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Synthesis of a (β-acetamido-α-acetoxyethyl)boronic ester via azido boronic esters

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ABSTRACT

(Azidomethyl)boronic esters of 1,2-dicyclohexyl-1,2-ethanediol ("DICHED") and pinanediol have been prepared from the corresponding (bromomethyl)boronic esters. Conversion to (2-azido-1-chloro- or bromoethyl)boronic esters by reaction with a (dihalomethyl)lithium followed. Attempted displacement of halide from DICHED (2-azido-1-haloethyl)boronates with alkoxides failed. Reaction of either pinanediol or DICHED (2-azido-1-chloromethyl)boronate with sodium acetate in acetic acid yielded the 1-acetoxy derivative as a ~1:1 mixture of diastereomers, indicating probable involvement of an α-boryl carbocation intermediate. Hydrogenation of the pinanediol azido boronic ester over platinum in a solution of hydrogen chloride in dioxane was accompanied by deacetylation to form the impure (2-amino-1-hydroxyethyl)boronic ester hydrochloride. Attempted purification of this material resulted in deboronation to ethanolamine. Acetylation yielded pinanediol (2-acetamido-1-acetoxyethyl)boronate.

1. Introduction

Boronic acids bearing functional substituents are of interest as analogs of biologically significant carboxylic acids [1,2]. The most noteworthy example to date is the successful proteasome inhibitor bortezomib (Velcade™, Millennium Pharmaceuticals) [3], an α-amido boronic acid that has been approved for treatment of relapsed multiple myeloma and mantle cell lymphoma in the United States and numerous other countries. The functionalized boronic acids 2-amino-6-boronohexanoic acid [4] and *S*-[2-boronoethyl]cysteine [5] have received recent attention as arginase inhibitors capable of increasing biological nitric oxide levels.

Syntheses of the foregoing examples involved introduction of amine functionality into boronic esters, which for remote amino groups was easy [4,5] and for α-amido boronic esters [2,3] was a difficult problem that was solved some time ago [6]. β-amino boronic esters pose some synthetic problems and have received much less attention. Soon after the discovery of β-halo boronic esters, replacement of the β-halide by nitrogen nucleophiles was shown not to be a possibility because of rapid base catalyzed elimination of boron and halogen [7]. Butler and Soloway made (2-ureidoethyl)boronic acid via hydroboration of vinylurea in 1965 [8]. A boronic acid analog of aspartic acid, β-(dihydroxyboryl)alanine, has been made from a (halomethyl)boronic ester via an amidomalonic ester synthesis [9] or from a β-lithiated Boc-protected amine [10]. These routes are not suitable for making β-amino boronic esters bearing α-heteroatom substituents.

α-Heteroatom substituted (β-aminoalkyl)boronic acid derivatives have proved unusually difficult to make. The synthesis of silylated (2-amino-1-chloroethyl)boronic esters from silylated aminomethyl boronic esters has been described [11]. The 1-chloride was displaced by sodio(methanethiol), and desilylation and treatment with trimethylsilyl isocyanate led to the [2-ureido-1-(methylthio)ethyl]boronic ester [11]. It appeared that dimethylamino substitution was also successful, though the product was not completely purified. Attempts to displace the chloride with benzyl oxide failed [11]. Attempted insertions of (dichloromethyl)lithium into silylated α-benzylamino- or α-formamido-β-trityloxy boronic esters failed [11].

The failure of the alkoxide substitution was unexpected, though a previous failure of alkoxide substitution has been observed with an α-chloroallylboronic ester [12], even though silylated amino substitution on the same compound proceeded normally [13]. α-Azido boronic esters have been homologated with (chloromethyl)lithium to provide asymmetric syntheses of α-amino alcohols [14], α-amino acids [15], and an α-cyanomethyl-β-azido-γ-silyloxy boronic ester [16]. This study was begun in the hope that the β-azido substituent also might not interfere with α-chloride replacement by alkoxide and thus might provide (α-alkoxy-β-azidoalkyl)boronic esters as potentially useful synthetic intermediates.

