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Asymmetric synthesis of 1-acyl-3,4-disubstituted pyrrolidine-2-boronic acid derivatives

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Abstract

An analogue of *N*-acetylkainic acid having a cyano group and a boronic acid group in place of the two carboxyl groups has been synthesized with high stereocontrol via a series of chain extensions of pinanediol [(trityloxy)methyl]boronate with (dihalomethyl)lithium followed by appropriate nucleophilic substitution of the resulting chloro or bromo boronic ester. Substituents were introduced in the order isopropenyl, cyanomethyl, and bis(trimethylsilyl)amino. The last of these was converted to acetamido, the hydroxyl function was unmasked and mesylated, and the pyrrolidine ring was closed. Attempts to carry out further chain extension on the boronic ester resulted in low yields, evidently the highly polar amido substituent interferes with the (dichloromethyl)lithium insertion process. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

[(Trityloxy)methyl]boronic esters are easily prepared and are useful intermediates for asymmetric synthesis.[1,2] The present study is an exploration of the synthetic utility of boronic esters bearing the trityloxy group plus polar substituents. Kainic acid, a neurotoxic glutamate receptor agonist,[3] was chosen as the synthetic target. Although this target has not been reached, all of the corresponding three chiral centers have been assembled in a boronic ester analogue of *N*-acetylkainic acid. The present sequence begins from the end of the series of chiral centers opposite to that explored previously.[2]

2. Results

The previously reported (*S*)-pinanediol (*S*)-[1-chloro-2-(trityloxy)ethyl]boronate (**1**), which is easily prepared via (*S*)-pinanediol [(trityloxy)methyl]boronate,[1] was chosen as the starting point for the present

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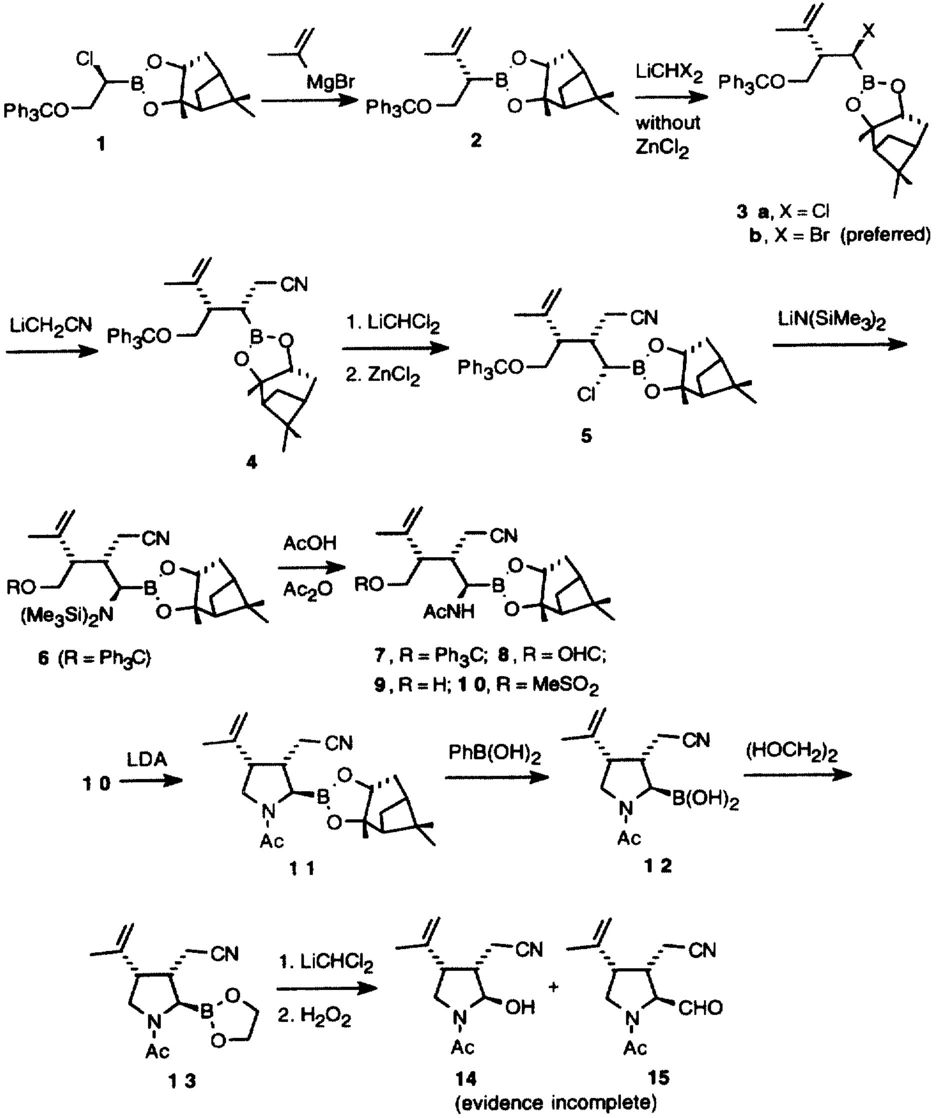
work. Treatment of **1** with isopropenylmagnesium bromide yielded the expected substitution product **2**. Minor byproducts found in the reaction mixture included (*S*)-pinanediol isopropenylboronate (~2%), which corresponds to the replacement of the original alkyl group on boron by isopropenyl, and trityl (3-methyl)-2-butenyl ether (~1%), the product of protodeboronation of **2** with allylic rearrangement.



