Hydrolysis of Substituted 1,3,2-Dioxaborolanes and an Asymmetric Synthesis of a Differentially Protected *syn,syn*-3-Methyl-2,4-hexanediol

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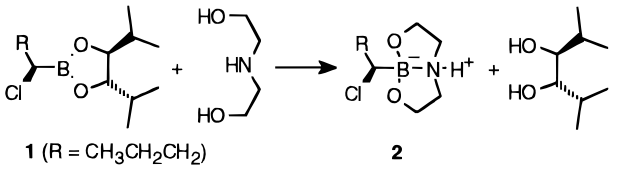
Carbon chain extension by means of asymmetric boronic ester chemistry potentially allows free choice of the absolute configuration of each new stereogenic carbon introduced,[1] and the method is capable of very high stereoselectivity.[2,3] Although many combinations of configurations of two or three adjacent stereogenic centers can be achieved with a single asymmetric diol boronic ester group as chiral director,[1−3] other combinations require removal of the first diol and replacement by its enantiomer,[1] or, with pinanediol esters, a double S_N2 inversion sequence.[4] Accordingly, an efficient general method for hydrolyzing a sterically hindered boronic ester of a diol to the corresponding boronic acid and diol would have synthetic application. Such a hydrolysis would also be useful for converting boronic ester precursors to boronic acids of interest as enzyme inhibitors.[5−8]

The hydrolysis of C_2-symmetrical 1,2-diol boronic esters [(4α,5β)-2-alkyl-4,5-dialkyl-1,3,2-dioxaborolanes] has proved to be surprisingly difficult, and pinanediol esters are even more resistant. Unfavorable equilibrium constants are the major obstacle, with slow equilibration rates a lesser problem.

Transesterification with diethanolamine has been used to convert (*S,S*)-2,5-dimethyl-3,4-hexanediol (*R*)-(1-chlorobutyl)boronate (**1**) to the corresponding diol and diethanolamine ester **2** (Scheme 1), from which the boronic acid can be generated easily by treatment with dilute aqueous acid.[3] However, this procedure requires that the diethanolamine ester crystallize from the solution during the reaction so as to drive the equilibrium toward the products and is not generally applicable.

Pinanediol boronic esters have been cleaved only by destruction of the pinanediol with boron trichloride,[1,5−7] reduction to borohydride with lithium aluminum hydride, or conversion to a borinic ester,[9] or, if the boronic acid is water soluble, transesterification with phenylboronic acid in a two-phase system.[8] The method of hydrolysis reported in this note appears to be generally useful for boronic esters of C_2-symmetrical diols but falls short of complete hydrolysis of pinanediol esters.

Scheme 1



1 (R = $CH_3CH_2CH_2$) **2**

Results

Synthetic Route. A major goal of this work was synthesis of 1,3-diol derivatives having the stereochemical relationships of (3*R*,4*S*,5*S*)-5-(benzyloxy)-4-methyl-3-hexanol (**11**). The precursor **10** has to be a boronic ester of (*S,S*)-1,2-dicyclohexylethanediol [(*S,S*)-DICHED] (**6S**) in order to have the correct absolute configurations at the last two stereogenic centers installed, but precursor **8** is not the diastereomer accessible via reaction of a boronic ester of **6S** with (dichloromethyl)lithium. It was necessary to make the boronic ester **5**, derived from (*R,R*)-DICHED (**6R**), and then to find an efficient means of cleaving **6R** from **5** so that the boronic acid **7** could be esterified with **6S** to form **8**.

The preparation of (*R,R*)-DICHED (*R*)-[1-(benzyloxy)-ethyl]boronate (**5**)[10] from (*R,R*)-DICHED methylboronate (**3**)[11] via the (*S*)-(1-chloroethyl)boronate (**4**) followed well-established procedures (Scheme 2).[11−14] The hydrolysis of **5** to (*R,R*)-DICHED (**6R**) and (*R*)-[1-(benzyloxy)ethyl]-boronic acid (**7**) was carried out with sodium hydroxide and a tris(hydroxymethyl)methane derivative (**17**) in a two-phase system, as described in the next subsection. The ratio of boronic ester **8** to diastereomeric impurity (**5** + ***ent*-5**) was ≥40:1 by NMR analysis. Chain extension of **8** with (dichloromethyl)lithium and treatment of the resulting α-chloro boronic ester with methylmagnesium bromide yielded **9**, and a second chain extension followed by ethylmagnesium bromide yielded **10**, which was deboronated to **11** with hydrogen peroxide.

