.68°, d^{19} 0.9202). In another run the α-chloro boronic ester (**3b**(c-Hx)) was isolated by distillation before conversion to (*S*)-1-cyclohexylethanol, which was converted to the hydrogen phthalate ester, did not crystallize but appeared pure by NMR (CCl_4): δ 1.1–2.0 (m, cyclohexyl), 1.38 (d, CH_3), 5.16 (m, OCH), 7.8 (m, C_6H_4), 12.55 (s, CO_2H); $[\alpha]^{21}_D$ +33.6° (c 2.3, ethanol) (lit.[32] $[\alpha]^{20}_D$ +55.4°; lit.[31] $[\alpha]^{30}_D$ +48.6°).

(*R*)-1-Phenylethyl Acetate (7(Me,Ph,Ac). (+)-Pinanediol methaneboronate (**1b**(Me)), ee 92%, was homologated by the usual procedure to (+)-pinanediol (*S*)-1-chloro-ethane-1-boronate (**3b**-

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(Me)): bp 92–95 °C (0.2 torr); 57%; NMR data indicated considerable impurity. This material was treated with phenylmagnesium bromide according to the general method to yield impure (+)-pinanediol (*R*)-1-phenyl-ethane-1-boronate, bp 118 °C (0.3 torr), which was oxidized by the general method to 1-phenylethanol and acetylated to predominantly (*R*)-1-phenylethyl acetate (**7**(Me,Ph,Ac)), $[\alpha]^{23}_D$ +56.5° (lit.[27] $[\alpha]_D$ +124.5°).

(+)-Pinanediol (*S*)-3-Chloro-1-propene-3-boronate (3b(Vi)). (+)-Pinanediol etheneboronate[20] (or vinylboronate) (**1b**(Vi)) was homologated with (dichloromethyl)lithium by the general procedure, modified as described for the preparation of **3b**(Ph). After 1 h at 0 °C, the reaction mixture was treated with concentrated aqueous ammonium chloride and ether and the organic phase was distilled to yield **3b**(Vi): bp 98–100 °C (0.5 torr); 85%; 200-MHz ^{1}H NMR ($CDCl_3$) δ 0.8–2.45 (m, 15), 4.03 (d, J = 8.0 Hz, 1, CHCl), 4.38 (dd, 1, CHOB), 5.18 (dd, J = 9.2 and 1 Hz, 1, H*H*C=CH), 5.35 (dd, J = 16.8 and 1 Hz, 1, *H*HC=CH), 6.03 (m, 1, HHC=C*H*). Anal. Calcd for $C_{13}H_{20}BClO_2$: C, 61.34; H, 7.92; B, 4.25; Cl, 13.93. Found: C, 61.22; H, 8.09; B, 4.33; Cl, 13.68.

(+)-Pinanediol (*S*)-1-Heptene-3-boronate (5b(Vi,Bu)). Conversion of **1b**(Vi) to **3b**(Vi) was carried out as described in the preceding paragraph, and after 1 h at 0 °C the reaction mixture was cooled and treated with butylmagnesium bromide according to the general procedure. The yield of **5b**(Vi,Bu) was 90%: bp 104 °C (0.6 torr); 200-MHz ^{1}H NMR ($CDCl_3$) δ 0.8–2.5 (m, 25), 4.27 (dd, 1, CHOB), 4.90–5.04 (m, 2, CH_2=CH), 5.81 (m, 1, CH_2=C*H*). Anal. Calcd for $C_{17}H_{29}BO_2$: C, 73.92; H, 10.58; B, 3.91. Found: C, 74.06; H, 10.60; B, 3.97.

