the light yellow solid residue was separated by flash column chromatography on silica gel. Elution with 9:1 hexane–ethyl acetate afforded a mixture of isomers of 4-chloro-1-methyl-3-(phenylseleno)cyclopentanecarboxylic acid (0.550 g, 81%) as a white solid. No attempt was made to separate these compounds: ^{1}H NMR ($CDCl_3$): δ 11.90 (br s, 1 H), 7.58 (m, 2 H), 7.30 (m, 3 H), 4.20 (m, 1 H), 3.78 (m, 1 H), 3.07 (m, 1 H), 2.68 and 2.52 (dd, J = 14.6, 5.6 Hz, 1 H), 2.38 and 2.33 (dd, J = 14.6, 5.6 Hz, 1 H), 1.92 and 1.68 (dd, J = 14.6, 6.0 Hz, 1 H), 1.48 and 1.34 (s, 3 H). This mixture was converted into compound **18B**. A solution of this mixture (0.550 g, 1.73 mmol) and silver tetrafluoroborate (0.500 g, 2.57 mmol) in dichloromethane (10 mL) was stirred at 25 °C for 4 h. The mixture changed quickly from brown to black. After this period the mixture was filtered through silica gel with dichloromethane as eluent. After the solvent was removed from the filtrate, a yellow solid was obtained, which was separated by column chromatography on silica gel. Elution with 9:1 hexane–ethyl acetate afforded unreacted 4-chloro-1-methyl-3-(phenylseleno)cyclopentanecarboxylic acid (0.232 g, 0.73 mmol) and compound **18B** (0.186 g, 38%). Compound **18B** was a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 7.52 (m, 2 H), 7.29 (m, 3 H), 4.62 (br s, 1 H), 3.60 (m, 1 H), 2.14–2.30 (m, 2 H), 2.03 (m, 1 H), 1.61 (dd, J = 14.1, 5.1 Hz, 1 H), 1.33 (s, 3 H); IR (CH_2Cl_2) 3060 (w), 2962 (w), 1785 (s), 1482 (w), 1440 (w), 1322 (w), 1090 (m), 915 (m) cm^{-1}. This compound was converted to alcohol **19** without further purification.

Preparation of (1β,3β)-(±)-1-Carbobenzoxy-3-hydroxy-1-methylcyclopentane (19) from 18B. Tributylstannyl hydride (0.280 g, 0.96 mmol), selenide **18B** (0.186 g, 0.66 mmol), and AIBN (0.005 g, 0.03 mmol) were dissolved in benzene (5 mL). The mixture was heated to reflux for a period of 2 h. The solution was cooled to 25 °C after this period, and benzyl alcohol (0.180 g, 1.67 mmol) and *p*-toluenesulfonic acid (0.010 g, 0.06 mmol) were added. The resulting mixture was heated to 70 °C with stirring for a period of 10 h. After this period, the solvent was removed on a rotary evaporator, and the residue was separated by silica gel preparative TLC with 7:3 hexane–ethyl acetate as eluent. Alcohol **19** was obtained as a colorless oil (0.075 g, 48%): ^{1}H NMR ($CDCl_3$) δ 7.33 (br s, 5 H), 5.13 (s, 2 H), 4.32 (m, 1 H), 2.18–2.45 (m, 2 H), 1.95 (m, 1 H), 1.75 (m, 1 H) overlapping with 1.73 (dd, J = 15.2, 6.0 Hz, 1 H), 1.47–1.62 (m, 2 H), 1.30 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.1, 136.0, 128.6, 128.2, 127.9, 74.0, 66.7, 48.4, 47.2, 36.5, 35.4, 25.4; IR (CH_2Cl_2) 3605 (w), 2972 (m), 1723 (s), 1435 (w), 1220 (w), 1162 (m, br), 1050 (m) cm^{-1}; MS (CI) m/e 235 (M + 1, 17), 217 (15), 204 (7.2), 188 (17), 171 (9.8), 143 (92), 127 (98), 105 (92), 97 (100); HRMS m/e calcd for $C_{14}H_{19}O_3$ 235.1334, found 235.1326.

Preparation of (1β,2α,3β,4α,5α)-(±)-1-Carbobenzoxy-4-(carbo-*p*-nitrobenzoxy)-2,3,5-trimethylcyclopentane (15F-PNB). To a solution of alcohol **15F** (0.005 g, 0.019 mmol) in pyridine (1.0 mL) was added 4-nitrobenzoyl chloride (0.020 g, 0.11 mmol). The mixture was stirred at 25 °C for 12 h. After the solvent was removed on a rotary evaporator, the residue was separated by silica gel preparative TLC with 3:2 hexane–ethyl acetate as eluent. Compound **15F-PNB** was obtained as a yellow oil (0.007 g, 91%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (m, 2 H), 8.13 (m, 2 H), 7.30 (m, 5 H), 5.11 (s, 2 H), 4.72 (dd, J = 5.8, 4.6 Hz, 1 H), 2.51 (m, 1 H), 2.40 (m, 1 H), 2.20 (m, 1 H) overlapping with 2.19 (t, J = 9.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 174.7, 164.6, 150.5, 136.0, 135.7, 130.7, 128.6, 128.2, 128.0, 123.5, 88.2, 66.5, 56.3, 44.1, 42.7, 39.1, 18.3, 14.9, 12.9; MS (CI) m/e 412 (M + 1, 4.6), 382 (26), 262 (4.5), 245 (13), 227 (10), 215 (7.6), 199 (5.2), 153 (16), 137 (100), 120 (82), 109 (35), 91 (40); HRMS m/e calcd for $C_{23}H_{26}NO_6$ 412.1760, found 412.1765.

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Stereoselective Reaction of an Enolate with Chiral α-Halo Boronic Acid Esters[1]

Donald S. Matteson* and T. John Michnick

Department of Chemistry, Washington State University, Pullman, Washington 99164-4630

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Reaction of *tert*-butyl *trans*-lithiopropionate (**6**) with (*S*,*S*)-diisopropylethanediol ("DIPED") (1*R*)-(1-bromopentyl)boronate (**9a**) yielded semipurified *tert*-butyl (2*S*,3*S*)-3-hydroxy-2-methylheptanoate (**11a**) ("threo") in a 60:1 ratio to the "erythro" diastereomer. Other threo/erythro ratios included DIPED (1*R*)-(1-bromo-2-methylpropyl)boronate (**9b**) to crude **11b**, 15:1, DIPED (α-bromobenzyl)boronate (**9c**) to crude **11c**, 8:1; (3*S*,4*S*)-2,5-dimethoxy-2,5-dimethyl-3,4-hexanediol (1*R*)-(1-bromo-pentyl)boronate (**9d**) to semipurified **11a**, 10:1; and pinacol (1-bromopentyl)boronate (**5**) via **7** to semipurified racemic **11a**, >100:1. These reactions are sluggish, and α-bromo boronic acid esters generally give better yields than the corresponding chloro compounds. Less hindered ester enolates appear to undergo Claisen condensation under the reaction conditions, and only the *tert*-butyl ester proved useful. An efficient synthesis of (3*S*,4*S*)-2,5-dimethoxy-2,5-dimethyl-3,4-hexanediol (**16**) and its use as a chiral director for chain extension of boronic acid esters are described.

Introduction

Displacement reactions of enolates such as diethyl sodiomalonate or methyl sodiocyanoacetate with (iodomethyl)boronic acid esters have been reported,[2] as well as those of *tert*-butyl lithioacetate with pinacol (1-chloroallyl)boronate,[3] (*R*)-pinanediol (1*R*)-(1-chloroethyl)boronate,[4] and pinacol (iodomethyl)boronate.[5] In view of the

(1) Dedicated to the memory of John K. Stille.

(2) Matteson, D. S.; Cheng, T.-C. *J. Org. Chem.* **1968**, *33*, 3055–3060.
(3) Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 1529–1535.