The particular target **11** was chosen because it could serve as a precursor to derivatives of (4*R*,5*S*)-5-hydroxy-4-methyl-3-hexanone (**12**) used as intermediates for our

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(10) Systematic names of DICHED boronic esters: **3**, [*R*-(4α,5β)]-4,5-dicyclohexyl-2-methyl-1,3,2-dioxaborolane; **4**, [4*R*-(2*S**,4α,5β)]-2-(1′-chloroethyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane; **3**, [4*R*-(2*R**,4α,5β)]-4,5-dicyclohexyl-2-[1′-(phenylmethoxy)ethyl]-1,3,2-dioxaborolane; **6**, [4*S*-(2*S**,4α,5β)]-4,5-dicyclohexyl-2-[1-(phenylmethoxy)ethyl]-1,3,2-dioxaborolane; **7**, [4*S*-[2(1*S**,2*R**),4α,5β]]-2-[2′-(phenylmethoxy)-1′-methylpropyl-4,5-dicyclohexyl-1,3,2-dioxaborolane; **8**, [4*S*-[2(1*S**,2*R**,3*R**),-4α,5β]]-4,5-dicyclohexyl-2-[1-ethyl-2-methyl-3-(phenylmethoxy)butyl]-1,3,2-dioxaborolane.

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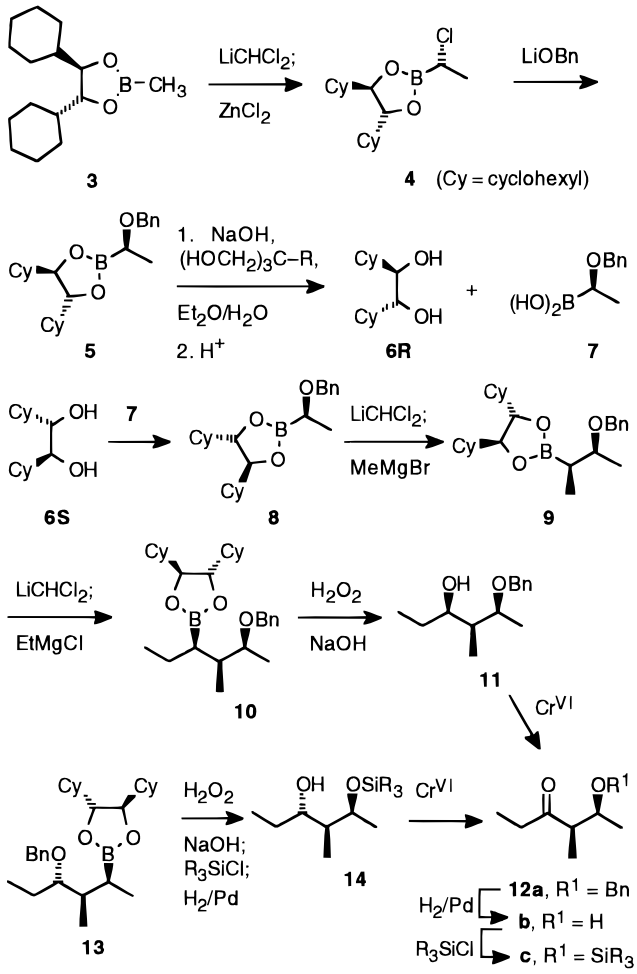
Scheme 2