Reaction of **2** with (dichloromethyl)lithium or (dibromomethyl)lithium under the usual conditions[1,4] resulted in low yields of impure homologation product **3**. When zinc chloride was omitted, the yields were substantially improved, and although the diastereomeric ratio estimated from the proton NMR spectrum was only ~10:1, the major isomer was purifiable by crystallization.

Attempted displacement of chloride from **3a** or bromide from **3b** by *tert*-butyl lithioacetate failed, in contrast to earlier results in synthetic pathways to eldanolide[4] and glutamic acid.[5] Displacement of the halide by lithioacetonitrile proved considerably more efficient with the bromo compound **3b** than with the chloro analogue **3a**. The resulting cyanomethyl substitution product **4** was homologated with (dichloromethyl)lithium with the usual aid of zinc chloride to produce **5**.

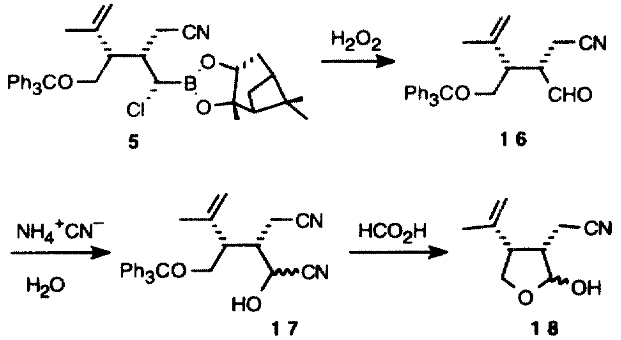
Conversion of **5** to the α-amido boronic ester **7** was accomplished via the usual reaction with lithiohexamethyldisilazane to generate intermediate **6** and desilylation/acylation to **7**.[6] The detritylation of **7** to alcohol **9** proved unexpectedly complicated. Formic acid treatment of **7** yielded formate ester **8** or a mixture of **8** and **9**. After several experiments described in Section 2.1, it was found that refluxing for 6 days with potassium thiocyanate in methanol converted **8** to **9**, which was then converted to the mesylate **10** by treatment with methanesulfonyl chloride and triethylamine. Triethylamine slowly converted **10** to the pyrrolidineboronic ester **11**, but this process was made rapid by treatment with LDA.

Treatment of **11** with (dichloromethyl)lithium resulted in very slow and inefficient homologation. This problem has been reported for other amido boronic esters elsewhere.[7] At first, we thought it might be a steric problem, and tried conversion of the pinanediol ester **11** to the boronic acid **12** by equilibration with phenylboronic acid,[8] a method which is generally applicable to water soluble boronic acids. Conversion of **12** to the ethylene glycol ester **13** was followed by treatment with (dichloromethyl)lithium and zinc chloride. Hydrogen peroxide oxidation then yielded a mixture that appeared by NMR analysis to consist mainly of **14** (from direct oxidation of **13**) and aldehyde **15** in a ratio of ~15:1. The aldehyde doublet of **15** appeared at δ 9.57 in the ^{1}H-NMR, and the mass spectrum showed peaks at m/e 208 (**14**) and 220 (**15**). Attempts to obtain a pure sample of **15** were unsuccessful.

2.1. Attempted alternatives

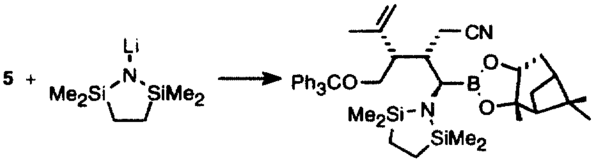
Several procedures were tested that turned out to lead to unanticipated products.

Peroxidic oxidation of chloro boronic ester **5** to aldehyde **16** proceeded smoothly, but attempts to convert **16** to the aminonitrile with cyanide and ammonia (Strecker synthesis) yielded only the cyanohydrin **17**, perhaps because no solvent was found that permitted high concentrations of both ammonium cyanide and **16**. Treatment of **17** with formic acid yielded **18**, which results from loss of cyanide as well as detritylation. Treatment of **16** with trimethylsilyl cyanide yielded the trimethylsilylated cyanohydrin (TMS-**17**), but this lost cyanide and reverted to **16** on treatment with water.



We had expected to achieve nitrogen substitution on **5** by the use of sodium azide with a phase transfer catalyst in dichloromethane/water.[4,5] However, no reaction was observed up to 15 h, and longer reaction times would be hazardous because of possible generation of explosive diazidomethane.[9] In other attempts to convert **5** to the azide, sodium azide in DMSO was tried as an alternative to the phase transfer system, but the ^{1}H-NMR spectrum indicated that ~10% conversion to aldehyde **16** was all that occurred. The bromo analogue of **5** was tested in the phase transfer system and appeared to yield ~20% of aldehyde **16**.

Conversion of **5** to its 2,2,5,5-tetramethyl-1,2,5-disilazole derivative **19** was readily accomplished, but attempted reaction of **19** with (dichloromethyl)lithium failed.



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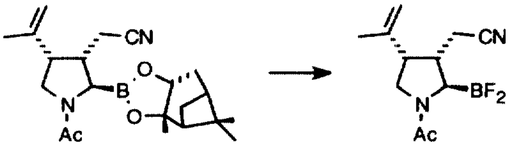
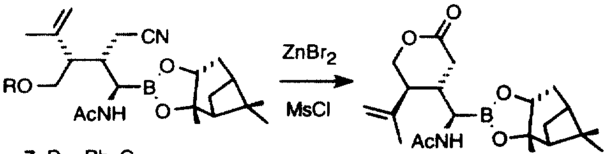
Intermediate pinandiol boronic ester **11** was converted to the corresponding difluoroboryl derivative **20**.[10] However, **20** did not appear to react with (dichloromethyl)lithium, as the mixture darkened on warming, indicating decomposition of the lithium reagent.