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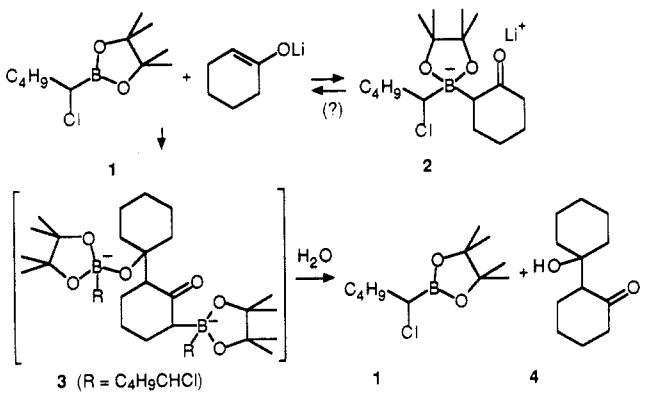
high degree of stereocontrol that has been achieved in the preparation of α-halo boronic acid esters,[4,6,7] it was of interest to determine whether a propionate enolate would react with a halo boronic acid ester in a diastereoselective manner at the enolate carbon, which would result in the efficient construction of two adjacent chiral centers.

Results

The use of enolates to displace halides from α-halo boronic acid esters introduces some complications not encountered with simpler nucleophiles. The possibility of reaction at oxygen instead of carbon was initially of concern, but this has not been observed. A previously studied reaction of an allylic α-halo boronic acid ester that was believed to involve attack on boron by the oxygen of an ester enolate[3] is now known not to proceed via that mechanism.[8]

The side reaction that does occur is the simple enolate dimerization of the carbonyl compound. This was encountered previously in the reaction of (*S*)-pinanediol (chloromethyl)boronate with *tert*-butyl lithioacetate, which apparently led to the formation of *tert*-butyl acetoacetate, and the problem was solved by the use of the more reactive (iodomethyl)boronic acid ester.[5]

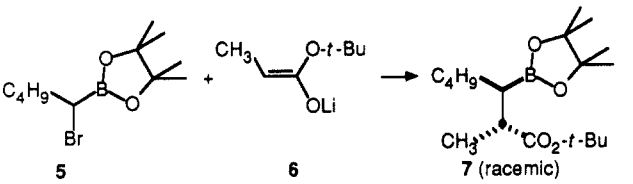
A number of attempts were made to displace chloride ion from pinacol (1-chloropentyl)boronate (**1**)[3] with lithiocyclohexanone. After aqueous workup, the products isolated were unchanged **1** and the aldol condensation product from cyclohexanone, 2-(1-hydroxycyclohexyl)-cyclohexanone (**4**). On the basis of other results described



below, the expected adduct **2** of the boronic acid ester and enolate is probably formed, but if so, the formation is reversible. The boronated version **3** of the aldol condensation product **4** is a possible form in which the product might exist prior to hydrolytic workup.

We then tried the ester enolate from ethyl propionate. This also appeared to yield much Claisen condensation and little substitution. *tert*-Butyl *trans*-lithiopropionate (**6**) (95% trans, 5% cis) was prepared from *tert*-butyl propionate and lithium diisopropylamide[9] and proved to be better, yielding ~30% of the substitution product with **1**. (Trans refers to the relationship of the propionate methyl group to the enolate oxygen.[10]) The readily available pinanediol analogue of **1**[4] failed to yield displacement product.

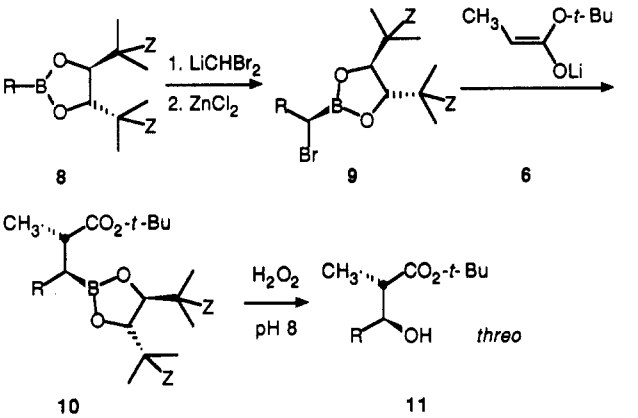
The final improvement was the use of pinacol (1-bromopentyl)boronate (**5**), which gave a satisfactory (~60%) yield of the substitution product **7**. Evidence that



7 is the diastereomer illustrated is provided by oxidation to the β-hydroxy ester and comparison of NMR data with known compounds.[11]

It was of more interest to carry out the reaction with boronic acid esters of high enantiomeric purity, and two series of compounds were tested. One was the diisopropylethanediol ("DIPED")[12] esters (**8–10**, Z = H), the other the (3*S*,4*S*)-2,5-dimethoxy-2,5-dimethyl-3,4-hexanediol esters (**8–10**, Z = OCH_3). Highly satisfactory results were obtained with the DIPED ester series. 2,5-Dimethoxy-2,5-dimethyl-3,4-hexanediol (**16**) was chosen as an easily prepared chiral director having methoxy substituents that might influence stereoselectivity, but the influence turned out to be in the wrong direction.

The reaction sequence tested is illustrated by the conversion of (*S*,*S*)-DIPED butylboronate (**8a**) to the (1*R*)-(1-bromopentyl)boronate (**9a**) via the previously established reaction with (dibromomethyl)lithium prepared in situ from dibromomethane and lithium diisopropylamide.[13]



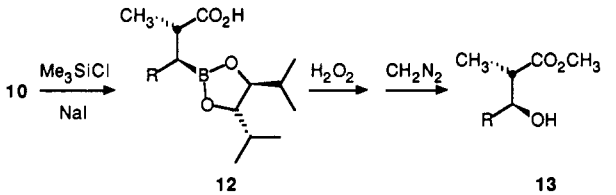
a, R = *n*-C_4H_9, Z = H; **b**, R = $(CH_3)_2CH$, Z = H; **c**, R = C_6H_5, Z = H; **d**, R = *n*-C_4H_9, Z = OCH_3.

The bromo ester was treated at −78 °C with *tert*-butyl *trans*-lithioacetate [(*Z*)-1-(1,1-dimethylethoxy)-1-lithioxy-1-propene] (**6**) [prepared by the method of Heathcock and co-workers[9]] and allowed to rearrange at 25 °C to form the coupled product **10a**. Deboronation of **10a** with hydrogen peroxide yielded *tert*-butyl (2*S*,3*S*)-2-

(4) Matteson, D. S.; Sadhu, K. M.; Peterson, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 810–819.
(5) Matteson, D. S.; Beedle, E. C. *Tetrahedron Lett.* **1987**, *28*, 4499–4502.
(6) Tripathy, P. B.; Matteson, D. S. *Synthesis* **1990**, 200–206.
(7) (a) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535–1551. (b) Matteson, D. S. *Acc. Chem. Res.* **1988**, *21*, 294–300.
(8) Matteson, D. S.; Michnick, T. J. To be published.
(9) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066–1081.
(10) Proper assignment of priorities by the Cahn–Prelog–Ingold system makes this the *Z* isomer, but relationships between ester and ketone enolates are easier to keep track of with the simple cis/trans nomenclature.[8] For another example, see: Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111. The alternative nomenclature *Z*(O) and *E*(O) has also been proposed for cis and trans, respectively: Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521–5523.
(11) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294–4299.
(12) (a) Matteson, D. S.; Kandil, A. A. *Tetrahedron Lett.* **1986**, *27*, 3831–3834. (b) Matteson, D. S.; Beedle, E. C.; Kandil, A. A. *J. Org. Chem.* **1987**, *52*, 5034–5036.
(13) Matteson, D. S.; Peterson, M. L. *J. Org. Chem.* **1987**, *52*, 5116–5121.

methyl-3-hydroxyheptanoate (**11a**), designated as the threo isomer in the aldol literature, as inferred from comparison of the ^1H and ^{13}C NMR spectra with the data reported for the corresponding methyl ester.[11] A similar sequence starting from (*S,S*)-DIPED isopropylboronate (**8b**) led to the analogous threo β-hydroxy ester **11b**, and the phenylboronate **8c** similarly led to **11c**.