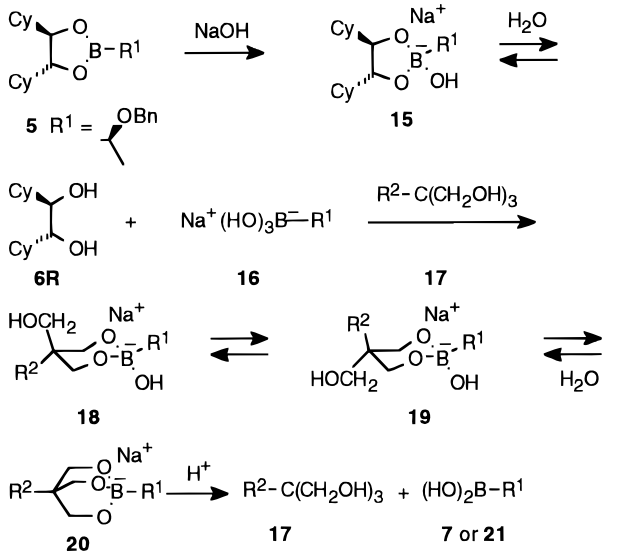


recent synthesis of stegobinone.[12,15] Our first sample of pure stegobinone was derived from **12c** prepared via **3**−**11** (Scheme 2). However, oxidation of **11** to the ketone **12a** deletes a stereogenic center, and only the route to **12** via boronic ester **13** and (3*S*,4*S*,5*S*)-diol derivative **14**, which requires no change of chiral director, was reported.[12]

Hydrolysis of DICHED Ester 5. The hydrolysis of **5** was initially attempted by stirring an ethereal solution of **5** with excess 10 or 3 M aqueous sodium hydroxide, which resulted in immediate precipitation of the sodium salt of the boronic ester **15** instead of the desired boronic acid salt **16**, as indicated by recovery of boronic ester **5** on acidification (Scheme 3). The use of higher dilution and 1 M sodium hydroxide avoided precipitation of **15**, and monitoring of the contents of the ether phase by NMR indicated that the equilibrium values (Table 1) were reached after stirring ~18 h. The predominant constituent of the ether phase was (*R*,*R*)-DICHED (**6R**), but a substantial proportion of unchanged boronic ester **5** remained unless impractically low concentrations (~0.01 M) were used (see Table 1).

(15) Our first attempted route to stegobinone involved esterification of **12b** with (2*S*,3*S*)-2-methyl-3-[(*tert*-butyldimethylsilyl)oxy]pentanoic acid. Cyclization of a similar ester has been described: Mori, K.; Ebata, T. *Tetrahedron* **1986**, *42*, 4413−4420. However, our attempts at ring closure failed. Our chiral carboxylic acid had been made via (*R*,*R*)-DICHED (*S*)-(1-bromopropyl)boronate and *tert*-butyl lithiopropanoate, a process subsequently shown to be stereochemically flawed but to have a viable boronic ester-based alternative.[11] A revised carboxylic ester ring closure route has recently been applied successfully to a homologue of stegobiol, serricorone: Oppolzer, W.; Rodriguez, I. *Helv. Chim. Acta* **1993**, *76*, 1275−1281; 1282−1291.

Scheme 3



[a] R^1 of **7**, $CH(OBn)CH_3$. R^1 of **21**, **a**, Ph; **b**, $CH(NHAc)CH_2Ph$. R^2 of **17**, **a**, $HOCH_2$; **b**, $^-O_3S(CH_2)_3NH^-$; **c**, $^-O_3S(CH_2)_2NH^-$; **d**, $^-O_2CCH_2NH^-$; **e**, H_2N^-; **f**, H_3C^-. R^1 and R^2 of **18**−**20**, intermediates not isolated, defined by context.

Table 1. Hydrolysis of (*R*,*R*)-1,2-Dicyclohexylethanediol [(1*R*)-1-(Benzyloxy)ethyl]boronate (5) to (*R*,*R*)-1,2-Dicyclohexylethanediol (6R) in Equal Volumes of Diethyl Ether and 1 M Sodium Hydroxide

mole ratios[a]			
NaOH/**5**	**17**/**5**	triol **17**	ratio of (**6R**)/(**5**)
6.6	0	none	5:1
100	0	none	42:1
38	3	$(HOCH_2)_3CCH_2OH$ (**a**)	242:1
6.6	3	$(HOCH_2)_3CNH(CH_2)_3SO_3^-$ (**b**)	33:1
38	3	$(HOCH_2)_3CNH(CH_2)_3SO_3^-$ (**b**)	500:1
6.6	1.5	$(HOCH_2)_3CNH(CH_2)_2SO_3^-$ (**c**)	10:1
38	3	$(HOCH_2)_3CNH(CH_2)_2SO_3^-$ (**c**)	92:1
38	3	$(HOCH_2)_3CNHCH_2CO_2^-$ (**d**)	86:1
38	3	$(HOCH_2)_3CNH_2$ (**e**)	99:1
14	3	$(HOCH_2)_3CCH_3$ (**f**)	20:1
38	3	$(HOCH_2)_3CCH_3$ (**f**)	92:1
100	3[b]	$(HOCH_2CH_2)_2NCH_2CO_2^-$ [b]	43:1