11 20

Detritylation of **7** with zinc bromide resulted in hydrolysis of the nitrile and lactonization with the hydroxyl group to form **21** and was not pursued further.



7, R = Ph$_3$C 21

As noted above, detritylation with formic acid yielded formate ester **8**. If worked up under basic conditions, **8** yielded pinanediol as the major ether soluble product. It was surmised that the alcohol might have cyclized to the boron to form a stable six-membered 1,2-oxaborin ring, a reaction for which there is precedent,[11] but this hypothetical water soluble product was not isolated. Cleavage of the formate ester **8** was then attempted via a published procedure with potassium cyanide in methanol,[12] but this treatment resulted in decomposition. Refluxing **8** with methanol alone did not yield measurable **9**. Though the transesterification of **8** to **9** catalyzed by the weakly basic nucleophile potassium thiocyanate was very slow, the side reactions seen under other conditions did not occur.

3. Discussion

The crystallinity of intermediates **1**, **3a**, and **3b**, and the high melting point of **7**, may be attributed to the presence of the trityloxy substituent. Most boronic esters prepared in earlier work have been liquids.[13]

In accord with previous work,[13] ^{1}H-NMR data indicate that all of the boronic ester intermediates are initially produced in high diastereomeric purity, with the exception of the conversion of **2** to **3** in the absence of zinc chloride. The estimated diastereomer content of a crude sample of **3b** was 9%, with 3% unchanged **2**. Because **3a** and **3b** can be recrystallized from ether/pentane, upgrading to high purities is readily accomplished. No attempt has been made to determine the amount of minor diastereomer formed in the other reactions of boronic esters with (dihalomethyl)lithium in this series, but no evidence for the minor isomers was seen, suggesting that the levels were near 1% or below.

It was unexpected that zinc chloride would be deleterious in the reaction of allylic boronic ester **2** with (dichloromethyl)lithium to form α-halo boronic esters **3**. It was suspected, though not proved, that zinc chloride promotes electrophilic cleavage or rearrangement of the allylic boronic ester **2**.

Assembly of the carbon skeleton up to intermediate **7** was fairly efficient, 27% from **1** based on the successive yields of purified intermediates. Considerable losses were encountered in the ring closure process, which was not necessarily optimized, and the overall yield of pinanediol pyrrolidineboronic ester **11** from **1** was ~10%.

A large part of the difficulty encountered in the later stages of this synthetic route appears to be associated with the polarity of the highly functionalized boronic esters. The rearrangement of *B*-dichloromethyl- and other *B*-α-haloalkyl-borate anions is catalyzed by metal cations,[13,14] and binding of the cation to such groups as cyano, acetamido, and alkoxy instead of or in addition to the boronic ester function may interfere with the haloalkylborate anion rearrangement. Difficulties with amide or amine functionality have been observed with other boronic esters.[7] After the attempted homologation of pyrrolidineboronic ester **13**, it appeared from the ^{1}H-NMR spectrum that there was at least 25–30% of the corresponding α-chloro boronic ester, and the exceedingly low yield of aldehyde **15** may be the result of water solubility and failure of ethyl acetate extraction, though it is odd if the hydroxy compound **14** is more readily extracted than **15**.

4. Summary

An analogue of *N*-acetylkainic acid having a cyano group and a boronic acid group in place of the two carboxyl groups has been synthesized with excellent stereocontrol via a series of chain extensions of pinanediol [(trityloxy)methyl]boronate with (dihalomethyl)lithium followed by nucleophilic substitution. The expected chloro boronic ester was not obtained when the isopropenyl boronic ester **2** was treated with (dihalomethyl)lithium and zinc chloride[4] under the usual conditions, possibly as a result of allylic isomerization or cleavage, but this step was accomplished without zinc chloride at the cost of a reduction in stereocontrol to ~90%, which was mitigated by crystallization of the major diastereomer **3**. The bromo boronic ester **3b** proved efficient in the reaction with lithioacetonitrile to form **4**. The amido boronic ester **7** was prepared via the established route, and detritylation and cyclization to the boronic ester **11** and the boronic acid **12** followed known methods. Attempts to introduce the last carbon needed for kainic acid appear to have resulted in low yields of the aldehyde **15**, which would only require oxidation of the aldehyde and hydrolysis of the nitrile and amide functions to provide kainic acid. However, the inefficiency of production of **15** discouraged further pursuit of this route.