The *tert*-butyl ester **11c** has been reported previously, though with limited physical data,[11] and **11a** and **11b** are new compounds. In order to provide unequivocal comparison with a proven structure, boronic acid ester **10b** was converted to the known methyl (2*S*,3*S*)-2,4-dimethyl-3-hydroxypentanoate (**13b**).[11,14] Cleavage of the *tert*-butyl ester of **10b** with trimethylsilyl chloride and sodium iodide[15] proved compatible with the boronic acid ester group and readily yielded β-hydroxy acid **12b**. Deboronation



12 13

a, R = *n*-C_4H_9; b, R = $(CH_3)_2CH$; c, R = C_6H_5.

and esterification by conventional means yielded **13b**, shown to be mainly the threo isomer by ^1H and ^{13}C NMR data. Methyl (2*S*,3*S*)-2-methyl-3-hydroxyheptanoate (**13a**) was prepared via a similar route.

Although **12c** was easily prepared, the phenyl substituent sufficiently destabilizes the β-hydroxy ester that extensive elimination product (^1H NMR: vinylic proton at δ 5.16) formed during the deboronation with buffered hydrogen peroxide or the subsequent acid workup. Esterification of **12c** with diazomethane was then attempted, but the boronic acid ester function rapidly polymerizes diazomethane, and the methyl ester showed considerable extra absorption in the methylene proton region of the ^1H NMR.

Isomer Ratios. The threo/erythro isomer ratio of *tert*-butyl (2*S*,3*S*)-2-methyl-3-hydroxyheptanoate (**11a**) prepared via DIPED boronic ester **10a** was ~60:1 as measured by 75-MHz ^{13}C NMR spectroscopy, based on the relative heights of the threo isomer peaks at δ 14.04, 45.84, and 73.53 compared to the erythro peaks at δ 10.85, 45.06, and 71.87. The diastereomeric purity of the racemic **11a** prepared from the pinacol ester **7** was even higher, apparently >99%. Although NMR data have not been previously reported for **11a**, a well-characterized model would be methyl 2-methyl-3-hydroxypentanoate (threo δ 13.7, 44.9, 74.4 versus erythro δ 10.6, 44.1, 73.2).[11]

The samples of **10a** and **11a** had been chromatographed to remove gross impurities. Thus, the final isomer ratio does not necessarily prove the initial diastereoselection, although the broad fraction cuts included all detectable material eluting near the product, and thin-layer chromatography (TLC) of the crude reaction mixture did not reveal any isomer separation. The 2,5-dimethoxy-2,5-dimethyl-3,4-hexanediol boronic esters **8d–10d**, (Z = CH_3O) led to 8–9% diastereomeric impurity in the **11a** produced, even though **10d** and **11a** were partially purified by chromatography.

Preparation of *tert*-butyl (2*S*,3*S*)-2,4-dimethyl-3-hydroxypentanoate (**11b**) via **10b** without chromatography of intermediates yielded a 15:1 threo/erythro ratio based on the diagnostic sets of 125.4-MHz ^{13}C NMR integrals at δ 14.80, 43.04, 78.18 and δ 10.39, 42.54, 76.35 (obscured by $CDCl_3$), respectively. An authentic mixture of **11b** and its erythro isomer was prepared from 2-methylpropanal and *tert*-butyl lithiopropionate by the procedure of Heathcock and co-workers.[9]

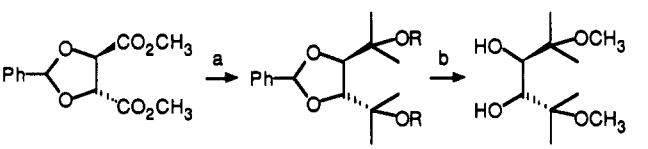
The 200-MHz ^1H NMR spectrum of *tert*-butyl (2*S*,3*S*)-2-methyl-3-hydroxy-3-phenylpropanoate (**11c**) showed 89% of the benzylic C*H*OH at δ 4.70 (d, *J* = 8.2 Hz (lit.[11] δ 4.60, d, *J* = 8.5 Hz)) with 11% apparent erythro isomer at δ 4.97 (*J* = 4.8 Hz (lit.[11] δ 4.80, d, *J* = 6.0 Hz)). This conversion was carried out without chromatography of **10c** or **11c**.

As noted in the preceding section, methyl (2*S*,3*S*)-2,4-dimethyl-3-hydroxypentanoate (**13b**) was prepared because it has been fully characterized.[11] No chromatography was used at any stage of the synthesis. The threo/erythro diastereomer ratio was initially ~15:1, but after storage for a few days in the NMR tube, the sample showed a substantial decrease in this ratio as well as marked growth of impurity peaks. Both the ^1H and ^{13}C NMR spectra were fully consistent with those reported previously,[11] and the preparation of an authentic sample of a mixture of **13b** and its erythro isomer[9] provide unequivocal proof of identity. The (−)-rotation in the same range as the literature value[14] provides corroborative evidence for the absolute configuration.

The analogous preparation of methyl (2*S*,3*S*)-2-methyl-3-hydroxyheptanoate (**13a**) also resulted in a threo/erythro diastereomer ratio of ~15:1. It is not known whether this result could reflect instability of **13a** toward epimerization, as described for **13b** above.

2,5-Dimethoxy-2,5-dimethyl-3,4-hexanediol as the Chiral Director. The 2,5-dimethoxy-2,5-dimethyl-3,4-hexanediol boronic acid esters gave disappointing chiral direction in the chain extension process, for example, the conversion of **8d** to **9d**. Two extra equivalents of zinc chloride catalyst had to be used in order to compensate for the retarding effect of the methoxy groups,[13] even then the ratio of **9d** to its diastereomer was only ~12:1. A similarly poor diastereomeric ratio has been observed previously in the reaction of diacetonemannitol butylboronate with (dichloromethyl)lithium, which required 3 extra equiv of zinc chloride and produced an isomeric ratio in the 10–15:1 range.[16]

(3*R*,4*R*)-2,5-Dimethoxy-2,5-dimethyl-3,4-hexanediol (**16**) has been synthesized previously and used as a chiral director,[17] but few experimental details have been described. Our straightforward route appears to be an improvement.



14 15 a, R = H; b, R = CH_3 16

(a) CH_3MgBr to **15a**, then KOH + CH_3I in DMSO to **15b**. (b) H_2/Pd.

Conditions for and isomer ratios in chain extensions of 2,5-dimethoxy-2,5-dimethyl-3,4-hexanediol (**16**) esters with (dichloromethyl)lithium were measured with the butylboronate to (α-chloropentyl)boronate conversion as a

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model. The (α-chloropentyl)boronate was transesterified with (S)-pinanediol to provide a known derivative for estimation of the (R)/(S) ratio at the α-carbon.[4] When the rearrangement of the adduct of 2,5-dimethoxy-2,5-dimethyl-3,4-hexanediol butylboronate with (dichloromethyl)lithium[4] was promoted by 0.7 equiv of zinc chloride, the yield of (α-chloropentyl)boronate was only 20% and 80% of the unchanged butylboronate remained. The (R)/(S) isomer ratio could not be determined by NMR analysis of this mixture. With 1.7 equiv of zinc chloride, the ratio of product to starting material was 1:1 and the product was 92% (±3%) (1R)-(1-chloropentyl)boronate. With 2.7 equiv of zinc chloride, the ratio of product to starting material rose to 9:1, and the (R)/(S) isomer ratio remained the same at ~92:8.

Discussion

It is already evident from this work that an α-bromo boronic acid ester can be used as the aldehyde synthon in the synthetic equivalent of an aldol condensation with a propionate ester enolate, which leads to the threo α-methyl-β-hydroxy carboxylic acid ester. This is the opposite diastereomer to that most easily prepared via aldol condensations. Also in contrast to the usual chiral enolate chemistry, the absolute configuration of the product is determined by the boronic acid ester (=the aldehyde synthon), and the enolate is achiral. Much remains to be learned about the scope and limitations of the method, but it is apparent that this work adds a new and useful synthetic application for α-halo boronic acid ester chemistry.