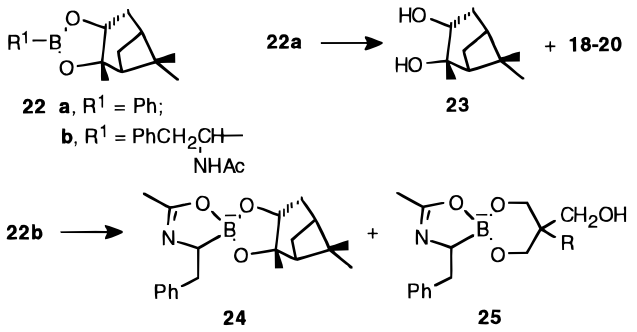
[a] A higher ratio of 1 M NaOH to **5** corresponds to a higher dilution of **5**. [b] *N*,*N*-Bis(hydroxyethyl)glycine yields the same equilibrium as observed with no additive.

To increase the ratio of **6R** to **5** in the ether phase, several different water-soluble tris(hydroxymethyl)-methanes **17** were tested in the hope of transesterifying **15** to a more water-soluble sodium salt and liberating **6R**. All of the **17** tested produced the desired effect, as indicated in Table 1. Pentaerythritol (**17a**) or TAPS (3-{[tris(hydroxymethyl)methyl]amino}propanesulfonic acid, **17b**) appeared to yield the best results, though the differences between these and **17c**−**f** are not necessarily greater than experimental error. When 1,1,1-tris(hydroxymethyl)ethane (**17f**) was used for preparation of boronic acid **7**, acidification of the aqueous phase and ether extraction yielded a ~1:1 mixture of **7** and its ester with **17f**. This problem was not observed with the more polar **17a**,**b**.

Recovery of the free (*R*)-[1-(benzyloxy)ethyl]boronic acid [**21**, R^1 = 1-(benzyloxy)ethyl] was readily accomplished by acidification of the aqueous solution of **18**, **19**, and **20** and extraction with ethyl acetate.

Borate Anions 18−20. For $R^1 = -CH(OBn)CH_3$, the ratios of monocyclic boronic ester anions **18**/**19** to bicyclic

Scheme 4



anions **20** were not determined. However, for R^1 = Ph, evidence for the presence of both types was obtained from the ^{1}H NMR spectrum of a solution prepared from phenylboronic acid (**21a**), sodium deuteroxide, and TAPS (**17b**-H^+) in D_2O. In this case, the major species present was the bicyclic anion **20**, as indicated by the singlet arising from the three identical bridging $-CH_2O-$ groups at δ 3.53. Uncomplexed TAPS appeared as a singlet at δ 3.21. TAPS bound to boron through only two of the CH_2O groups shows one isomer (**18** or **19**) as a doublet at δ 3.47 (J = 11 Hz) coupled to a doublet near δ 3.15−3.16, plus a geometric isomer (**19** or **18**) having a doublet at δ 3.37 (J = 11 Hz) coupled to a doublet overlapping with that of the first isomer at δ 3.15−3.16. In addition, each geometric isomer shows a singlet for the unbound CH_2OH group, one at δ 3.27 and the other at δ 3.22. The couplings were determined with the aid of COSY and HOMO2DJ spectra.

Pinanediol Phenylboronate. The hydrolysis of pinanediol phenylboronate (**22a**) remained incomplete under all conditions tested. Even with a 50-fold excess of sodium hydroxide and 10-fold excess of TAPS (**17b**), the ratio of free pinanediol (**23**) to ester **22a** in the ether phase was only 3.5:1 (Scheme 4). Although the method lacks synthetic utility for pinanediol esters, the data obtained were useful for optimizing the general hydrolysis conditions.[16]

Contrary to expectation, increasing the concentration of sodium hydroxide to 3 M actually decreased the conversion of **22a** to **23**, though it was not determined whether the effect might be kinetic, as the **23**/**22a** ratio increased from 1:1 after 1 day to 2:1 after 2 days. For the experiments with 1 M sodium hydroxide, equilibrium is the limiting factor, as shown by the reverse reaction of free pinanediol, phenylboronic acid (**21a**), TAPS (**17b**-H^+), and 1 M sodium hydroxide in the ratio 2:2:3:12, which after 18 h yielded a 0.6:1 ratio of **23**/**22a**. Glycerol is much less efficient than TAPS for promoting the liberation of **23** from **22a** (Table 2, in the supporting information).