2. Results

(*R*,*R*)-1,2-Dicyclohexyl-1,2-ethanediol ("DICHED") (bromomethyl)boronate (**1**) (ee >99%) [17] was converted to the (azidomethyl)boronate (**2**) in nearly quantitative yields according to

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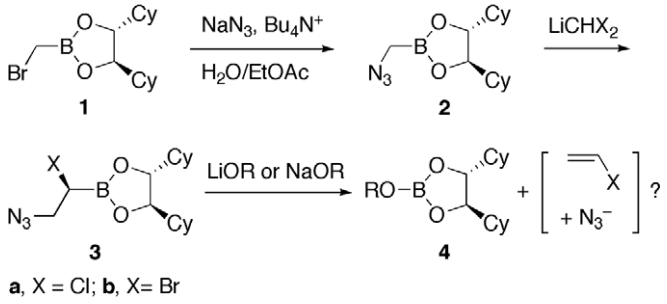
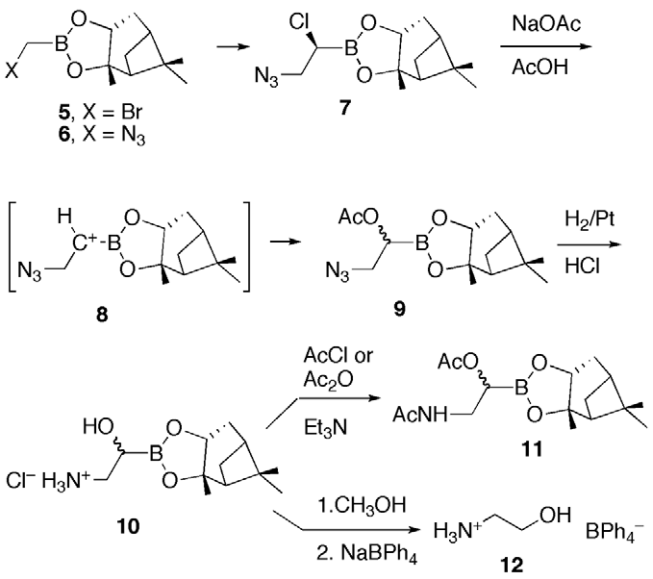
previously optimized phase-transfer conditions for reactions of α-halo boronic esters with sodium azide catalyzed by tetrabutylammonium bromide in water/ethyl acetate [16]. There being no need to keep the reaction temperature low to preserve stereoselection in the absence of a stereocenter at the reactive site, it was convenient to heat the mixture to reflux and shorten the reaction time to a few hours. Homologation of **2** with (dihalomethyl)lithium in the usual manner [14] provided DICHED (1-chloro-2-azidoethyl)boronate (**3a**) (76%) or its bromo analogue (**3b**) (64%) as nearly pure single diastereomers.



Although the preparations of the 2-azido-1-haloethylboronic esters **3** proceeded efficiently, the next anticipated step failed totally. Reactions of **3a** or **3b** with lithium or sodium benzyl oxide, sodium methoxide or *p*-methoxybenzyl oxide, or lithium phenoxide failed to yield any substitution product and resulted in deboronation to DICHED alkoxyborate (**4**), presumably with β-elimination of azide.

One other possibility for introducing an α-oxy substituent in the presence of a β-azido substituent remained. Displacement of halide from an α-halo boronic ester by sodium acetate in hot acetic acid had been reported in 1963 [18]. Because (+)-pinanediol (from (+)-α-pinene) is easier to make than DICHED and its boronic esters are even more resistant to hydrolysis, testing of this pathway was carried out with pinanediol esters. (+)-Pinanediol (bromomethyl)boronate (**5**) (ee ~99%) [19] was converted to the azido derivative **6** and on to pinanediol (1-chloro-2-azidoethyl)boronate (**7**) in the same manner as **1** was converted to **3a**. Reaction of **7** with sodium acetate in acetic acid did not proceed appreciably in 24 h at room temperature, but when heated overnight at ~90 °C produced a mixture of diastereomers **9** in a ratio between 2:3 and 1:1 in high yield. The α-boryl carbocation **8** is postulated to be an intermediate. The (*S*,*S*)-DICHED boronic ester ***ent*-3a** was also tested with sodium acetate in acetic acid. Again, after 24 h at 20-25 °C the starting material was unchanged except for a barely detectable acetyl CH_3 peak in the ^1H NMR. On heating at 95 °C for 20 h, conversion to a 1:1 mixture of diastereomeric acetates was nearly quantitative. This was further confirmed by transesterification of the DICHED ester mixture with (+)- and (−)-pinanediol, each of which yielded a 1:1 mixture of diastereomers having the same appearance in the ^1H NMR spectrum.