The best documented diastereoselectivity is that of the reaction of (S,S)-DIPED (1R)-(1-bromo-2-methylpropyl)boronate (**9b**) with ~95:5 trans/cis *tert*-butyl lithiopropionate (**6**) to produce coupling product **10b** with a ~94:6 threo/erythro ratio. The isomer ratio is only approximate because of the need to rely on ^{13}C NMR spectra, but the data for the β-hydroxy ester products **11b** and **13b** leave no doubt that these are correctly identified. The identifications are further strengthened by ^1H NMR data, but the use of products that had not been chromatographed in order to avoid isomer separation resulted in impurity peaks that interfered with the determination of the isomer ratios in the ^1H spectra.

The foregoing result suggests a nearly stereospecific attack of the boron atom of the chiral α-bromo boronic acid ester on a single enantioface of the enolate, followed by the usual stereospecific rearrangement of the resulting borate complex.[7]

As noted in the Results section, there is insufficient evidence to prove whether the reactions of *tert*-butyl *trans*-lithiopropionate (**6**) with DIPED (1R)-(1-bromopentyl)boronate (**9a**) and with the corresponding pinacol ester **5** really produce 60:1 and >100:1 diastereomeric ratios in **10a** and **7**, respectively. These substantially exceed the isomeric purity of the enolate **6** but could be rationalized on the basis that one diastereomer of the intermediate borate might rearrange faster than another. Care was taken during chromatography to include the entire product fractions, and the observation of 8–9% diastereomeric impurity in the *tert*-butyl ester **11a** produced via the 2,5-dimethoxy-2,5-dimethyl-3,4-hexanediol boronic acid ester **9d** further suggests that the diastereomer would be retained if present.

However, the ~6% threo isomer in crude methyl ester **13a** made via **10a** is contradictory evidence. In view of the observed instability of analogous **13b** in deuteriochloroform, it is possible that **13a** might have epimerized before the NMR spectrum was taken. The only firm conclusion is that ~15:1 is the lower bound for the initial threo/erythro ratio, and the process is therefore synthetically useful.

The yields, generally ~60% for conversion of **8** to **10**, are less than usual for displacements of halide from α-halo boronic acid esters. However, the presently described process has the advantage of simplicity for what it accomplishes. Otherwise, conversion of a boronic ester **8** to an α-methyl-β-hydroxy carboxylic acid ester **11** would require chain extension,[4] introduction of protected hydroxyl,[4,13] chain extension, methylation,[4] chain extension, oxidation to carboxyl,[5] esterification, and hydroxyl deprotection.[4,13]

Since α-halo boronic acid esters analogous to **9** are generally obtainable in ~99% diastereomeric purity,[7] the enantiomeric purity of the ultimate β-hydroxy ester products **11** should also be high. It has been shown that the epimer of the α-chloro analogue of **9b** reacts inefficiently with nucleophiles, and products of very high diastereomeric purity can be obtained from the major isomer,[18] opening the possibility that further enhancement of enantiomeric purities may occur in reactions of α-bromo boronic acids esters with enolates. However, enantiomeric purities have not been measured in the present work.

The catalysis of aldol or Claisen condensations by α-halo boronic acid esters was unanticipated and is not understood, though reasonable hypothetical mechanisms can be written. Perhaps an intermediate borylated carbonyl compound **2** can be converted to enolate by reaction with lithiocyclohexanone, regenerating free cyclohexanone. Then the cyclohexanone may condense either with the enolate of **2** or with lithiocyclohexanone to form a lithiated aldol, which can be boronated ultimately to **3** or its boron enolate. Deboronation of α-boryl ketone **3** in water has ample precedent.[19]

The isomer ratios obtained with 2,5-dimethoxy-2,5-dimethyl-3,4-hexanediol (**16**) boronic acid esters both in the chain extension with (dihalomethyl)lithium and in the reaction of α-bromo boronic acid esters with *tert*-butyl lithiopropionate (**6**) were disappointing. However, the differences between these and the DIPED esters suggest that the methoxy substituent might provide useful stereochemical influence in other reactions involving organometallic species.

Experimental Section

General Data. All reactions involving lithiated compounds were carried out under argon in glassware that had been dried at 110 °C. The tetrahydrofuran (THF) was freshly distilled from benzophenone ketyl. Acetonitrile was distilled from calcium hydride and stored over 4-Å molecular sieves. Lithium diisopropylamide (LDA), 1.5 M as the THF complex in cyclohexane, was purchased from Aldrich Chemical Company and was titrated with 2-propanol to the 1,10-phenanthroline end point. ^1H NMR spectra at 200 MHz were taken on a Nicolet NT-200 and are referred to internal tetramethylsilane. ^1H and ^{13}C NMR spectra at 500 and 125.4 MHz, respectively, were taken on a Varian VXR-500S and referred indirectly to tetramethylsilane via the $CHCl_3/CDCl_3$ solvent peaks. The optical rotation was measured with a Jasco DIP-181 digital polarimeter. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

Pinacol (1-Bromopentyl)boronate (5). This compound was prepared in the same manner as described below for **9a**. Reactants included pinacol (1-butyl)boronate[20] (0.93 g, 5.0 mmol), dibromomethane (8.0 mL), THF (40 mL), LDA (3.7 mL, 1.5 M), and anhydrous zinc chloride (1.15 g, 8.5 mmol). Crude **5** was used in the next step without further purification. From 200-MHz ^1H NMR data, 9% starting pinacol (1-butyl)boronate was present

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in crude **5**. A 250-mg sample of crude **5** was flash chromatographed through silica gel with 3% diethyl ether/petroleum ether to give 117 mg (47%) of **5** for NMR analysis. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86–0.98 (m, 5, C_2H_5), 1.22–1.85 (m, 4, $(CH_2)_2$), 1.28 (s, 12, $C(CH_3)_2$), 3.29 (t, 1, BrC*H*B).

1,1-Dimethylethyl (2*R,3*R**)-2-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxa-2-borolyl)heptanoate (7).** This compound was prepared from **5** in the same manner as described below for conversion of **9a** to **10a**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84–0.98 (m, 5, CH_2 + CH_3), 1.24 (s, 12, $CHCH_3)_2$), 1.43 (s, 9, $C(CH_3)_3$), 1.19–1.60 (m, 5, $(CH_2)_2$ + C*H*B), 2.46 (quintet, 1, CH_3CHCO). Anal. Calcd for $C_{18}H_{35}BO_4$: C, 66.26; H, 10.81; B, 3.31. Found: C, 66.37; H, 10.94; B, 3.30.

(4*S*,5*S*)-2-Butyl-4,5-bis(1-methylethyl)-1,3,2-dioxaborolane ((*S*,*S*)-DIPED (1-Butyl)boronate) (8a). This was prepared by the reported procedure.[21] ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80–0.90 (m, 5, CH_3CH_2 + CH_2), 0.91 (d, 12, $CH(CH_3)_2$), 1.38 (m, 4, C_2H_4), 1.67 (m, 2, $CH(CH_3)_2$), 3.81 (m, 2, CHOB). $[\alpha]^{21}_{546}$ −66.5° (*c* 2.75, $CHCl_3$) [lit.[21] $[\alpha]^{25}_{546}$ −66.8° (*c* 2.75, $CHCl_3$)].

(*S*,*S*)-DIPED (1-Methylethyl)boronate (8b). This compound has been reported without characterization data.[21] ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (dd, 12, $CHCH(CH_3)_2$), 0.98–1.21 (m, 7, $(CH_3)_2$CHB and $(CH_3)_2$CHB), 1.59–1.75 (m, 2, $(CH_3)_2$CHCH), 3.81 (m, 2, BOCHCH). Anal. Calcd for $C_{11}H_{23}BO_2$: C, 66.69 H, 11.70; B, 5.46. Found: C, 66.75; H, 11.78; B, 5.49.