5. Experimental

5.1. (S)-Pinanediol [(S)-1-isopropenyl-2-(triphenylmethoxy)ethyl]boronate 2

To a solution of (*S*)-pinanediol [(*S*)-1-chloro-2-(triphenylmethoxy)ethyl]boronate (**1**) (1.78 g, 3.56 mmol) in THF (15 ml), isopropenylmagnesium bromide (6.03 ml, 0.83 M, 5.00 mmol) was added dropwise at −78°C. The solution was allowed to warm to room temperature and kept for 18 h, then worked up by treatment with saturated aqueous ammonium chloride and diethyl ether. The ether solution was filtered through a column of anhydrous magnesium sulfate (5–10 g), and was then concentrated to give crude (*S*)-pinanediol [(*S*)-1-isopropenyl-2-(triphenylmethoxy)ethyl]boronate (**2**). It was purified by flash chromatography on silica gel with hexanes:diethyl ether (98:2); 1.51 g, 83.7%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 3), 1.18 (d, J=10.5 Hz, 1), 1.26 (s, 3), 1.35 (s, 3), 1.70 (m, 3), 1.75–2.35 (m, 6), 3.24 (m, 2), 4.28 (dd, J=1.92 and 8.79 Hz, 1), 4.60 (t, J=0.93 Hz, 1), 4.72 (m, 1), 7.15–7.55 (m, 15); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 23.27, 24.00, 26.46, 27.06, 28.61, 35.42, 38.13, 39.39, 51.19, 63.56, 77.82, 85.80, 86.28, 110.37, 126.74, 127.65, 128.85, 144.09, 144.44; HRMS calcd for $C_{39}H_{34}BO_3$ (M^+) 506.2992, found 506.2983. Byproduct identification: (*S*)-Pinanediol (isopropenyl)boronate (2%) and (1%) were separated from crude **2** by flash chromatography on silica gel with hexanes:diethyl ether (98:2), but these two compounds were not separated by chromatography. ^{1}H-NMR homodecoupling analysis of the mixture was used to make the following assignments: (*S*)-pinanediol (isopropenyl)boronate, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3, CH_3), 1.15 (d, *J*=11.1 Hz, 1, pinyl C*H*), 1.29 (s, 3, CH_3), 1.41 (s, 3, CH_3), 1.84 (t, *J*=1.53 Hz, 3, $CH_3C{=}CH_2$), 5.75 (m, 2, $CH_3C{=}CH_2$); triphenylmethyl 3-methyl-2-butenyl ether, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.47 (d, *J*=0.75 Hz, 3, CH_3), 1.73 (d, *J*=1.05 Hz, 3, CH_3), 3.57 (m, 2, $OCH_2CH{=}C$), 5.44 (m, 1, $CH{=}C(CH_3)_2$), 7.15–7.55 (m, 15, C_6H_5). Mixture, ^{13}C-NMR (75 MHz, $CDCl_3$) δ 18.10, 21.26, 23.99, 25.78, 26.44, 27.09, 28.66, 35.56, 38.14, 39.53, 51.39, 61.23, 77.98, 85.85, 86.60, 121.58, 126.80, 127.70, 128.71, 129.89, 144.41.

5.2. (*S*)-Pinanediol [(1*S*,2*S*)-1-chloro-2-isopropenyl-3-(triphenylmethoxy)propyl]boronate **3a**

To a solution of dichloromethane (0.55 ml, 8.48 mmol) in THF (10 ml) was added butyllithium (2.53 ml, 1.45 M, 3.67 mmol) at −78°C via cannula. The butyllithium solution was allowed to run down the cold wall of the reaction flask to be chilled before contacting the dichloromethane solution. After 5 minutes, a solution of (*S*)-pinanediol [(*S*)-1-isopropenyl-2-(triphenylmethoxy)ethyl]boronate (**2**) (1.43 g, 2.8 mmol) in THF (5 ml) was added to the solution via cannula. The mixture was stirred and allowed to come to 12°C for 13 h. It was worked up by treatment with saturated aqueous ammonium chloride and diethyl ether. The ether solution was dried by adding anhydrous sodium sulfate (5 g), and then was filtered and concentrated. Crystallization gave (*S*)-pinanediol [(1*S*,2*S*)-1-chloro-2-isopropenyl-3-(triphenylmethoxy)propyl]boronate (**3a**): 1.26 g, 81.1%; mp 152–154°C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.80 (s, 3), 1.09 (d, *J*=10.92 Hz, 1), 1.18 (s, 3), 1.26 (s, 3), 1.65 (m, 3), 1.75–2.35 (m, 5), 2.88–2.98 (m, 1), 3.07–3.22 (m, 2), 3.60 (d, *J*=9.3 Hz, 1), 4.25 (dd, *J*=2.04 and 8.88 Hz, 1), 4.92–4.99 (m, 2), 7.18–7.46 (m, 15); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 20.20, 23.96, 26.10, 26.96, 28.04, 35.11, 38.20, 39.27, 50.35, 51.17, 63.87, 78.31, 86.64, 86.73, 114.46, 126.89, 127.69, 128.78, 143.36, 143.92. Anal. calcd for $C_{35}H_{40}BO_3Cl$: C, 75.75; H, 7.27; B, 1.95; Cl, 6.39. Found: C, 75.05 (low); H, 7.34; B, 1.99; Cl, 6.66.

5.3. (*S*)-Pinanediol [(1*S*,2*S*)-1-bromo-2-isopropenyl-3-(triphenylmethoxy)propyl]boronate **3b**

A solution of (*S*)-pinanediol [(*S*)-1-isopropenyl-2-(triphenylmethoxy)ethyl]boronate (**2**) (2.29 g, 4.53 mmol) and dibromomethane (0.95 ml, 13.58 mmol) in THF (20 ml) was stirred at −78°C during the dropwise addition of LDA (2.94 ml, 2 M, 5.88 mmol). The mixture was stirred and the temperature was allowed to reach 14°C and maintained for 13 h. It was worked up by treatment with saturated aqueous ammonium chloride and diethyl ether. The ether solution was dried by adding anhydrous sodium sulfate (5 g), and then was filtered and concentrated. Crystallization gave (*S*)-pinanediol [(1*S*,2*S*)-1-bromo-2-isopropenyl-3-(triphenylmethoxy)propyl]boronate (**3b**); 2.17 g, 79.9%; mp 153–155°C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.81 (s, 3), 1.14 (s, 3), 1.15 (d, *J*=10.68 Hz, 1), 1.27 (s, 3), 1.66 (m, 3), 1.78–2.38 (m, 5), 2.95–3.05 (m, 1), 3.09–3.15 (m, 2), 3.39 (d, *J*=10.89 Hz, 1), 4.25 (dd, *J*=2.01 and 8.82 Hz, 1), 4.97 (m, 1), 5.01 (m, 1), 7.15–7.55 (m, 15); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.44, 23.99, 26.04, 26.95, 27.93, 35.12, 38.31, 39.22, 50.50, 51.28, 64.52, 78.16, 86.39, 86.75, 114.43, 126.89, 127.70, 128.79, 143.79, 143.85. Anal. calcd for $C_{35}H_{40}BO_3Br$: C, 70.13; H, 6.73; B, 1.80. Found: C, 70.45; H, 6.71; B, 2.01.