Pinanediol (1-acetoxy-2-azidoethyl)boronate (**9**) was hydrogenated at 10 atmospheres over platinum in dioxane in the presence of hydrogen chloride. Unfortunately, hydrogenation under these acidic conditions was accompanied by deacetylation to the α-hydroxy boronic ester **10**, which proved unstable on attempted purification. Prompt acetylation of **10** led to pinanediol 1-acetoxy-2-acetamidoethylboronate (**11**). When the hydrogenation was carried out in methanol, deboronation of **10** occurred and the product isolated on treatment with aqueous sodium tetraphenylborate was ethanolamine tetraphenylborate (**12**), which showed a characteristic pair of triplets in the ^1H NMR at δ 2.88 and 3.66, J = 5.3 Hz, and matched an authentic sample of **12** prepared from aqueous ethanolamine and hydrochloric acid with sodium tetraphenylborate.



3. Discussion

Although the results of this study are disappointing from a synthetic point of view, they do reveal significant information about the behavior of this highly functionalized series of boronic esters.

The lack of stereoselectivity in the reaction of the pinanediol 2-azido-1-chloroethylboronate (**7**) or the corresponding (*S*,*S*)-DICHED ester ***ent*-3a** with sodium acetate in acetic acid strongly implies that this displacement occurs via a carbocation (S_N1) pathway. The rationale for testing ***ent*-3a** was that previous studies of solvolytic substitution or elimination reactions of α-halo boronic esters have indicated that these reactions proceed with considerable nucleophilic assistance by the solvent [7], and that reactions involving coordination of a nucleophile to boron bound to a C_2-symmetrical diol can result in a high degree of kinetic resolution [20]. Although the hypothesis that the lack of stereoselection could result from epimerization of **7** or ***ent*-3a** prior to substitution has not been rigorously ruled out, it seems unlikely that acetate could displace chloride where alkoxide fails, and unlikely that there would be no kinetic differentiation between ***ent*-3a** and its epimer in a substitution process. The total lack of stereoselection in the sodium acetate reactions implies that the chiral diol units are too far from the substitution site to interact sterically, and that assistance by the boron atom in the acetate connection process must be negligible.

The instability of the α-hydroxy boronic ester **10** was not anticipated, inasmuch as other α-hydroxy boronic esters have been generated as intermediates by cleavage of benzylic ethers and converted to stable derivatives [16,21], though isolation has not been attempted. Instability of α-hydroxy boronic esters in basic solution is a possible but unproved explanation for the high yields of 1-hexanol obtained from hydroboration of 1-hexyne followed by alkaline oxidation with hydrogen peroxide [22,23]. The well documented instability of α-amino boronic esters in their free amine form [6] implies very strongly that deprotonated α-hydroxy boronic esters would rearrange rapidly to the corresponding trialkoxyboranes. Hydrolysis of methylboronic acid to methane and boric acid, $CH_3B(OH)_2 + H_2O = CH_4 + B(OH)_3$, is exothermic by an

estimated 112.4 kJ/mol (26.9 kcal/mol) [24]. The alcoholysis or hydrolysis of an α-hydroxy boronic ester to an alcohol and borate ester or boric acid should be similarly exothermic, and the presence of the α-hydroxy or alkoxide group evidently provides a pathway for hydrolysis that does not exist for simple alkylboron compounds.

Alkoxides are the only common nucleophiles that fail to displace chloride from certain α-chloro boronic esters, including β-azido boronic esters, as noted above [11–15]. The exothermic character of reactions that replace B–C bonds by B–O bonds [24] is undoubtedly a major factor in some cases. Alkoxide displacements fail when there is another pathway accessible for the decomposition of the (α-chloroalkyl)(trialkoxy)borate intermediate, β-elimination in the case of the azido compounds and perhaps dissociation to an α-chloroallylic anion in the case of certain α-chloro boronic esters [12]. The reason for failure of silylated β-amino boronic esters to undergo α-chloro displacement by alkoxide was not clear [11]. In retrospect, it appears all the more remarkable that β-elimination of boron and oxygen from (β-alkoxy-α-chloroalkyl)(trialkoxy)borates was not evident in the assembly of a sequence of four adjacent benzyloxy substituted carbons for an asymmetric synthesis of ribose [25], though it could have been an unrecognized factor in the inefficiency of the process for introducing a fifth carbon in the same manner.