(*S*)-1-Hepten-3-ol (7(Vi,Bu,H)). Hydrogen peroxide (30%, 1 mL) was added to a stirred mixture of **5b**(Vi,Bu) (1.57 g), sodium hydroxide (0.6 g), THF (20 mL), and water (5 mL) at 0 °C, resulting in immediate precipitation of (+)-pinanediol borate. After 1 h at 20 °C the mixture was filtered and the organic phase was separated and distilled; yield of **7**(Vi,Bu,H) 0.55 g (84%): 200-MHz ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3, CH_3), 1.25–1.63 (m, 6, CH_2), 1.80 (s, 1, OH), 4.10 (q, 1, C*H*OH), 5.09 (d of t's, J = 10.2 and 2 Hz, 1, H*H*C=CH), 5.21 (d of t's, J = 17.9 and 2 Hz, 1, *H*HC=CH), 5.87 (m, 1, H_2C=C*H*); $[\alpha]^{23}_{589}$ +20.7° (*c* 2.25, ethanol) (corrected for 92% ee pinanediol, [α](calcd) +22.5° (lit.[33] $[\alpha]^{25}_D$ +21.0° (*c* 13, ethanol)).

(+)-Pinanediol Iodomethaneboronate (1b(ICH_2)). A solution of 7.05 g of dibutyl iodomethaneboronate[34] and 4.0 g of (+)-pinanediol (ee 92%) in 25 mL of THF was stirred overnight and the product **1b**(ICH_2) distilled at 95–98 °C (0.3 torr); 86%. The analytical sample was obtained by TLC on silica. Anal. Calcd for $C_{11}H_{18}BIO_2$: C, 41.49; H, 5.67; B, 3.38; I, 39.66. Found: C, 41.49; H, 5.78; B, 3.50; I, 39.81.

(+)-Pinanediol (Benzyloxy)methaneboronate (1b($PhCH_2OCH_2$)). Lithium benzyl oxide in DME was prepared as described in the preceding article,[1a] treated at −78 °C with an equivalent amount of (+)-pinanediol iodomethaneboronate (**1b**(ICH_2)), kept 6 h at room temperature, and refluxed 13 h. The **1b**($PhCH_2OCH_2$) was distilled: bp 138–140 °C (0.3 torr); 68%; analytical sample purified by TLC on silica with chloroform. Anal. Calcd for $C_{18}H_{25}BO_3$: C, 71.87; H, 8.48; B, 3.49. Found: C, 72.14; H, 8.39; B, 3.60.

Attempted Homologation of (+)-Pinanediol (Benzyloxy)methaneboronate (1b($PhCH_2OCH_2$)). Several attempts to homologate **1b**($PhCH_2OCH_2$) with (dichloromethyl)lithium failed, yielding only unchanged **1b** in each case. These included the standard procedure with the mixture stirred at 20–25 °C for 2 days; the same followed by 30-min reflux; the standard procedure followed by concentration and refluxing the residue in DME; and the standard procedure but with 1 equiv of TMEDA added after room temperature had been reached.

Diacetone Mannitol Butaneboronate (1a(Bu)). Diacetone mannitol[5] and an equivalent amount of moist butaneboronic acid were stirred in ether with magnesium sulfate overnight, and the product **1a**(Bu) was distilled: bp 98 °C (0.05 torr); 60-MHz NMR (CCl_4) δ 0.92 (m), 1.32 (s, CH_3), 1.43 (s, CH_3), 4.07 (m, 8). Anal. Calcd for $C_{16}H_{29}BO_6$: C, 58.55; H, 8.91; B, 3.29. Found: C, 58.56; H, 9.02; B, 3.41.

Diacetone Mannitol Benzeneboronate (1a(Ph)). This compound was made from benzeneboronic acid in the same manner as the butaneboronic ester: bp 152 °C (0.05 mm); 66%; NMR (CCl_4) δ 1.36 (s, 6, CH_3), 1.47 (s, 6, CH_3), 4.15 (m, 8, OCH), 7.5 (m, 3, Ar*H*), 7.9 (m, 2, Ar*H*).