(*S*,*S*)-DIPED (1-Phenyl)boronate (8c). A solution of 6.10 g (50 mmol) of phenylboronic acid and 7.31 g (50 mmol) of (*S*,*S*)-DIPED in 100 mL of diethyl ether was stirred overnight and then washed with 2 × 20 mL of water. The organic phase was dried over sodium sulfate and filtered, and the solvent was removed by vacuum. Flash chromatography was performed on the residue through silica gel with 5% diethyl ether/petroleum ether to give 11.26 g (97%) of **8c**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, 12, $CH(CH_3)_2$), 1.71 (m, 2, $CH(CH_3)_2$), 3.89 (m, 2, BOCH), 7.43 (m, 0.5, C_6H_5). Anal. Calcd for $C_{14}H_{21}BO_2$: C, 72.44; H, 9.12; B, 4.66. Found: C, 72.69; H, 9.33; B, 4.71.

(*R*,*R*)-2,5-Dimethoxy-2,5-dimethyl-3,4-hexanediol (1-Butyl)boronate (8d). Butylboronic acid (10.7 g, 10.5 mmol) and (3*R*,4*R*)-2,5-dimethoxy-2,5-dimethyl-3,4-hexanediol (2.06 g, 10.0 mmol) in 20 mL diethyl ether was stirred overnight. The solution was washed three times with water, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography through silica gel with 10% diethyl ether in hexanes to yield 2.70 g (99%) of **8d**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80–1.43 (m, 9, C_4H_9B), 1.10 (s, 6, $C(CH_3)_2$), 1.16 (s, 6, $C(CH_3)_2$), 3.23 (s, 6, OCH_3), 4.08 (s, 2, BOCH). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 13.90, 19.11, 21.03, 25.33, 26.28, 49.58, 75.74, 82.45. Anal. Calcd for $C_{14}H_{29}BO_4$: C, 61.78; H, 10.74; B, 3.97. Found: C, 61.81, H, 10.79, B, 3.98.

(*S*,*S*)-DIPED (1*R*)-(1-Bromopentyl)boronate (9a). To a solution of 1.06 g (5.0 mmol) of (*S*,*S*)-DIPED butylboronate (**8a**) and 8.7 g (50 mmol) of dibromomethane in 75 mL of rigorously dried tetrahydrofuran at −78 °C was added 4.0 mL of 1.5 M lithium diisopropylamide (LDA). After the solution stirred for 15 min, 1.9 equiv of anhydrous zinc chloride (1.29 g, 9.5 mmol) was added and the solution was allowed to warm slowly to 20 °C. After stirring for 8 h, 75 mL of petroleum ether was added to the solution, followed by 75 mL of aqueous saturated ammonium chloride. The aqueous phase was separated and washed with 2 × 25 mL of 20% diethyl ether/petroleum ether. The combined organic phases were dried by filtration through a plug of magnesium sulfate, and the solvent was removed under reduced pressure to give crude **9a** containing an 85:15 mole ratio of **9a**:**8a** based on 200-MHz ^{1}H NMR analysis. The α-bromo boronic acid esters decompose easily[22] and therefore are usually not purified before they are used in the next step of the reaction sequence. Flash chromatography was performed on crude **9a** through silica gel with 4% diethyl ether/petroleum ether to give 51% of pure **9a**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.74–0.90 (m, 3, CH_3CH_2), 0.87 (s, 12, $CH(CH_3)_2$), 1.04–1.70 (m, 8, $(CH_2)_3$ and $CH(CH_3)_2$), 3.34 (t, 1, BrCHB), 3.82, (m, 2, CHOB).

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(*S*,*S*)-DIPED (1*R*)-(1-Bromo-2-methylpropyl)boronate (9b). This compound was prepared by the same method as **9a** from (*S*,*S*)-DIPED (1-methylethyl)boronate (**8b**) (1.98 g, 10 mmol), dibromomethane (17.4 g, 100 mmol), 1.5 M LDA (8.00 mL), and anhydrous zinc chloride (2.60 g) to yield crude **9b**, which was used directly in the next step. An analytical sample was obtained by chromatography on silica. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (dd, 12, $BCHCH(CH_3)_2$), 1.19–1.27 (m, 7, $(CH_3)_2$CHB and $(CH_3)_2$CHCHB), 1.60–1.74 (m, 2, $(CH_3)_2$CHCH), 3.23 (d, 1, CHCHBrB), 3.82 (m, 2, $CHCH(CH_3)_2$). Anal. Calcd for $C_{12}H_{24}BBrO_2$: C, 49.52; H, 8.31; B, 3.71; Br, 27.46. Found: C, 49.81; H, 8.69; B, 3.75; Br, 27.80.

(*S*,*S*)-DIPED (*R*)-[(Bromo)(phenyl)methyl]boronate (9c). This compound was prepared in the same manner as described above for **9a** from (*S*,*S*)-DIPED (1-phenyl)boronate (**8c**) (2.30 g, 10 mmol), dibromomethane (17.4 g, 100 mmol), 1.5 M LDA (8.0 mL), and anhydrous zinc chloride (2.60 g). Crude **9c** was used directly in the next step. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, 12, $CH(CH_3)_2$), 1.70 (m, 2, $CH(CH_3)_2$), 3.95 (m, 2, BOCH), 7.39 (m, 5, C_6H_5). Anal. Calcd for $C_{15}H_{22}BBrO_2$: C, 55.43; H, 6.82; B, 3.33; Br, 24.58. Found: C, 55.69; H, 7.01; B, 3.39; Br, 24.95.

(*R*,*R*)-2,5-Dimethoxy-2,5-dimethyl-3,4-hexanediol (1*R*)-(1-Bromopentyl)boronate (9d). This compound was prepared in the same manner as described above for **9a**. Reactants included 0.54 g (1.98 mmol) of (*R*,*R*)-2,5-dimethoxy-2,5-dimethyl-3,4-hexanediol (1-butyl)boronate (**8d**), 3.41 g (19.8 mmol) of dibromomethane, 20 mL of THF, 1.6 mL of 1.5 M LDA, and 1.05 g (7.7 mmol) of anhydrous zinc chloride. Workup with petroleum ether (30 mL) and aqueous saturated ammonium chloride (30 mL) was the same as for **9a**. The solvent was removed by vacuum to give crude **9d**. Flash chromatography of a 300-mg sample on silica gel with 5% diethyl ether/petroleum ether yielded 178 mg (59%) of pure **9d**. The 200-MHz ^{1}H NMR spectrum of crude **9d** showed 9% starting butyl boronic acid ester **8d**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85–1.73 (m, 9, C_4H_9), 1.10 (s, 6, $C(CH_3)_2$), 1.16 (s, 6, $C(CH_3)_2$), 3.21 (s, 6, OCH_3), 3.39 (t, 1, BrCHB), 4.14 (s, 2, BOCH).

1,1-Dimethylethyl (2*S*,3*S*)-3-[(4*S*,5*S*)-4,5-Bis(1-methylethyl)-1,3,2-dioxa-2-borolyl]-2-methylheptanoate (10a). A mixture of 4.0 mL of 1.5 M LDA and 75 mL of rigorously dried THF was cooled to −78 °C. A solution of 0.78 g of *tert*-butyl propionate dissolved in 10 mL of THF cooled to −78 °C was added dropwise slowly via cannula, followed immediately by dropwise addition of crude (*S*,*S*)-DIPED (1*R*)-(1-bromopentyl)boronate (**9a**) (crude, 1.69 g, 5.0 mmol scale) in 10 mL of dry THF cooled to −78 °C. The solution warmed to 25 °C overnight, and the solvents were removed under vacuum. Crude **10a** was dissolved into 20 mL of 10% diethyl ether/petroleum ether and 20 mL of saturated aqueous ammonium chloride. A white precipitate appeared and slowly dissolved into the aqueous phase upon shaking in a separatory funnel. The aqueous phase was separated, and the organic phase was washed with 2 × 10 mL of water. The organic phase was dried over sodium sulfate and filtered. The solvent was removed under vacuum. The residue was purified by flash chromatography through silica gel with 5% ethyl acetate/petroleum ether to yield 1.08 g (61%, based on starting butylboronate **8a**) of **10a**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (d, 12, $CH(CH_3)_2$), 1.45 (s, 9, $C(CH_3)_3$), 0.79–1.67 (m's, 15, $CH_3(CH_2)_3$ + CH_3CHCO + $CH(CH_3)_2$ + CHB), 2.61 (m, 1, CH_3CHCO), 3.80 (m, 2, BOCH). Anal. Calcd for $C_{20}H_{39}BO_4$: C, 67.79; H, 11.09; B, 3.05. Found: C, 67.83; H, 11.28; B, 3.11.