(1-Acetamido-2-phenylethyl)boronic esters. A cyclic structure for the sodium salt of (1*R*)-(1-acetamido-2-phenylethyl)boronic acid (**21b**) is indicated by the ^{1}H NMR spectrum, in which the acetyl methyl singlet appears at δ 1.43, substantially upfield from its position in the free boronic acid **21b**, δ 2.1.

(1-Acetamido-2-phenylethyl)boronic acid (**21b**, 0.1 M), sodium deuteroxide (1 M), and TAPS (**17b**, 0.07 M) in D_2O indicated a preponderance (~85%) of the monocyclic TAPS esters, which appear to be better represented by structure **25** than by **18**/**19**. The ^{1}H NMR spectrum showed ~35% of the TAPS hydroxymethyl CH_2 as a singlet at δ 3.18. There was a partially obscured AB pattern, J = 5 Hz, at δ 3.20 and 3.22, consistent with the ring CH_2 groups of monocyclic anion, ~55%, and the remaining 10% appeared as a singlet at δ 3.48, typical of bicyclic TAPS esters **20**. Overlapping peaks prevented further interpretation.

Treatment of pinanediol (1-acetamido-2-phenylethyl)-boronate (**22b**) with 6.5 equiv of 1 M sodium hydroxide and 4 volumes of diethyl ether resulted in ~50% hydrolysis. Inclusion of 3 equiv of TAPS (**17b**) increased the proportion of hydrolysis to ~80%, though the best recovery of boronic acid **21a** (as its DICHED ester) was only 59%.[16] Diethyl ether extracted free pinanediol (**23**) from the basic solution, but part of the **23** was held in the aqueous solution, presumably in the form of the spiro borate ester **24**. Acidification then liberated unchanged **22b**, which was easily extracted into organic solvents, and the free water-soluble boronic acid **21b**. Addition of DICHED converted **21b** to the corresponding ester, which could be extracted with ethyl acetate.

Discussion

Synthetic Utility. The ability to remove a chiral director and replace it by its enantiomer allows the chemist free choice of the absolute configuration of each carbon atom in a series of several chiral centers. The approach described here has been demonstrated to be practical for making *syn*,*syn*-diols such as **11** and should also be applicable to *anti*,*anti*-diols by postponing the change of chiral directors until after the second chiral center has been installed. For a similar synthetic objective, the still unsolved impasse in the cleavage of pinanediol boronic esters has been circumvented by a double S_N2 inversion sequence,[4] the second inversion of which would be sterically incompatible with diols of C_2-symmetry.[3]

Although the route to ketones **12** via **13** and **14** requires only one chiral director, it was not obvious in advance that this would be more efficient than the route via **11**. Both (*R*,*R*)- and (*S*,*S*)-DICHED are available and easily recoverable. Our initial synthetic objective, β-hydroxy ketone **12b**,[15] was reached in three easy steps from **10** but required five steps from **13**. Loss of silyl protection plagued the reported route to **14**,[12a] and a better route to stegobinone via a keto boronic ester was ultimately found.[12b]

Thermodynamics of Ligand Exchange. Because the major obstacle to hydrolysis of 1,3,2-dioxaborolanes is thermodynamic, it is relevant to consider what factors are involved. Hydrolysis is opposed by the unfavorable entropy of converting three molecules to two:

$$RB[O_2(CHR')_2] + 2H_2O = RB(OH)_2 + R'CH(OH)CH(OH)R'$$

Hydroxylation of both the boronic ester and acid in basic solution does nothing to overcome this entropy barrier, but transesterification to a water-soluble diol keeps the number of molecules constant, and on acidification, the water-insoluble boronic acid becomes separable by extraction.