5.4. (S)-Pinanediol [(1S,2S)-1-cyanomethyl-2-isopropenyl-3-(triphenylmethoxy)propyl]boronate 4

To the solution of LDA (1.43 ml, 2 M, 2.86 mmol) in THF (4 ml), a solution of acetonitrile (0.108 g, 2.63 mmol), in THF (2 ml) was added at −78°C. After 30 minutes, a solution of (*S*)-pinanediol [(1*S*,2*S*)-1-bromo-2-isopropenyl-3-(triphenylmethoxy)propyl]boronate (**3b**) (1.56 g, 2.60 mmol) in THF (10 ml) was added to the above mixture at −78°C. The mixture was stirred and allowed to warm to room temperature and kept for 16 h. It was worked up by treatment with saturated aqueous ammonium chloride and diethyl ether. The ether solution was dried by adding anhydrous sodium sulfate (5 g), and was filtered and concentrated to give crude (*S*)-pinanediol [(1*S*,2*S*)-1-cyanomethyl-2-isopropenyl-3-(triphenylmethoxy)propyl]boronate (**4**) (1.49 g), which contained ~3% unreacted **3b**. Crude **4** was chromatographed on silica gel with hexanes:diethyl ether (10:1); 1.25 g, 86.0%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.81 (s, 3), 1.12 (d, *J*=10.95 Hz, 1), 1.27 (s, 3), 1.28 (s, 3), 1.67 (m, 3), 1.72–1.82 (m, 2), 1.87 (m, 1), 1.98–2.04 (t, *J*=5.79 Hz, 2), 2.10–2.35 (m, 1), 2.25 (d, *J*=7.53 Hz, 2), 2.48–2.59 (m, 1), 3.09 (dd, *J*=6.03 and 9.48 Hz, 1), 3.21 (dd, *J*=5.31 and 9.45 Hz, 1), 4.23 (dd, *J*=2.07 and 8.82 Hz, 1), 4.85 (m, 1), 4.90 (t, *J*=1.44 Hz, 1), 7.18–7.48 (m, 15); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 16.64, 21.73, 23.99, 26.35, 27.02, 28.33, 35.26, 38.16, 39.40, 47.36, 51.10, 63.88, 78.03, 86.17, 86.57, 113.41, 119.83, 126.95, 127.76, 128.68, 144.01, 145.27; HRMS calcd for $C_{37}H_{42}BO_3N$ (M^+) 559.3258, found 559.3257.

5.5. (S)-Pinanediol [(1S,2S,3S)-1-chloro-2-cyanomethyl-3-isopropenyl-4-(triphenylmethoxy)butyl]boronate 5

To a solution of dichloromethane (0.67 g, 7.88 mmol) in THF (20 ml) was added butyllithium (2.1 ml, 1.52 M, 3.18 mmol) at −100°C via cannula. The butyllithium solution was allowed to run down the cold wall of the flask to be chilled before contacting the dichloromethane solution. After 5 minutes, a solution of (*S*)-pinanediol [(1*S*,2*S*)-1-cyanomethyl-2-isopropenyl-3-(triphenylmethoxy)propyl]boronate (**4**) (1.48 g, 2.65 mmol), in THF (5 ml) was added to the solution via cannula. The solution was allowed to warm to room temperature and kept for 18 h. It was worked up by treatment with saturated aqueous ammonium chloride and diethyl ether. The ether solution was dried by adding anhydrous sodium sulfate (5 g), and then was filtered and concentrated to yield crude (*S*)-pinanediol [(1*S*,2*S*,3*S*)-1-chloro-2-cyanomethyl-3-isopropenyl-4-(triphenylmethoxy)propyl]boronate (**5**) containing <5% unchanged **4**. Crude **5** was chromatographed on silica gel with hexanes:diethyl ether (10:1); 1.35 g, 80.1%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 3), 1.16 (d, *J*=10.98 Hz, 1), 1.28 (s, 3), 1.43 (s, 3), 1.66 (s, 3), 1.85–2.40 (m, 6), 2.45 (m, 2), 2.60 (m, 1), 3.12 (dd, *J*=6.30 and 9.72 Hz, 1), 3.29 (dd, *J*=5.28 and 9.66 Hz, 1), 3.72 (d, *J*=3.66 Hz, 1), 4.37 (dd, *J*=1.74 and 8.64 Hz, 1), 4.94 (s, 1), 5.01 (t, *J*=1.47 Hz, 1), 7.20–7.48 (m, 15); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 17.69, 20.59, 23.93, 26.15, 27.00, 28.01, 34.93, 38.26, 38.39, 39.30, 48.98, 51.29, 63.72, 78.72, 87.09, 87.45, 115.24, 118.78, 127.11, 127.89, 128.61, 143.49, 143.73; HRMS calcd for $C_{38}H_{43}BO_3NCl$ (M^+) 607.3025, found 607.3038.