1,1-Dimethylethyl [(2*S*,3*S*)-2,4-Dimethyl-3-[(4*S*,5*S*)-4,5-bis(1-methylethyl)-1,3,2-dioxa-2-borolyl]pentanoate (10b). This compound was prepared in the manner described above for **10a** from **9b** (crude, 10 mmol scale, *tert*-butyl propionate 1.43 g, 11 mmol), THF (10 mL), and 1.5 M LDA (7.70 mL) diluted with THF (20 mL). After workup and flash chromatography (silica gel with 15% ethyl acetate/petroleum ether), 2.01 g (59% based on **8b**) of **10b** was isolated. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90–1.19 (m, 7, $(CH_3)_2$CHCHB and CH_3CHCHB), 0.92 (dd, 12, OCHCH-$(CH_3)_2$), 1.21 (d, 3, CH_3CHCO), 1.45 (s, 9, $C(CH_3)_3$), 1.60–1.82 (m, 3, $(CH_3)_2CHCHO$ and $(CH_3)_2CHCHB$), 2.55 (quintet, 1, CH_3CHCO), 3.75 (m, 2, $OCHCH(CH_3)_2$). Anal. Calcd for $C_{19}H_{37}BO_4$: C, 67.06; H, 10.96; B, 3.18. Found: C, 67.27; H, 11.14; B, 3.21.

1,1-Dimethylethyl (2*S*,3*R*)-2-Methyl-3-phenyl-3-[(4*S*,5*S*)-bis(1-methylethyl)-1,3,2-dioxa-2-borolyl]propanoate

(10c). This compound was prepared in the manner described above for **10a** from (*S,S*)-DIPED (1*R*)-(1-bromo-1-phenylmethyl)boronate (**9c**, crude, 9.8 mmol scale) in THF (10 mL), *tert*-butyl propionate (1.41 g, 10.8 mmol) in THF (10 mL), and LDA (7.50 mL of 1.5 M) in THF (20 mL). After the usual workup and flash chromatography (silica gel with 15% ethyl acetate/petroleum ether), 2.10 g of **10c** (57% based on starting DIPED phenylboronate **8c**) was isolated. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 (dd, 12, $CH(CH_3)_2$), 1.15–1.73 (m, 5, CH_3CHCO and $CH(CH_3)_2$), 1.26 (d J = 8.0 Hz, 1, C_6H_5CHB), 1.45 (s, 9, $C(CH_3)_3$), 2.72 (m, 1, CH_3CHCO), 3.85 (m, 2, BOC*H*), 7.29 (s, 5, C_6H_5). Anal. Calcd for $C_{22}H_{35}BO_4$: C, 70.59; H, 9.42; B, 2.89. Found: C, 70.82; H, 9.69; B, 2.94.

1,1-Dimethylethyl (2*S*,3*S*)-3-[(4*R*,5*R*)-4,5-Bis(1-methoxy-1-methylethyl)-1,3,2-dioxa-2-borolyl]-2-methylheptanoate (10d). This compound was prepared in the same manner as described above for **10a** from *tert*-butyl propionate (0.31 g, 2.4 mmol) in THF (10 mL), LDA (1.60 mL of 1.5 M in THF (30 mL) cooled to −78 °C), followed by **9d** (crude, 2.0 mmol scale) in THF (10 mL). After workup and flash chromatography on silica gel with 10% ethyl acetate/petroleum ether, 0.48 g (58% based on **8d**) of **10d** was isolated. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10 (s, 6, $CH(CH_3)_2$), 1.16 (s, 6, $CH(CH_3)_2$), 1.43 (s, 9, $C(CH_3)_3$), 0.85–1.48 (m's, 13, $CH_3(CH_2)_3$ + CH_3CHCO + CHB), 2.60 (d of q's, 1, CH_3CHCO), 3.20 (s, 3, OCH_3), 3.23 (s, 3, OCH_3), 4.09 (m, 2, BOC*H*). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 10.96, 14.06, 22.98, 23.72, 28.91, 29.69, 30.34, 38.70, 68.12, 76.81, 77.16, 78.08, 167.70. Anal. Calcd for $C_{22}H_{43}BO_6$: C, 63.77; H, 10.46; B, 2.61. Found: C, 64.30; H, 10.54; B, 2.70.

1,1-Dimethylethyl (2*S*,3*S*)-3-Hydroxy-2-methylheptanoate (11a). A solution of 354 mg (1.0 mmol) of **10a** in 20 mL of THF was stirred at 0 °C and was treated with 0.37 mL of 3.0 M sodium hydroxide, 1.0 mL of 30% hydrogen peroxide, and 10 mL of pH 8.6 borate buffer. The mixture was stirred overnight and then treated with 20 mL of diethyl ether. After separation of the phases, the aqueous phase was washed with 3 × 10 mL of diethyl ether. The combined organic phases were dried over sodium sulfate and filtered, and the solvent was removed by vacuum. Flash chromatography was performed on the residue (silica gel, 15% ethyl acetate/petroleum ether) to give 53.9 mg (85%) of the β-hydroxy ester **11a**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.83–0.94 (m, 5, CH_3 + CH_2), 1.12–1.63 (m, 4, $(CH_2)_2$), 1.18 (d, 3, CH_3CHCO), 1.46 (s, 9, $C(CH_3)_3$), 2.44 (m, 1, CH_3CHCO), 2.72 (br s, 1, O*H*), 3.60 (m, 1, C*H*OH). ^{13}C NMR (75.18 MHz, $CDCl_3$) δ 14.04 (CH_3CHCO), 14.41, 22.69, 27.81, 28.12, 34.62, 45.84 (CH_3CHCO), 73.53 (*C*HOH), 80.97, 175.59. When this compound was prepared from **10a**, the erythro (2*R*,3*S*) isomer was observed at δ 10.85 (CH_3CHCO), 45.07 (CH_3CHCO), and 71.87 (*C*HOH), each peak being $^1/_{60}$th the height of the corresponding threo isomer peaks. When prepared from **10d**, the erythro isomer was 9%. The racemate prepared via **5** and **7** showed no evidence of erythro isomer at a signal to noise ratio of >100:1. Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.79; H, 11.32.

1,1-Dimethylethyl (2*S*,3*S*)-2,4-Dimethyl-3-hydroxypentanoate (11b). This compound was prepared from **10b** (340 mg, 1.0 mmol), sodium hydroxide (0.37 mL of 3.0 M), 30% hydrogen peroxide (1.0 mL), and pH 8.6 borate buffer (10 mL) in the manner described above for **11a**. The usual workup and flash chromatography through silica gel with 20% ethyl acetate/petroleum ether yielded 186 mg (86%) of **11b**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (d, 6, $(CH_3)_2CH$), 1.27 (d, J = 7.0 Hz, 3, CH_3CHCO), 1.45 (s, 9, $(CH_3)_3C$), 1.80 (m, 1, $(CH_3)_2CH$), 2.71 (m, 1, CH_3CHCO), 2.79 (br s, 1, O*H*), 3.74 (dd, J = 4, J = 7.7 Hz, 1, CH_3CHO). ^{13}C NMR (125.4 MHz) 14.80 (CH_3CHCO), 17.36, 18.32, 27.75, 30.37, 43.04 (CH_3CHCO), 78.18 (*C*HOH), 80.95, 176.03; erythro (~7%) 10.39, 42.54, 76.35 (obscured by $CDCl_3$). Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.45; H, 11.09.

1,1-Dimethylethyl [(2*S*,3*R*)-(2-Methyl-3-hydroxy-3-phenyl)]propanoate (11c). This compound was prepared from **10c** (374 mg, 1.0 mmol), 3.0 M sodium hydroxide (0.37 mL), 30% hydrogen peroxide (1.0 mL), and pH 8.6 borate buffer (10 mL) in the manner described above for **11a**. After workup and flash chromatography through silica gel with 20% ethyl acetate/petroleum ether, 213 mg (90%) of **11c** was isolated. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.32 (d, 3, CH_3CHCO), 1.44 (s, 9, $C(CH_3)_3$), 2.71 (m, 1, CH_3CHCO), 2.75 (br s, 1, O*H*), 4.71 (d, J = 8.1 Hz, 1, C_6H_5CHO). A sample that had not been subjected to chromatography at any stage also showed δ 4.97 (d, J = 4.8 Hz, 11%, possibly C_6H_5CHO of erythro isomer). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.29; H, 8.64.