Other factors that affect equilibrium constants include the influence of steric repulsions on enthalpy and the entropies of internal rotations of free diols. 1,3,2-Dioxaborolanes derived from (*R**,*R**)-DICHED are favored by

(16) Details are included in the supporting information.

minimal steric repulsions between the *trans*-4,5-substituents, which eclipse hydrogen atoms.[17,18] Methyl group interactions destabilize pinacol esters, which are easily transesterified with (*R**,*R**)-DICHED or (*R**,*R**)-diisopropylethanediol.[14,17] The extreme hydrolytic resistance of pinanediol boronic esters results from the orientation of hydroxyl groups and rigidity of the free diol. Our NMR data suggest that the favorable entropy of elimination of water from the monocyclic 1,3,2-dioxaborins **18** and **19** to form the bicyclic ester anions **20** is largely offset by increased strain. The apparent formation of spiro esters **24** and **25** from (1-acetamido-2-phenylethyl)boronic acid (**21b**) and TAPS (**17b**) is consistent with the known structure of an α-amido boronic ester[6] as well as the easy hydrolysis of 3- or 4-(hydroxyalkyl)-1,3,2-dioxaborolanes to cyclic derivatives.[12b,14]

Experimental Section

(*R*,*R*)-DICHED (*R*)-[1-(Benzyloxy)ethyl]boronate (5). Similar procedures have been reported elsewhere for synthesis of the homologous [1-(benzyloxy)propyl]boronate,[12] and a detailed procedure is described in the supporting information for this paper. The ^{1}H NMR spectra are not useful for distinguishing **5** from its diastereomer **8**, but chemical shift differences in the ^{13}C spectra are measurable: for **5**, 125-MHz ^{13}C NMR ($CDCl_3$) δ 16.8, 25.9, 26.0, 26.4, 27.3, 28.2, 42.9, 62.5 (br), 71.7, 83.7, 127.3, 127.8, 128.2, 139.2. The ratio of **5** to its (1*S*)-diastereomer (***ent*-8**) estimated by 125-MHz ^{13}C NMR was 250:1.

Hydrolysis of (*R*,*R*)-1,2-DICHED *R*-[1-(Benzyloxy)ethyl]boronate (5). A solution of (*R*,*R*)-1,2-dicyclohexylethanediol (*R*)-1-(benzyloxy)ethyl]boronate (**5**) (28 g, 75.6 mmol) in diethyl ether (750 mL) was stirred with 3-{[tris(hydroxymethyl)methyl]amino}propanesulfonic acid (TAPS, **17b**-H$^+$) (56 g, 230 mmol) in aqueous 1 M sodium hydroxide (750 mL) at room temperature for 18 h under argon. The ether phase was separated and filtered through a short pad of magnesium sulfate. Concentration of the ether solution yielded (*R*,*R*)-1,2-dicyclohexylethanediol (**6R**) (17 g, 99%). The aqueous sodium hydroxide solution containing the boronate salt was acidified to pH < 3 by addition of 12 M hydrochloric acid and extracted with ethyl acetate (700 mL). The ethyl acetate solution was dried over magnesium sulfate and concentrated under vacuum to yield (*R*)-[(1-benzyloxy)ethyl]boronic acid (10.6 g, 77%): 500-MHz ^{1}H NMR ($CDCl_3$) δ 1.30 (d, J = 7.5 Hz, 3), 3.34 (q, J = 7.5 Hz, 1), 4.41 + 4.60 (AB pattern, J = 12 Hz, 2), 6.5 (br, 2), 7.2−7.4 (m, 5). Further extraction of the aqueous solution with pinacol (14 g) in pentane (500 mL), followed by washing the pentane solution with water and concentration, yielded pinacol (*R*)-[(1-benzyloxy)ethyl]boronate (2.6 g, 12%); total recovery of **7** plus its pinacol ester, 89%.