5.6. (S)-Pinanediol [(1S,2S,3S)-1-bromo-2-cyanomethyl-3-isopropenyl-4-(triphenylmethoxy)butyl]boronate, Br analogue of 5

A solution of (*S*)-pinanediol [(1*S*,2*S*)-1-cyanomethyl-2-isopropenyl-3-(triphenylmethoxy)propyl]boronate (**4**) (10.20 g, 18.25 mmol) and dibromomethane (9.52 g, 54.76 mmol) in THF (50 ml) was stirred at −78°C during the dropwise addition of LDA (11.9 ml, 2 M, 23.72 mmol). After 10 minutes, zinc chloride (10.18 g, 74.83 mmol), which was fused before use, was added to the solution. The solution was warmed to room temperature and kept for 18 h, it was then worked up by treatment with saturated aqueous ammonium chloride and diethyl ether. The ether solution was filtered through a column of anhydrous magnesium sulfate (20 g), then concentrated to yield (*S*)-pinanediol [(1*S*,2*S*,3*S*)-1-bromo-2-cyanomethyl-3-isopropenyl-4-(triphenylmethoxy)butyl]boronate (Br analogue of **5**) containing less than 10% unreacted (**4**), and 20% of unknown material. This crude material was used in the next step without further purification; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 3), 1.23 (d, *J*=10.41 Hz, 1), 1.28 (s, 3), 1.41 (s, 3), 1.66 (s, 3), 1.80–2.70 (m, 9), 3.14 (dd, *J*=6.60 and 9.66 Hz, 1), 3.33 (dd, *J*=5.37 and 9.72 Hz, 1), 3.63 (d, *J*=4.86 Hz, 1), 4.36 (dd, *J*=1.83 and 8.76 Hz, 1), 4.94 (s, 1), 5.00 (t, *J*=1.47 Hz, 1), 7.2–7.45 (m, 15); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.37, 20.50, 23.95, 26.12, 26.98, 28.06, 35.01, 37.57, 38.34, 39.25, 49.91, 51.31, 63.59, 78.63, 87.11, 87.15, 115.33, 118.75, 127.10, 127.89, 128.62, 143.25, 143.72; HRMS calcd for $C_{38}H_{43}BO_3NBr$ (M+) 651.2519, found 651.2503.

5.7. (S)-Pinanediol [(1R,2S,3S)-1-bis(trimethylsilyl)amino-2-cyanomethyl-3-isopropenyl-4-(triphenylmethoxy)butyl]boronate 6

A solution of lithiohexamethyldisilazane (9.83 mmol) was prepared by the addition of butyllithium (6.2 ml, 1.6 M, 9.83 mmol) to 1,1,1,3,3,3-hexamethyldisilazane (1.74 g, 10.77 mmol) in THF (20 ml) with stirring at −78°C. To lithiohexamethyldisilazane solution, (*S*)-pinanediol [(1*S*,2*S*,3*S*)-1-chloro-2-cyanomethyl-3-isopropenyl-4-(triphenylmethoxy)propyl]boronate (**5**) (5.69 g, 9.37 mmol) in THF (25 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The solvents were removed under reduced pressure. The residue was redissolved in pentane and filtered through a column of Celite and magnesium sulfate. Concentration in a rotary evaporator gave (*S*)-pinanediol [(1*R*,2*S*,3*S*)-1-bis(trimethylsilyl)amino-2-cyanomethyl-3-isopropenyl-4-(triphenylmethoxy)butyl]boronate (**6**); 3.89 g, 56.7%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 18), 0.82 (s, 3), 1.17 (d, *J*=10.83 Hz, 1), 1.28 (s, 3), 1.41 (s, 3), 1.78 (s, 3), 1.85–2.35 (m, 7), 2.58 (dd, *J*=4.74 and 16.95 Hz, 1), 2.67 (d, *J*=9.42 Hz, 1), 2.94–2.99 (dt, *J*=2.97 and 5.94 Hz, 1), 3.22 (d, *J*=6.06 Hz, 2), 4.32 (dd, *J*=1.62 and 8.61 Hz, 1), 4.84 (s, 1), 4.99 (t, *J*=1.44 Hz, 1), 7.12–7.50 (m, 15); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 3.70, 16.88, 22.38, 23.95, 26.28, 27.05, 28.07, 34.90, 38.15, 39.36, 40.93, 44.36, 51.32, 61.39, 78.37, 85.87, 86.81, 113.10, 120.47, 126.96, 127.67, 129.90, 143.67, 145.75; HRMS calcd for $C_{44}H_{61}BO_3N_2Si_2$ (M^+) 732.4314, found 732.4355.