Dimethyl L-Tartrate Butaneboronate (1d(Bu)). Equivalent amounts of (+)-dimethyl L-tartrate and butaneboronic acid in benzene were refluxed with a Dean-Stark trap until the water was removed (2 h), and the product **1d**(Bu) was distilled: 97%; bp 97–98 °C (0.05 torr); 60-MHz NMR (CCl_4) δ 0.8–1.6 (m, 9, C_4H_9), 3.85 (s, 6, OCH_3), 4.83 (s, 2, OCH). Anal. Calcd for $C_{10}H_{17}BO_6$: C, 49.21; H, 7.02; B, 4.43. Found: C, 49.28; H, 6.94; B, 4.22.

Diethyl L-Tartrate Butaneboronate (1e(Bu)). This was prepared in the same manner as the dimethyl analogue from diethyl tartrate: bp 94–95 °C (0.05 torr); 98%; 60-MHz NMR (CCl_4) δ 0.93 (m), 1.34, (t, CH_3, superimposed on m) 4.30 (q, 4, OCH_2CH_3), 4.78 (s, 2, OCH). Anal. Calcd for $C_{12}H_{21}BO_6$: C, 52.97; H, 7.78; B, 3.97. Found: C, 53.13; H, 7.90; B, 3.97.

Nopol Methyl Ether Diol Butaneboronate (1c(Bu)). This was prepared from nopol methyl ether diol in the same manner as the tartrate esters: bp 90 °C (0.025 torr); 100%; 60-MHz NMR (CCl_4) δ 0.8–2.5 (m + CH_3's at δ 0.90, 1.30, 1.31), 3.31 (s, OCH_3), 3.48 (t, OCH_2), 4.43 (m, 1, OCH). Anal. Calcd for $C_{16}H_{29}BO_3$: C, 68.58; H, 10.43; B, 3.86. Found: C, 67.95; H, 10.13; B, 3.87.

Diacetone Mannitol 1-Chloropentaneboronate (3a(Bu)). Diacetone mannitol butaneboronate was homologated with (dichloromethyl)lithium by the general procedure, and the product **3a**(Bu) was distilled: bp 105 °C (0.05 torr); 60%; 60-MHz NMR (CCl_4) δ 0.8–2 (with CH_3's at δ 1.33, 1.45) (m), 3.40 (t, 1, CHClB), 4.1 (m, 8, OCH). Anal. Calcd for $C_{17}H_{30}BClO_6$: C, 54.21; H, 8.03; B, 2.87; Cl, 9.41. Found: C, 54.44; H, 8.26; B, 3.01; Cl, 9.22.

(*S*)-2-Hexanol from Diacetone Mannitol 1-Chloropentaneboronate (3a(Bu)). The α-chloro boronic ester (**3a**(Bu)) was treated with methyllithium/lithium bromide according to the general procedure. The boronic ester product was not isolated but was oxidized in the usual manner to yield 84% 2-hexanol: distilled bulb-to-bulb at 70–90 °C (100 mm); $[\alpha]^{20}_D$ +4.0° (*c* 3.3, ethanol) (lit.[29] $[\alpha]^{20}_D$ +10.9°).

1-Phenylethanol from Diacetone Mannitol Benzeneboronate (1a(Ph)). The homologation, treatment with methyllithium, and oxidation were carried out in the usual manner without isolating any of the intermediates. The 1-phenylethanol had no measurable rotation.

Attempted Homologation of Dimethyl L-Tartrate Butaneboronate (1d(Bu)). Attempted homologation of 25 mmol of dimethyl L-tartrate butaneboronate according to the general method resulted in a dark solution and recovery of 14.4 mmol of unchanged starting boronic ester **1d**(Bu) with much undistillable residue. Similar results were obtained with the diethyl analogue.

Attempted Homologation of Nopol Methyl Ether Diol Butaneboronate (1c(Bu)). Attempted homologation of this boronic ester according to the general procedure led to recovery of 80% unchanged **1c**(Bu) with some evidence of a small amount of higher boiling material that may have included homologous α-chloro boronic ester.