(*S*,*S*)-DICHED (*R*)-[1-(Benzyloxy)ethyl]boronate (8). A solution of crude (*R*,*R*)-DICHED (*R*)-[1-(benzyloxy)ethyl]boronate (**5**) (67.73 g) in ether (1 L) was stirred with aqueous sodium hydroxide (1 L, 1 M), pentaerythritol (**17a**) (51 g, 375 mmol), and TAPS (3-{[tris(hydroxymethyl)methyl]amino}propanesulfonic acid) (**17b**-H$^+$) (46 g, 189 mmol) for 18 h at room temperature. The aqueous layer was separated and washed with ether (300 mL) to remove any (*R*,*R*)-DICHED (**6R**) or (*R*,*R*)-DICHED (*R*)-[1-(benzyloxy)ethyl]boronate (**5**). The combined ether phase was washed with water (500 mL) and dried over magnesium sulfate. Concentration under vacuum yielded (*R*,*R*)-DICHED (**6R**) [36 g, 150 mmol, 85% based on (*R*,*R*)-DICHED methylboronate (**3**)]. The sodium hydroxide solution was acidified to pH 3 by hydrochloric acid (12 M) at 0 °C and extracted with ethyl acetate (3 × 500 mL). The combined organic phase was dried over magnesium sulfate. Distillation of the solvent yielded a mixture of pentaerythritol (*R*)-[1-(benzyloxy)ethyl]boronate and (*R*)-[1-(benzyloxy)ethyl]boronic acid (**7**). The mixture was dissolved in hexane and stirred with (*S*,*S*)-DICHED (**6S**) (36 g, 150 mmol) (ee ~99%) for 18 h. The solution was washed with water (3 × 200 mL) and dried over magnesium sulfate. Distillation of the solvent gave (*S*,*S*)-DICHED (*R*)-[1-(benzyloxy)ethyl]boronate (**8**) [52.88 g, 76% based on (*R*,*R*)-DICHED methylboronate (**3**)], which was used in the next step without further purification: 500-MHz ^{1}H NMR ($CDCl_3$) δ 0.96−1.40 and 1.56−1.82 (m, 22), 1.34 (d, J = 7.5 Hz, 3), 3.45 (q, J = 7.5 Hz, 1), 3.91−3.93 (m, 2), 4.55 (d, J = 11.5 Hz, 1), 4.58 (d, J = 11.5 Hz, 1), 7.25−7.37 (m, 5); 125-MHz ^{13}C NMR ($CDCl_3$) δ 17.0, 25.9, 26.0, 26.4, 27.3, 28.4, 43.0, 62 (br), 71.8, 83.9, 127.3, 127.8, 128.2, 139.2; HRMS calcd for $C_{23}H_{35}BO_3$ (M$^+$) 370.2679, found 370.2687. The ratio of **8** to its diastereomer (*R**,*R**)-DICHED (*R**)-[1-(benzyloxy)ethyl]boronate (**5** + ***ent*-5**) was ≥40:1 based on 125-MHz ^{13}C NMR analysis.

(*R*)-[1-(Benzyloxy)ethyl]boronic Acid (7). The procedure of the foregoing paragraph carried out with TAPS but without pentaerythritol allowed isolation of **7**, which was not purified: 500-MHz ^{1}H NMR ($CDCl_3$) δ 1.30 (d, J = 7.5 Hz, 3), 3.34 (q, J = 7.5 Hz, 1), 4.41 (AB, J = 12 Hz, 1), 4.60 (d, J = 12 Hz, 1), 6.4−6.6 (br s, 1), 7.2−7.4 (m, 5).

(*S*,*S*)-DICHED (1*R*,2*S*)-[2-(Benzyloxy)-1-methylpropyl]boronate (9). Addition of **8** to preformed (dichloromethyl)lithium according to the usual procedure yielded the crude α-chloroboronic ester, which with methylmagnesium bromide under the usual conditions led to crude **9**.[12,16]