4. Conclusions

(1) Attempted replacement of chloride from (1-halo-2-azidoethyl)boronic esters with alkoxide nucleophiles is superseded by β-elimination of boron and azide. (2) Replacement of chloride from α-chloro boronic esters by acetate in acetic acid apparently proceeds via a carbocation mechanism. (3) Chiral direction by the 1,2-dicyclohexyl-1,2-ethanediol boronic ester group does not extend to nucleophilic attack on an α-boryl carbocation site. (4) Catalytic hydrogenation of a (1-acetoxy-2-azidoethyl)boronic ester in acid yields a (1-hydroxy-2-aminoethyl) boronic ester salt that is highly susceptible to protodeboronation. Other methods of reduction that might preserve the acetoxy group have not been extensively explored. (5) α-Acetoxy boronic esters can be generated efficiently as gross diastereomeric mixtures, separable in principle, but no diastereoselective route has been found.

5. Experimental

5.1. (4*R*,5*R*)-4,5-Dicyclohexyl-2-(bromomethyl)-1,3,2-dioxaborolane (*1*)

Diisopropyl (bromomethyl) boronate (37.27 g, 0.167 mol) [17] was stirred for 15 h with (*R*,*R*)-1,2-dicyclohex-1,2-ethanediol (37.84 g, 0.167 mol) [26] in diethyl ether (150 mL) at 20-25 °C. Concentration at reduced pressure yielded white crystalline **1** (50.79 g, 92%); 300 MHz ^{1}H NMR (C_6D_6) δ 0.88–1.79 (m, 22H), 2.60 (s, 2H), 3.94 (d, 2H, J = 5.1 Hz); 75 MHz ^{13}C NMR (C_6D_6) δ 26.2, 26.3, 26.7, 27.5, 28.6, 43.2, 84.3.

5.2. (4*R*,5*R*)-4,5-Dicyclohexyl-2-(azidomethyl)-1,3,2-dioxaborolane (*2*)

A solution of (4*R*,5*R*)-4,5-dicyclohexyl-2-(bromomethyl)-1,3,2-dioxaborolane (**1**) (10.00 g, 0.304 mol) in ethyl acetate (50 mL) was stirred with a solution of sodium azide (59.25 g, 0.91 mol) and tetrabutylammonium bromide (4.89 g, 15.19 mmol) in water (150 mL) under argon at 20–25 °C for 48 h. The ethyl acetate phase was concentrated and a solution of the residue in a mixture of ether and pentane was extracted repeatedly with aqueous ammonium chloride to ensure removal of tetrabutylammonium salts. Concentrated under reduced pressure yielded crystalline **2** (7.66 g, 87%); IR 2099 cm^{-1} (N_3); 300 MHz ^{1}H NMR (C_6D_6) δ 0.85–1.76 (m, 22H), 2.70 (ab, J = 17.4 Hz, J = 21.3 Hz, 2H), 3.71 (diastereotopic pair, 0.013 δ separation, 2H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 25.9, 26.1, 26.5, 27.4, 28.5, 42.9, 84.3. HRMS Calc. for $C_{15}H_{26}BN_3O_2$: 291.2118. Found: 291.2123%. Flash chromatography on silica (Rf 0.76, 30% diethyl ether in petroleum ether) provided further purification of **2**.