5.8. (S)-Pinanediol [(1R,2S,3S)-1-acetamido-2-cyanomethyl-3-isopropenyl-4-(triphenylmethoxy)butyl]boronate 7

A solution of lithiohexamethyldisilazane (22.69 mmol) was prepared by the addition of butyllithium (14.2 ml, 1.6 M, 22.69 mmol) to 1,1,1,3,3,3-hexamethyldisilazane (3.662 g, 22.69 mmol) in THF (25 ml) with stirring at −78°C. To lithiohexamethyldisilazane solution, (*S*)-pinanediol [(1*S*,2*S*,3*S*)-1-chloro-2-cyanomethyl-3-isopropenyl-4-(triphenylmethoxy)propyl]boronate (**5**) (12.53 g, 20.62 mmol) in THF (50 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 18 h to form **6**, which was not isolated. The solution was cooled to −78°C again, and acetic anhydride (8.42 g, 82.48 mmol) and acetic acid (1.857 g, 30.93 mmol) were added dropwise. The solution was stirred overnight at room temperature, and then the solvents were removed under reduced pressure. The residue was treated with dichloromethane (300 ml) and water (250 ml). The aqueous phase was separated and extracted with dichloromethane (2×20 ml). The combined organic phases were dried over magnesium sulfate and filtered. Concentration in a rotary evaporator followed by washing with pentane and ether yielded (*S*)-pinanediol [(1*R*,2*S*,3*S*)-1-acetamido-2-cyanomethyl-3-isopropenyl-4-(triphenylmethoxy)butyl]boronate (**7**); 7.61 g, 58.6%; mp 232–233°C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ

0.86 (s, 3), 1.28 (s, 3), 1.38–1.43 (m, 4), 1.72 (s, 3), 1.78–1.93 (m, 2), 1.95–2.05 (m, 1), 1.98 (s, 3), 2.13–2.40 (m, 3), 4.40–2.60 (m, 3), 3.09 (dd, *J*=2.97 and 6.0 Hz), 3.19 (dd, *J*=4.62 and 9.96 Hz, 1), 3.30 (dd, *J*=5.97 and 9.99 Hz, 1), 4.27 (dd, *J*=2.1 and 8.73 Hz, 1), 4.87 (s, 1), 4.96 (t, *J*=1.41 Hz, 1), 6.91 (br s, conc. dependent, 1), 7.20–7.45 (m, 15); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 17.01, 19.95, 21.71, 24.22, 26.57, 27.25, 28.91, 36.15, 37.76, 38.23, 39.90, 47.94, 51.94, 64.42, 77.21, 84.06, 87.40, 113.95, 119.98, 127.18, 127.96, 128.54, 143.58, 144.97, 173.72; HRMS calcd for $C_{40}H_{47}BO_4N_2$ (M^+) 630.3629, found 630.3630. Anal. calcd for $C_{40}H_{47}BO_4N_2$: C, 76.15; H, 7.51; B, 1.75; N, 4.44. Found: C, 76.11; H, 7.62; B, 1.95; N, 4.40.

5.9. *(S)-Pinanediol [(1R,2S,3S)-1-acetamido-2-cyanomethyl-3-isopropenyl-4-(formyloxy)butyl]boronate 8*

(*S*)-Pinanediol [(1*R*,2*S*,3*S*)-1-acetamido-2-cyanomethyl-3-isopropenyl-4-(triphenylmethoxy)butyl]boronate (**7**) (5.91 g, 9.38 mmol) was dissolved in a mixture of formic acid (188 ml), and diethyl ether (188 ml). The solution was stirred at room temperature overnight and was diluted with diethyl ether (250 ml), washed successively with brine and saturated sodium bicarbonate until neutral, dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica gel with diethyl ether:methanol (98:2); 2.30 g, 59.0%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 3), 1.28 (s, 3), 1.35–1.45 (m, 4), 1.50–1.83 (s+m, 4), 1.83–2.05 (m, 2), 2.11–2.30 (m, 6), 2.55 (dd, *J*=4.83 and 17.37 Hz, 1), 2.65 (dt, *J*=3.84 and 8.4 Hz, 1), 2.78 (dd, *J*=5.46 and 17.37 Hz, 1), 3.04 (dd, *J*=2.04 and 7.98 Hz, 1), 4.24 (dd, *J*=2.2 and 8.73 Hz, 1), 4.38 (dd, *J*=8.85 and 11.79 Hz, 1), 4.57 (dd, *J*=3.13 and 11.85 Hz, 1), 5.03 (m, 1), 5.09 (t, *J*=1.2 Hz, 1), 7.98 (br s, conc. dependent, 1), 8.05 (s, 1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 16.25, 19.10, 21.57, 24.17, 26.47, 27.17, 29.04, 36.30, 36.90, 38.13, 39.89, 45.95, 51.92, 62.74, 76.65, 83.70, 114.33, 119.41, 142.28, 174.90; HRMS calcd for $C_{22}H_{33}BO_3N_2$ (M^+) 416.2482, found 416.2496.

5.10. *(S)-Pinanediol [(1R,2S,3S)-1-acetamido-2-cyanomethyl-3-isopropenyl-4-(hydroxy)butyl]boronate 9*

A solution of (*S*)-pinanediol [(1*R*,2*S*,3*S*)-1-acetamido-2-cyanomethyl-3-isopropenyl-4-(formyloxy)-butyl]boronate (**8**) (2.58 g, 6.20 mmol), and potassium thiocyanate (1.4 g) in methanol (130 ml) was heated under reflux for 6 days. After removal of the solvent, the residue was dissolved in dichloromethane (200 ml). The dichloromethane solution was washed with water and saturated aqueous sodium chloride, dried over sodium sulfate (15–20 g), and concentrated in a rotary evaporator to yield crude (*S*)-pinanediol [(1*R*,2*S*,3*S*)-1-acetamido-2-cyanomethyl-3-isopropenyl-4-(hydroxy)butyl]boronate (**9**), containing less than 1% unreacted **8**. Crude **9** was used in the next step without further purification; 2.23 g, ~92.7%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 3), 1.28 (s, 3), 1.35–1.43 (m, 4), 1.77–1.82 (m, 4), 1.85–2.05 (m, 2), 2.10 (s, 3), 2.15–2.40 (m, 4), 2.49–2.55 (m, 1), 2.61 (dd, *J*=4.8 and 17.25 Hz, 1), 2.76 (dd, *J*=5.94 and 17.22 Hz, 1), 3.04 (dd, *J*=2.16 and 7.8 Hz, 1), 3.75 (dd, *J*=5.58 and 10.8 Hz, 1), 3.94 (dd, *J*=6.27 and 10.8 Hz, 1), 4.24 (dd, *J*=2.07 and 8.67 Hz, 1), 4.86 (s, 1), 5.05 (t, *J*=1.38 Hz, 1), 7.89 (br s, conc. dependent, 1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 16.57, 19.33, 22.11, 24.23, 26.50, 27.23, 29.06, 36.23, 36.66, 38.21, 39.94, 48.68, 51.98, 61.24, 76.62, 83.81, 114.21, 120.05, 144.27, 174.26; HRMS calcd for $C_{21}H_{33}BO_4N_2$ (M^+) 388.2533, calcd for $C_{21}H_{31}BO_3N_2$ (M^+-H_2O) 370.2428, found 370.2458.