(*S*,*S*)-DICHED (1*R*,2*S*,3*S*)-{[3-(Benzyloxy)-2-methyl-1-ethyl]butyl}boronate (10). (Dichloromethyl)lithium was prepared from dichloromethane (22 mL) in THF (150 mL) at −100 °C with butyllithium (160 mmol) in the usual manner.[2a] A solution of crude **9** (45.23 g, 114 mmol) was added via cannula, followed after 10 min by anhydrous zinc chloride (13.1 g, 95.6 mmol). The solution was kept at ambient temperature for 36 h and then concentrated and worked up in the usual way with hexanes (200 mL) and aqueous ammonium chloride (2 × 200 mL). The concentrated crude chloroboronic ester (47 g) was used in the next step without further purification: 500-MHz ^{1}H NMR ($CDCl_3$) δ 0.87−1.78 (m, 22), 1.13 (d, J = 6.5 Hz, 3), 1.20 (d, J = 6.5 Hz, 3), 2.18 (dp, J = 5, 6.5 Hz, 1), 3.52 (d, J = 7 Hz, 1), 3.67 (p, J = 6 Hz, 1), 3.75−3.76 (m, 2), 4.48 (AB, J = 15 Hz, 1), 4.51 (AB, J = 15 Hz, 1), 7.30−7.34 (m, 5); 125-MHz ^{13}C NMR ($CDCl_3$) δ 13.50, 15.86, 25.65, 25.69, 26.26, 27.53, 28.20, 42.37, 42.43, 47 (br), 70.87, 76.78, 84.10, 127.21, 127.45, 128.09, 138.94. Ethylmagnesium chloride (56 mL, 1.88 M, 105 mmol) was added dropwise to the crude boronic ester (47 g) in THF (150 mL) at −78 °C. After 48 h at 20−25 °C, the solution was concentrated and worked up in the usual way with hexanes (200 mL) and aqueous ammonium chloride (2 × 200 mL). Concentration of the organic phase, followed by flash column chromatography (silica, 5% ether/hexanes), yielded boronic ester **10** (32.3 g, 73.3 mmol, 64% from **9**); 500-MHz ^{1}H NMR ($CDCl_3$) δ 0.85−1.80 (m, 26), 0.89 (t, J = 7.5 Hz, 3), 0.98 (d, J = 7 Hz, 3), 1.18 (d, J = 6 Hz, 3), 3.47 (p, J = 6 Hz, 1), 3.68−3.70 (m, 2), 4.41 (AB, J = 12 Hz, 1), 4.55 (AB, J = 12 Hz, 1), 7.23−7.36 (m, 5); 125-MHz ^{13}C NMR ($CDCl_3$) δ 12.58, 14.02, 17.27, 22.94, 25.85, 25.92, 26.44, 27.85, 28.64, 40.96, 42.93, 70.76, 78.64, 83.35, 127.16, 127.68, 128.16, 139.57. Anal. Calcd for $C_{28}H_{45}O_3B$: C, 76.35; H, 10.3; B, 2.45. Found: C, 76.84; H, 10.52; B, 2.47.

(3*R*,4*S*,5*S*)-5-(Benzyloxy)-4-methyl-3-hexanol (11). To a solution of boronate (**10**) (21.2 g, 48 mmol) in 80 mL of THF and 17 mL of sodium hydroxide (3 M) was added hydrogen peroxide (20 mL, 30%) at 0 °C. The solution was allowed to warm to room temperature, kept for 18 h, and partially concentrated under reduced pressure to remove THF. The aqueous solution was extracted with ether (2 × 200 mL). The combined organic phase was washed with ammonium chloride (100 mL) and dried over magnesium sulfate and then concentrated to a solid residue, which was treated with pentane to crystallize (*S*,*S*)-DICHED and dissolve **11**. The (*S*,*S*)-DICHED was filtered, and the mother liquor was concentrated and separated by flash column chromatography (silica, 20% ethyl acetate/hexanes) to yield alcohol **11** (9.2 g, 86%): 500-MHz ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.5 Hz, 3), 0.96 (d, J = 6.5 Hz, 3), 1.24 (d, J = 6.5 Hz, 3), 1.36−1.41 (m, 2), 1.50−1.58 (m, 1), 3.70−3.73 (dt, J = 7, 2 Hz, 1), 3.79 (dq, J = 2.5, 6 Hz, 1), 4.39 (AB, J = 11 Hz, 1), 4.65 (AB, J = 11 Hz, 1), 7.25−7.35 (m, 5); 125-MHz ^{13}C NMR ($CDCl_3$) δ 5.33, 10.46, 16.86, 27.59, 41.82, 70.28,

(17) Ho, O. C.; Soundararajan, R.; Lu, J.; Matteson, D. S.; Wang, Z.; Chen, X.; Wei, M.; Willett, R. D. *Organometallics* **1995**, *14*, 2855−2860.

(18) In a 4,5-unsubstituted 2-(1-amidoalkyl)-1,3,2-dioxaborolane, bonding to the amide oxygen makes the boron tetracoordinate and the CH_2 groups staggered,[6] geometry which also favors *trans*-disubstitution.

77.27, 79.90, 127.58, 127.60, 128.41, 138.15. Anal. Calcd for $C_{14}H_{23}O_2$: C, 75.63 H, 9.97. Found: C, 74.4; H, 9.94.

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Supporting Information Available: Experimental details for preparations of compounds **5**, **9**, and **12a**−**c**, and for the partial hydrolysis of pinanediol boronic esters (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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