5.3. [2(1*S*),4*R*,5*R*]-4,5-Dicyclohexyl-2-(1-chloro-2-azidoethyl)-1,3,2-dioxaborolane (*3a*)

Butyllithium (1.6 M in hexanes, 13.4 mL, 21.5 mmol) was added to a solution of dichloromethane (4.15 mL, 64.4 mmol) in THF (60 mL) stirred under argon at −100 °C to generate (dichloromethyl)lithium. After 5 min (4*R*,5*R*)-4,5-dicyclohexyl-2-(azidomethyl)-1,3,2-dioxaborolane (**2**) (5.00 g, 17.17 mmol) in THF (5 mL) was added via cannula. Anhydrous powdered zinc dichloride (4.68 g, 34.34 mmol) was added. The bath temperature was allowed to rise to 20–25 °C and the mixture was stirred for 48 h. After concentration under reduced pressure, diethyl ether (30 mL) was added. The ether solution was washed three times with ammonium chloride solution and the ether phase was dried over anhydrous magnesium sulfate and filtered. Concentration yielded clear, viscous liquid **3a** (4.40 g, 76%); IR 2102 cm^{-1} (N_3); 300 MHz ^{1}H NMR (C_6D_6) δ 0.84–1.79 (m, 22H), 3.26 (m, 2H), 3.39 (m, 1H), 3.80 (d, J = 5.4 Hz, 2H); 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.8–1.9 (m), 3.6–3.7 (m, 3H), 3.90 (m, 2H); 75 MHz ^{13}C NMR (C_6D_6) δ 26.4, 26.5, 26.9, 27.7, 28.7, 41.6 (broad, C-B), 43.3, 54.8, 84.5. HRMS Calc. for $C_{16}H_{27}BClN_3O_2$ (M^+-N_2): 311.1823. Found: 311.1820%. No evidence for the diastereomer of **3a** was observed, though it might not have been noticed at the 1–2% level.

5.4. [2(1*S*),4*R*,5*R*]-4,5-Dicyclohexyl-2-(1-bromo-2-azidoethyl)-1,3, 2-dioxaborolane (*3b*)

To a solution of (4*R*,5*R*)-4,5-dicyclohexyl-2-(azidomethyl)-1,3,2-dioxaborolane (**2**) (2.96 g, 10.16 mmol) in THF (70 mL) was added dibromomethane (2.13 mL, 30.49 mmol). The mixture was cooled to −78 °C and lithium diisopropylamide (1.5 M in cyclohexane, 10.16 mL, 15.24 mmol) was added dropwise. After 5 min, zinc dichloride (1.0 M in diethyl ether, 45.7 mL) was added. The bath temperature was allowed to rise to 20–25 °C and the reaction mixture was stirred under inert atmosphere for 24 h. Solvents were removed under reduced pressure and diethyl ether was added (30 mL). The diethyl ether solution was washed three times with ammonium chloride solution and the ether phase was dried over anhydrous magnesium sulfate and filtered. Concentration at reduced pressure yielded yellow, viscous liquid **3b** (1.77 g, 64%); 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.97–1.78 (m, 22H), 3.42 (m, 1H), 3.72 (m, 2H), 3.98 (d, J = 5.1 Hz, 2H). HRMS Calc. for $C_{16}H_{27}BBrN_3O_2$ (M^+-N_2): 357.1298. Found: 357.1290%.

5.5. Attempted displacements of chloride from [2(1*S*),4*R*,5*R*]-4,5-dicyclohexyl-2-(1-chloro-2-azidoethyl)-1,3,2-dioxaborolane 3a by alkoxides

Several attempts to displace chloride from **3** by various alkoxides led to mixtures of unchanged **3** and what appeared to be [2(1*S*),4*R*,5*R*]-4,5-dicyclohexyl-2-alkoxy-1,3,2-dioxaborolane (**4**) or its hydrolysis products, with loss of the azido group and the CH_2CHCl fragment. Sodium *p*-methoxybenzyl oxide [from *p*-methoxybenzyl alcohol (3.2 mmol) in anhydrous DMSO (dimethyl sulfoxide) (35 mL) and sodium hydride (3.1 mmol) 24 h]

with **3a** (3 mmol) in DMSO (12 mL) at 20–25 °C for 24 h resulted in partial decomposition of **3a** to **4** (R = *p*-methoxybenzyl) as indicated by 300 MHz ^{1}H NMR, 75 MHz ^{13}C NMR, and IR spectra. Lithium benzyl oxide [from benzyl alcohol (9.4 mmol) in THF (65 mL) and butyllithium (8.6 mmol) at −78 °C] with **3a** (7.8 mmol) in THF (10 mL) 24 h at 20–25 °C led to a mixture of unchanged **3a**, benzyl alcohol, free DICHED, and unknown minor byproducts by ^{1}H NMR analysis, and the azide peak in the IR was diminished in intensity. Inclusion of an equivalent of DMSO or running the reaction in DMSO as solvent did not change the result. Similar partial decomposition was seen with lithium or sodium phenoxide in THF or DMSO and **3a**. Lithium methoxide in THF at 40 °C for 24 h yielded no substitution product.