(2*S*,3*S*)-3-[(4*S*,5*S*)-4,5-Bis(1-methylethyl)-1,3,2-dioxa-2-borolyl]-2-methylheptanoic Acid (12a). This compound was prepared by the method of Olah and co-workers[1] by using 3.06 g (8.6 mmol) of **10a** and 3.87 g (25.8 mmol) of sodium iodide in 20 mL of dry acetonitrile, followed by addition of 3.27 mL (25.8 mmol) of chlorotrimethylsilane. After the usual workup and a 10% aqueous sodium bicarbonate extraction followed by acidification, 1.84 g (6.2 mmol) of **12a** (72%) was obtained. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.96 (s, 6, $C(CH_3)_2$), 0.98 (s, 6, $C(CH_3)_2$), 0.85–1.93 (m, 15, aliphatic CH + CHB), 2.61 (m, 1, CH_3CHCO), 3.79 (m, 2, BOC*H*), 10.24 (br s, 1, CO_2H). Anal. Calcd for $C_{17}H_{31}BO_4$: C, 65.82; H, 10.07; B, 3.48. Found: C, 65.95; H, 10.13; B, 3.51.

(2*S*,3*S*)-2,4-Dimethyl-3-[(4*S*,5*S*)-4,5-bis(1-methylethyl)-1,3,2-dioxa-2-borolyl]pentanoic Acid (12b). This compound was prepared in a same manner as **12a** by using 1.87 g (5 mmol) of **10b** and 2.25 g (15 mmol) of sodium iodide in 10 mL of dry acetonitrile, followed by addition of 1.90 mL (15 mmol) of chlorotrimethylsilane. After the usual workup and a 10% aqueous sodium bicarbonate extraction with acidification, 1.13 g (3.98 mmol) of **12b** (80%) was obtained. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (s, 6, $C(CH_3)_2$), 0.96 (s, 6, $CH_3)_2$), 0.91–1.29 (m, 10, aliphatic CH + CH B), 1.57–1.96 (m, 3, CH $(CH_3)_2$), 2.74 (m, 1, CH_3CHCO), 3.76 (m, 2, BOC*H*), 10.21 (br s, 1, CO_2H). Anal. Calcd for $C_{15}H_{29}BO_4$: C, 63.39; H, 10.29; B, 3.80. Found: C, 63.51; H, 10.35; B, 3.85.

(2*S*,3*R*)-2-Methyl-3-phenyl-3-[(4*S*,5*S*)-4,5-bis(1-methylethyl)-1,3,2-dioxa-2-borolyl]propanoic Acid (12c). This compound was prepared in the same manner as **12a** by using 2.50 g (6.7 mmol) of **10c** and 2.99 g (20 mmol) of sodium iodide in 20 mL of dry acetonitrile, followed by addition of 2.53 mL (20 mmol) of chlorotrimethylsilane. After the usual workup and a 10% aqueous sodium bicarbonate workup, 1.69 g (5.3 mmol) of acid **12c** (79%) was isolated. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (s, 6, $C(CH_3)_2$), 0.97 (s, 6, $C(CH_3)_2$), 0.91–1.15 (m, 4 CH_3C + CH B), 1.34–1.82 (m, 2, $CH(CH_3)_2$), 2.63 (m, 1, CH_3CHCO), 3.75 (m, 2, BOC*H*), 7.11 (m, 5, C_6H_5), 9.97 (br s, 1, CO_2H). Anal. Calcd for $C_{18}H_{27}BO_4$: C, 67.94; H, 8.55; B, 3.40. Found: C, 68.13; H, 8.63; B, 3.45.

Methyl (2*S*,3*S*)-3-Hydroxy-2-methylheptanoate (13a). (2*S*,3*S*)-3-Hydroxy-2-methylheptanoic acid was prepared from **12a** (1.48 g, 5.0 mmol), sodium hydroxide (1.83 mL of 3.0 M), 30% hydrogen peroxide (5.0 mL), and 0.1 M borate buffer at pH 8.6 (20 mL) under similar conditions to those described above for the preparation of **11a**. The aqueous phase was separated and treated with dilute hydrochloric acid until it was acidic to pH paper. The aqueous phase was extracted with 3 × 20 mL of diethyl ether. The combined ethereal phases were dried over sodium sulfate. After filtration, the solvent was removed under vacuum to yield 713 mg (4.45 mmol) of the β-hydroxy acid (89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86–1.46 (m, 12, CH_3 + CH_2), 2.68 (m, 1, CH_3CHCO), 3.49 (1, 1, C*H*OH), 4.73 (concentration dependent) (br s, 2, O*H* + CO_2H). Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 60.12; H, 10.15. The esterification of the β-hydroxy acid (641 mg, 4 mmol) was accomplished with excess diazomethane in diethyl ether; 627 mg (3.6 mmol) of **13a** (91%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85–0.98 (m, 6, $CH_3(CH_2)_3$ + CH_3CHCO), 1.09–1.59 (m, 6, $CH_3(CH_2)_3$), 2.55 (quintet, 1, J = 7.1 Hz, CH_3CHCO), 3.54–3.71 (m, 1, C*H*OH), 3.73 (s, 3, CH_3O), 5.13 (concentration dependent) (br s, 1, O*H*). ^{13}C NMR (125.4 MHz, $CDCl_3$) δ 14.04, 14.34, 22.65, 27.81, 34.44, 45.24, 51.79, 73.47, 176.85; erythro (~7%) 10.84, 44.47, 71.82. The erythro isomer of **13a** has been reported without characterization data.[23]

Methyl (2*S*,3*S*)-2,4-Dimethyl-3-hydroxypentanoate (13b). (2*S*,3*S*)-2,4-Dimethyl-3-hydroxypentanoic acid was prepared from **12b** (1.42 g, 5.0 mmol), sodium hydroxide (1.83 mL of 3.0 M), 30% hydrogen peroxide (5.0 mL), and 0.1 M borate buffer at pH 8.6 (20 mL) in the same manner described above for the preparation of **13a**. Following the usual workup, 614 mg (4.2 mmol) of the

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β-hydroxy acid was isolated (84%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.96–1.26 (m, 10, $(CH_3)_2CH + CH_3$), 2.71 (m, 1, CH_3CHCO), 3.49 (1, 1, CHOH), 6.15 (concentration dependent) (br s, 2, OH + CO_2H). The esterification of the β-hydroxy acid (585 mg, 4 mmol) was accomplished by using excess diazomethane in diethyl ether to yield 609 mg of **13b** (95%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (s, 3, $(CH_3)_2CH$), 0.97 (s, 3, $(CH_3)_2CH$), 1.21 (d, 3, CH_3CHCO), 1.65–1.80 (m, 1, $CH_3)_2CH$), 2.67 (quintet, 1, J = 7.1 Hz, CH_3CHCO), 3.39 (t, 1, CHOH), 3.71 (s, 3, CH_3O), 4.78 (concentration dependent) (br s, 1, OH). ^{13}C NMR (125.4 MHz, $CDCl_3$) δ 14.81 (CH_3CHCO), 16.37, 19.79, 31.05, 42.60 (CH_3CHCO), 51.77, 78.30 (CHOH), 177.01; erythro (~7%) at 10.16, 41.69 (76.45 obscured by $CDCl_3$) (lit.[11] 10.3, 42.0, 76.7). $[\alpha]^{25}_D$ −12.4° (c 1.05, $CHCl_3$) (lit.[14] $[\alpha]^{23}_D$ − 12.5° (c 1.04, $CHCl_3$); lit.[24] $[\alpha]^{25}_D$ −9.1° (c 1.2, solvent not stated). The erythro content of this sample increased on standing a few days. Spiking the 93% threo sample with an erythro/threo mixture[9] resulted in the expected increase in the intensity of the peaks at δ 10.16, 41.69, and 76.45.