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Registry No. **1a**(Bu), 87190-21-4; **1a**(Ph), 87190-22-5; **1b**(Bu), 85167-10-8; **1b**(Ph), 76110-78-6; **1b**(c-Hx), 87190-23-6; **1b**(Me), 84110-38-3; **1b**(ICH_2), 87190-24-7; **1b**($PhCH_2OCH_2$), 87190-25-8; **1b**(Vi), 84110-32-7; **1b**(OH), 87190-36-1; **1c**(Bu), 87190-26-9; **1c**(diol), 87247-47-0; **1d**(Bu), 87190-27-0; **1e**(Bu), 87190-28-1; **3a**(Bu), 87190-29-2; **3b**(Bu), 85167-13-1; **3b**(Ph), 76110-79-7; **3b**(c-Hx), 87190-39-4; **3b**(Me), 85167-12-0; **3b**(Vi), 85893-32-9; **3b**(PhMeCH), 87190-30-5; **4b**(Bu), 87247-48-1; **4b**(Ph), 85922-61-8; **4b**(c-Hx), 87247-49-2; **4b**(Me), 87247-50-5; **4b**(Vi), 87247-51-6; **5b**(PhMe), 76110-80-0; **5b**(BuPh), 87190-31-6; **5b**(BuMe), 87190-32-7; **5b**(c-HxMe), 87190-33-8; **5b**(ViBu), 87190-34-9; **6b**(PhMe), 87247-46-9; **6b**(BuPh), 87247-53-8; **6b**(BuMe), 87247-52-7; **6b**(c-HxMe), 87247-54-9; **6b**(ViBu), 87247-55-0; **7**(PhMeH), 1445-91-6; **7**(PhMeAc), 16197-93-6; **7**(BuMeH), 52019-78-0; **7**(BuMeCOPh),

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87190-38-3; 7(BuPhAc), 87190-35-0; 7(c-HxMeH), 3113-98-2; 7-(c-HxMe)(hydrogen phthalate), 87190-40-7; 7(MePhH), 1517-69-7; 7(MePhAc), 16197-92-5; 7(ViBuH), 87247-44-7; 8(BuMeCOPh), 87190-41-8; 8(BuPhAc), 87190-42-9; 8(c-HxMeH), 3113-99-3; 8-(ViBuH), 87247-56-1; 9, 76110-81-1; 10, 74365-65-4; 10 (3-nitrophthalate), 87190-37-2; 11, 76101-96-7; 12, 76155-63-0; 13, 76155-64-1; 14, 76155-51-6; 14(3-nitrophthalate), 87247-45-8; $LiCHCl_2$, 2146-67-0; BCl_3, 10294-34-5; MeBr, 74-83-9; MeLi, 917-54-4; PhBr, 108-86-1; BuBr, 109-65-9; butaneboronic acid, 4426-47-5; benzeneboronic acid, 98-80-6; (+)-pinanediol, 18680-27-8; (−)-pinanediol, 22422-34-0; cyclohexaneboronic acid, 4441-56-9; methaneboronic anhydride, 823-96-1; *anti*-(+)/(+)-sodium bis[(+)-pinanediol] borate, 87248-20-2; *syn*-(+)/(+)-sodium bis-[(+)-pinanediol] borate, 87247-42-5; *anti*-(−)/(−)-sodium bis-[(−)-pinanediol] borate, 87190-20-3; *syn*-(−)/(−)-sodium bis-[(−)-pinanediol borate, 87247-43-6; sodium borate, 14312-40-4; benzoyl chloride, 98-88-4; dibutyl iodomethaneboronate, 13251-29-1; lithium benzyloxide, 15082-42-5; diacetone mannitol, 1707-77-3; (+)-dimethyl L-tartrate, 608-68-4; diethyl L-tartrate, 87-91-2.