5.6. Attempted reduction of the azide group of β-azido-α-chloro boronic ester *3a*

A solution of stannous chloride (0.43 mmol) and concentrated hydrochloric acid (0.07 mL) in methanol (1 mL) was stirred with **3a** (0.29 mmol) in methanol (1 mL) followed for 0.5 h, then concentrated under reduced pressure. No evidence of reduction was shown by 300 MHz ^{1}H NMR and 75 MHz ^{13}C NMR data.

5.7. Pinanediol (azidomethyl)boronate (*6*)

(*S*)-Pinanediol (bromomethyl)boronate (**5**) [19] was prepared from diisopropyl (bromomethyl)boronate and (*S*)-pinanediol under conditions similar to those used for preparation of **1**. A solution of **5** (7.2 g, 26.4 mmol) in ethyl acetate (250 mL) was stirred with a solution of sodium azide (17.1 g, 264 mmol) and tetrabutylammonium bromide (4.25 g, 13.2 mmol) in water (70 mL) at 75 °C for 8 h. After cooling to room temperature the mixture was extracted twice with ethyl acetate (2 × 50 mL) and washed with water (3 × 50 mL). The combined organic layer was dried over anhydrous magnesium sulfate and filtered. Removal of solvent on a rotary evaporator afforded (*S*)-pinanediol (azidomethyl)boronate (**6**) (5.95 g, 96%); IR (neat): 2924, 2091, 1387, 1295 cm^{-1}; ^{1}H NMR δ 4.36 (dd, J = 2.0, 8.9 Hz, 1H), 3.10 (s, 2H), 2.30 (m, 2H), 2.07 (m, 1H), 1.92 (m, 2H), 1.43 (s, 3H), 1.3 (s, 3H), 1.11 (d, J = 11.1 Hz, 1H), 0.85 (s, 3H); ^{13}C NMR δ 86.65, 78.24, 50.84, 39.20, 37.90, 34.96, 28.27, 26.82, 26.28, 23.77. Anal. Calc.: C, 56.20; H, 7.72; B, 4.60. Found: C, 56.70; H, 7.55; B, 4.72%.

5.8. Pinanediol (1-chloro-2-azidoethyl)boronate (*7*)

(Dichloromethyl)lithium was prepared by the addition of *n*-butyllithium (13.5 mmol) to dichloromethane (2 mL, 31.14 mmol) in anhydrous THF (100 mL) at −100 °C under argon. A solution of azidoboronic ester **6** (92.44 g, 10.38 mmol) in anhydrous THF (15 mL) was added to the solution with vigorous stirring. After 10 min, anhydrous zinc chloride (20.77 mmol) in diethyl ether was added and the mixture was allowed to warm to room temperature slowly with stirring it for 15 h. Diethyl ether (200 mL) was added to the reaction mixture and washed with saturated ammonium chloride (3 × 50 mL) to remove zinc chloride, dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator. The crude product was filtered through a small silica gel column using 5% diethyl ether in pentane to afford (*S*)-pinanediol-2-azido-1-chloroethylboronate (2.5 g, 85%); IR (neat): 2927, 2103, 1397, 1288 cm^{-1}; ^{1}H NMR δ 4.40 (dd, J = 2.0, 9.0 Hz, 1H), 3.65 (m, 3H), 2.32 (m, 2H), 2.10 (m, 1H), 1.92 (m, 2H), 1.44 (s, 3H), 1.30 (s, 3H), 1.17 (d, J = 11.4 Hz, 1H), 0.85 (s, 3H); ^{13}C NMR δ 87.1, 78.7, 54.4, 50.9, 39.1, 38.0, 34.9, 28.2, 26.8, 26.1, 23.8. No evidence for the diastereomer of **7** was observed, though it might not have been noticed at the 1–2% level.