(4*R*,5*R*)-4,5-Bis(carbomethoxy)-2-phenyl-1,3-dioxolane [Dimethyl (2*R*,3*R*)-2,3-*O*-Benzylidenetartrate] (14). This compound was prepared by the literature method;[25] 78%; mp 71–72 °C; $[\alpha]^{21}_D$ −44.1° (c 1.0, C_6H_6) [lit.[26] mp 70–71 °C, $[\alpha]_D$ −44° (c 1.0, C_6H_6); lit.[27] mp 74 °C, $[\alpha]_D$ −44.2° (c 1.74, C_2H_5OH)]. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.79 (s, 3, CO_2CH_3), 3.84 (s, 3, CO_2CH_3), 4.98 (d, 1, J = 4.0 Hz, OCH), 4.85 (d, 1, J = 4.0 Hz, OCH), 6.13 (s, 1, O_2CHPh), 7.48 (m, 5, C_6H_6).

(4*R*,5*R*)-4,5-Bis(1-hydroxy-1-methylethyl)-2-phenyl-1,3-dioxolane (15a). A solution of (4*R*,5*R*)-4,5-bis(carbomethoxy)-2-phenyl-1,3-dioxolane (14) (126.7 g, 0.48 mol) in 200 mL of tetrahydrofuran was added dropwise to a mechanically stirred solution of 5 equiv of methylmagnesium bromide in 2.5 L of diethyl ether cooled to −78 °C. Stirring became difficult toward the end of addition due to a separate gummy phase. After standing overnight, the mixture was treated with excess saturated aqueous ammonium chloride and stirred until all solids were dissolved (*CAUTION*: methane evolution). The ether extract was dried over sodium sulfate, the ether was removed by vacuum, and the resulting solid was washed with light petroleum ether (bp 35–60 °C) and filtered: 122.97 g (97%); mp 82–85 °C, 200 MHz. ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 3, $C(CH_3)$), 1.29 (s, 3, $C(CH_3)$), 1.33 (s, 3, $C(CH_3)$), 1.36 (s, 3, $C(CH_3)$), 2.82 (br s, 2 OH), 4.00 (d, 1, J = 5.6 Hz, OCH), 4.10 (d, 1, J = 5.6 Hz, OCH), 6.03 (s, 1, O_2CHPh), 7.43 (m, 5, C_6H_6). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.68; H, 8.49.

(4*R*,5*R*)-4,5-Bis(1-methoxy-1-methylethyl)-2-phenyl-1,3-dioxolane (15b). A solution of 8 equiv of powdered potassium hydroxide (199 g, 3.55 mol) in 900 mL of dimethyl sulfoxide was stirred for 5 min before (4*R*,5*R*)-4,5-bis(1-hydroxy-1-methylethyl)-2-phenyl-1,3-dioxolane (**15a**) (118 g, 0.443 mol) was added, followed immediately by 4 equiv of methyl iodide (110.3 mL, 1.77 mol). The reaction vessel was fitted with a dry ice condenser and stirred under reflux for 12 h. The mixture was poured into water (1 L) and extracted with dichloromethane (3 × 500 mL). The combined organic extracts were washed with water (5 × 250 mL) and dried over sodium sulfate. The solution was concentrated under vacuum and crystallized from methanol/water: 117 g (94%); mp 75–78 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.16 (s, 3, $C(CH_3)$), 1.17 (s, 3, $C(CH_3)$), 1.25 (s, 3, $C(CH_3)$), 1.32 (s, 3, $C(CH_3)$), 3.24 (d, 6, OCH_3), 4.02 (d, 1, J = 3.7 Hz, OCH), 4.23 (d, 1, J = 3.7 Hz, OCH), 6.12 (s, 1, OCHPh), 7.42 (m, 5, C_6H_6). Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.52, H, 9.08.

(3*R*,4*R*)-2,5-Dimethoxy-2,5-dimethyl-3,4-hexanediol (16). In order to remove residual dimethyl sulfoxide or other sulfur compounds, which were found to poison the palladium catalyst, a solution of (4*R*,5*R*)-4,5-bis(1-methoxy-1-methylethyl)-2-phenyl-1,3-dioxolane (**15b**) (23.10 g, 82 mmol) and Raney nickel (5 g) in 75 mL of absolute ethanol was stirred overnight. The solution was filtered, and the Raney nickel was rinsed with ethanol. The sulfur-free ethanolic solution was then hydrogenated at 1 atm at 55 °C in the presence of 10 g of palladium on carbon catalyst overnight in a Brown[2] hydrogenator.[28] The palladium on carbon catalyst was removed by filtration followed by an ethanolic wash. Concentration gave crude (*R*,*R*)-2,5-dimethoxy-2,5-dimethyl-3,4-hexanediol (**16**), which was purified by flash chromatography through silica gel (20% ethyl acetate/hexane): 16.2–16.7 g (95–99%); $[\alpha]^{21}_{546}$ −9.47° (c 1.3, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.16 (s, 6, $C(CH_3)_2$), 1.22 (s, 6, $C(CH_3)_2$), 3.26 (s, 6, OCH_3), 3.57 (d of d, 4, J = 4.2, J = 23.1 Hz, OCH and OH). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 20.54, 21.64, 49.49, 73.80. Anal. Calcd for $C_{10}H_{22}O_4$: C, 58.23; H, 10.75. Found: C, 58.48; H, 10.86.

(*R*,*R*)-2,5-Dimethoxy-2,5-dimethyl-3,4-hexanediol Phenylboronate. This compound was prepared in the same manner as **8b** from phenylboronic acid (1.34 g, 11.0 mmol) and (*R*,*R*)-2,5-dimethoxy-2,5-dimethyl-3,4-hexanediol (2.06 g, 10.0 mmol) and was purified by flash chromatography through silica gel (10% ethyl acetate/hexanes), 2.78 g (93%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.16 (s, 6, $C(CH_3)_2$), 1.23 (s, 6, $C(CH_3)_2$), 3.24 (s, 6, OCH_3), 4.30 (s, 2, BOCH), 7.33–7.88 (m, 5, C_6H_6). Anal. Calcd for $C_{16}H_{25}BO_4$: C, 65.77; H, 8.62; B, 3.70. Found: C, 65.88; H, 8.79; B, 3.72.

(*R*,*R*)-2,5-Dimethoxy-2,5-dimethyl-3,4-hexanediol 1-Methylboronate. A solution of (*R*,*R*)-2,5-dimethoxy-2,5-dimethyl-3,4-hexanediol (10.6 g, 51.4 mmol) and diisopropoxymethylborane (7.4 g, 51.4 mmol) in 15 mL of tetrahydrofuran was stirred overnight. Concentration and flash chromatography through silica gel (10% ethyl acetate/hexanes) yielded 11.4 g (97%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.31 (s, 3, BCH_3), 1.11 (s, 6, $C(CH_3)_2$), 1.16 (s, 6, $C(CH_3)_2$, 3.23 (s, 6, OCH_3), 4.08 (s, 2, BOCH). Anal. Calcd for $C_{11}H_{23}BO_4$: C, 57.42; H, 10.07; B, 4.70. Found: C, 57.50; H, 10.15; B, 4.67.

(*R*,*R*)-2,5-Dimethoxy-2,5-dimethyl-3,4-hexanediol 1-Ethenylboronate. This compound was prepared in the same manner as the preceding from dibutyl ethenylboronate[29] and (*R*,*R*)-2,5-dimethoxy-2,5-dimethyl-3,4-hexanediol (98%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (s, 6, $C(CH_3)_2$), 1.18 (s, 6, $C(CH_3)_2$), 3.23 (s, 6, OCH_3), 4.17 (s, 2, BOCH), 5.81–6.27 (m, 3, CH_2=CHB). Anal. Calcd for $C_{12}H_{23}BO_4$: C, 59.53; H, 9.57; B, 4.47. Found: C, 59.60; H, 9.67; B, 4.45.

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