Diastereoselection in Reactions of Pinanediol Dichloromethaneboronate

David J. S. Tsai, Pradipta K. Jesthi, and Donald S. Matteson*

Department of Chemistry, Washington State University, Pullman, Washington 99164

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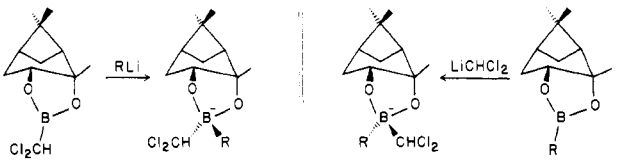
Dichloromethaneboronic acid was converted to its (+)-pinanediol ester (**1**) (92% ee), which was treated with lithium or Grignard reagents to form the corresponding intermediate borate complexes (**2**), diastereomeric with the borates **3** obtained by adding (dichloromethyl)lithium to the corresponding (+)-pinanediol boronic esters. Rearrangement of the lithium *n*-butylborate complex **2a** to the 1-chloropentane-1-boronic esters (**4a** and **5a**) followed by treatment with phenyllithium to form the 1-phenylpentane-1-boronic esters (**6a** and **1a**) and finally oxidation with alkaline hydrogen peroxide yielded predominantly (*R*)-(+)-1-phenyl-1-pentanol (**8r**) (0.92 × 31% ee). This low enantiomeric excess contrasts with the 80% ee obtained previously in a similar sequence from the oppositely assembled borate complex **3a**. Starting with the phenylborate complex **2b**, rearranging, treating with butyllithium, and oxidizing yielded (*S*)-(−)-1-phenyl-1-pentanol (**8s**) (0.92 × 37% ee). The magnesium isobutylborate complex **2c** was rearranged and converted to the 1-acetamido-3-methylbutane-1-boronic esters (**9c** and **10c**), which showed separate NH peaks in the ^1H NMR, ratio 34/66, opposite the stereoselectivity for **2a** and **2b**. Similarly, the methyl complex **2d** yielded a 22/78 ratio of **9d** and **10d**. Zinc chloride catalysis of the rearrangements of **2c** and **2d** yielded **9/10** ratios of 92/8 and 51/49, respectively.

Dichloromethaneboronic esters, $Cl_2CHB(OR')_2$ and alkyllithiums, RLi, have been found by Rathke and coworkers to yield α-chloro boronic esters, $RCHClB(OR')_2$.[1] The reaction must proceed by way of a borate complex, $Cl_2CHB(R)(OR')_2^-$, for which the components R and Cl_2CH can just as well be assembled in the reverse order, from (dichloromethyl)lithium and a boronic ester.[2] We have extended this reaction to pinanediol boronic esters and discovered a new and broadly useful method of directed chiral synthesis.[3-5] Two diastereomeric (+)-pinanediol borate complexes (**2** and **3**) are possible and may give different stereochemical results. In the present work, we have explored the possibility of starting the chiral synthesis from (+)-pinanediol dichloromethaneboronate (**1**). The results have proved disappointing from a practical point of view but do confirm that the diastereomers **2** and **3** behave very differently and that there is a very high degree of kinetic control in the formation of the useful isomer **3** from (dichloromethyl)lithium and (+)-pinanediol alkaneboronates.



1 2 3

Results

Dichloromethaneboronic acid[1] was esterified with (+)-pinanediol (92% ee) to yield **1**. Reaction of **1** with butyllithium to form **2a**, followed by the usual spontaneous rearrangement,[3] yielded a mixture of diastereomeric (+)-pinanediol 1-chloropentane-1-boronates (**4a** and **5a**). For an estimate of the **4a/5a** isomer ratio, the mixture was treated with phenyllithium and the resulting mixture of (+)-pinanediol 1-phenylpentane-1-boronates (**6a** and **7a**) was oxidized to (*R*)- and (*S*)-1-phenyl-1-pentanol (**8r** and **8s**), for which the absolute configuration and rotation have been established.[6] The *R* isomer **8r** was predominant, but

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