5.9. Pinanediol (1-acetoxy-2-azidoethyl)boronate (*9*)

1-Chloro-2-azidoethyl pinanediol boronate (**7**) (1 g, 3.53 mmol) was heated in glacial acetic acid (35 mL) with sodium acetate (2.89 g, 35.3 mmol) for 12 h at 100–110 °C. After the reaction, acetic acid was distilled, diethyl ether (200 mL) was added to the residue, and the remaining acid was neutralized with saturated sodium bicarbonate solution. Extracted with ether (3 × 50 mL) and washed with water (2 × 50 mL). The combined organic layer was evaporated off and the residue on flash column chromatography using 5% ether in pentane as eluant afforded 1-acetoxy-2-azidoethyl pinanediol boronate **9** as a colorless liquid (977 mg, 90%). IR (neat): 2925, 2100, 1733, 1376, 1288, 1244 cm^{-1}; ^{1}H NMR: δ 4.32 (m, 4H), 3.58 (m, 4H), 2.28 (m, 4H), 2.138 (s, 3H), 2.135 (s, 3H), 2.05 (m, 2H), 1.88 (m, 4H), 1.41 (s, 3H), 1.39 (s, 3H), 1.29 (s, 6H), 1.25 (d, J = 11.1 Hz, 1H), 1.23 (d, J = 10.8 Hz, 1H), 0.84 (s, 6H); ^{13}C NMR: δ 171.92, 171.67, 86.52, 86.41, 78.06, 78.03, 51.61, 51.51, 50.95, 50.94, 39.22, 37.97, 35.12, 35.09, 28.23, 26.85, 26.05, 26.03, 23.83, 20.15, 20.09; Anal. Calc.: C, 54.74; H, 7.22; N, 13.68; B, 3.52. Found: C, 55.00; H, 7.28; N, 13.50; B, 3.26%.

5.10. Pinanediol (2-aminoethyl-1-hydroxy)boronate hydrochloride (*10*)

Pinanediol (1-acetoxy-2-azidoethyl)boronate (**9**) (1 g, 3.25 mmol) was dissolved in hydrogen chloride solution in dioxane (4 M, 10 mL) and platinum dioxide (100 mg) was added. The mixture was hydrogenated at 10 atm (145 psi), 20–25 °C, for 1 h. The catalyst was removed by filtration and washed with ethanol and the filtrate was evaporated. The residue was triturated with cold pentane and dried under vacuum to give the hydroxyl derivative **10** as a gummy solid (825 mg, 92%). IR (neat): 3362, 2926, 1607, 1378 cm^{-1}; ^{1}H NMR: δ 4.43 (d, J = 8.4 Hz, 1H), 3.66 (m, 2H), 3.10 (m, 2H), 2.34 (m, 2H), 2.05 (t, J = 5.3 Hz, 1H), 1.90 (m, 2H), 1.43 (s, 3H), 1.32 (s, 3H), 1.15 (d, J = 11.1 Hz, 1H), 0.88 (s, 3H); ^{13}C NMR: 87.8, 79.4, 57.2, 52.2, 44.3, 44.2, 40.5, 38.9, 35.9, 29.0, 27.7, 27.1, 24.5.

5.11. Pinanediol (2-acetamido-1-acetoxyethyl)boronate (*11*)

A solution of pinanediol (2-aminoethyl-1-hydroxy)boronate hydrochloride (**10**) (422 mg, 1.53 mmol) was dissolved in acetic anhydride (4 mL) and stirred for 30 min. This mixture was then cooled to −22 °C and triethylamine (0.47 mL, 3.4 mmol) was added dropwise. The mixture was allowed to warm to 20–25 °C for 2 h. Excess acetic anhydride was evaporated under vacuum pump pressure. The crude mixture was extracted with diethyl ether (3 × 50 mL) and washed with water (3 × 50 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered. Removal of solvent on a rotary evaporator afforded **11** (243 mg, 49%). A sample was purified by recrystallization from diethyl ether/pentane, then recrystallized twice from methylcyclohexane, m.p. 146–149 °C (Fisher–Johns hot plate). IR (neat): 3286, 2919, 1728, 1634, 1576, 1451, 1373 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.97 (s, 1H), 4.26 (dd, J = 8.9 Hz, 2.3 Hz, 1H), 4.11 (dd, J = 6.5 Hz, 4.1 Hz, 1H), 3.57 (m, 2H), 2.29 (m, 2H), 2.11 (s, 3H), 2.03 (t, J = 5.6 Hz, 1H), 1.98 (s, 3H), 1.85 (m, 2H), 1.39 (s, 3H), 1.28 (s, 3H), 1.24 (d, J = 11.1 Hz, 1H), 0.83 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 172.87, 170.05, 86.51, 78.08, 64.48 (broad, C connected to B), 51.20, 39.96, 39.42, 38.17, 35.28, 28.30, 27.00, 26.11, 23.99, 23.28, 20.28; HRMS Calc. for $C_{16}H_{26}BNO_5$: m/e 323.1904. Found: 323.1890%.

5.12. (4S,5S,1′RS)-2-(1′-Acetoxy-2′-azidoethyl)-4,5-dicyclohexyl-1,3,2-Dioxaborolane [(S,S)-DICHED (RS)-(1-acetoxy-2-azidoethyl)boronate]

After it was found in a preliminary test that no more than a few percent reaction occurred at 20–25 °C in 24 h [300 MHz ^{1}H NMR ($CDCl_3$) δ 2.13 (s), 4.33 (m)], a solution of (4*S*,5*S*,1′*R*)-2-(2′-azido-1′-chloroethyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (***ent*-3**) (2.5 g) and sodium acetate (1.5 g) in acetic acid (20 mL) was stirred at 95 °C under argon for 20 h. After work up with diethyl ether and water followed by additional washing of the ether phase with water and sodium bicarbonate, concentration on a rotary evaporator yielded 2.5 g of residue (7.35 mmol, ~95%). Chromatography on silica and elution with 5% ether/pentane resulted in removal of gross impurities but no change in isomer ratio as judged by the multiplets centered at δ 4.41; 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.9–1.8 (m, ~22 H, + s at δ 1.6, ~10 H), 2.134 and 2.139 (s + s, 3H), 3.49−3.64 (m, 2H), 3.89 + 3.91 (overlapping d's, $J \sim 4.5$ Hz, 2H), 4.31 (dd, $J = 3.9$ Hz, 7.5 Hz, 0.5H), 4.37 (dd, $J = 3.6$ Hz, 7.8 Hz, 0.5H); 300 MHz ^{1}H NMR (C_6D_6) δ 0.6–1.6 (m, ~22 H, + s + s at δ 1.36 and 1.37, ~3 H), 2.92 (m, 1H), 3.02 (m, 1H), 3.52 (broad d, $J \sim 4.5$ Hz, 2H), 3.99 (m, 8 peaks of ~ equal amplitude, 1H); 75 MHz ^{13}C NMR + DEPT (C_6D_6) (dp = diastereomeric pair, separation in ppm) δ 19.6 (CH_3), 26.1 (dp 0.117, CH_2), 26.6 (dp 0.021, CH_2) 27.7 (dp <0.02, CH_2), 28.7 (dp 0.034, CH_2), 43.0 (dp 0.034, CH), 51.8 (dp 0.165, CH_2), 65.1 (br, CB), 84.3 (CH), (C_6D_6 127.9 t), 171.6 (dp 0.062, C=O). HRMS (FAB) Calc. for $C_{18}H_{31}BN_3O_4$ (M+H): 364.1211. Found: 364.2415.

*5.13. (+)- and (−)-Pinanediol (RS)-(2-acetamido-1-acetoxyethyl)boronate (**11**, ***ent*-11**) from the DICHED ester*

Portions (160 mg each) of (*S*,*S*)-DICHED 1-(*RS*)-(2-acetamido-1-acetoxyethyl)boronate were treated separately with (+)-pinanediol and (−)-pinanediol (75 mg each) in diethyl ether (5 mL) and methanol (0.5 mL) overnight. Concentration followed by treatment with pentane resulted in precipitation of the DICHED, and the pinanediol esters were further purified by chromatography on silica with diethyl ether/pentane. There was no apparent difference between the ^{1}H NMR spectra of the (+)-pinanediol and (−)-pinanediol esters, and both matched the material obtained when the entire reaction sequence was run with the pinanediol esters.

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