*5.11. (S)-Pinanediol {(1R,2S,3S)-1-acetamido-2-cyanomethyl-3-isopropenyl-4-[(methylsulfonyl)oxy]-butyl}boronate **10***

Methanesufonyl chloride (0.657 ml, 0.972 g, 8.49 mmol) was added dropwise to a solution of crude **9** (1.48 g, 3.81 mmol) and triethylamine (2.05 g, 20.26 mmol) in dichloromethane (80 ml) at 0°C under argon. After 30 minutes, the ice bath was removed, and the mixture was stirred for 4 h at room temperature. The reaction mixture was diluted with dichloromethane (80 ml) and extracted with water (50 ml) followed by aqueous hydrochloric acid (50 ml, 1 M), saturated aqueous sodium bicarbonate (2×25 ml), and saturated aqueous sodium chloride (40 ml). The organic phase was concentrated to yield (*S*)-pinanediol {(1*R*,2*S*,3*S*)-1-acetamido-2-cyanomethyl-3-isopropenyl-4-[(methylsulfonyl)oxy]butyl}boronate (**10**). It was purified by flash chromatography on silica gel with diethyl ether:methanol (98:2); 1.55 g, 87.3%; mp 136–138°C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 3), 1.28 (s, 3), 1.39 (d, J=10.83 Hz, 1), 1.40 (s, 3), 1.70–1.85 (m, 4), 1.85–1.95 (m, 1), 1.20 (t, J=5.31 Hz, 1), 2.15–2.25 (m, 4), 2.25–2.40 (m, 2), 2.64 (dd, J=5.16 and 17.43 Hz, 1), 2.76 (dd, J=6.11 and 13.47 Hz, 1), 2.85 (dd, J=5.43 and 17.4 Hz, 1), 3.06 (s, 3), 3.08 (d, J=2.76 Hz, 1), 4.24 (dd, J=2.04 and 8.64 Hz, 1), 4.47 (d, J=6.0 Hz, 2), 4.97 (s, 1), 5.10 (s, 1), 7.65 (br s, conc. dependent, 1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 16.10, 19.33, 21.77, 24.15, 26.45, 27.16, 28.99, 36.23, 36.77, 37.59, 38.13, 39.86, 46.66, 51.87, 68.96, 76.70, 83.78, 114.78, 119.56, 142.06, 174.92; HRMS calcd for $C_{22}H_{35}BO_6N_2S$ (M^+) 466.2309, found 466.2296. Anal. calcd for $C_{22}H_{35}BO_6N_2S$: C, 56.62; H, 7.57; B, 2.36; N, 6.01; S, 6.86. Found: C, 56.64; H, 7.61; B, 1.95; N, 5.98; S, 6.99.

*5.12. (S)-Pinanediol [(2R,3S,4S)-1-acetyl-3-cyanomethyl-4-isopropenyl]pyrrolidyl-2-boronate **11***

CAUTION: Structures bearing a close stereochemical and functional relationship to kainic acid may be toxic. The laboratory worker (J.L.) developed a temporary skin rash while working with compounds **11–15**, and it is not known whether possible exposure to any of these compounds might have been the cause. To a solution of (*S*)-pinanediol {(1*R*,2*S*,3*S*)-1-acetamido-2-cyanomethyl-3-isopropenyl-4-[(methylsulfonyl)oxy]butyl}boronate (**10**) (1.04 g, 2.23 mmol) in THF (20 ml) was added LDA (1.15 ml, 2 M, 2.34 mmol) at −78°C. The solution was allowed to warm to room temperature and kept for 13 h. The reaction was worked up by adding diethyl ether (150 ml) and saturated aqueous ammonium chloride (150 ml). The organic phase was dried over anhydrous magnesium sulfate. Removal of solvents gave an oil containing more than 85% (*S*)-pinanediol [(2*R*,3*S*,4*S*)-1-acetyl-3-cyanomethyl-4-isopropenyl]pyrrolidyl-2-boronate (**11**); 0.71 g; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3), 1.18–1.31 (m, 4), 1.44 (s, 3), 1.81 (q, J=0.69 Hz, 3), 1.85–2.05 (m, 3), 2.09 (d, J=0.72 Hz, 3), 2.15–2.45 (m, 4), 2.59–2.70 (m, 1), 3.00 (d, J=9.6 Hz, 1), 3.19 (dt, J=4.29 and 6.84 Hz, 1), 3.56 (dd, J=4.11 and 10.98 Hz, 1), 3.74 (dd, J=6.84 and 10.74 Hz, 1), 4.31 (dd, J=2.19 and 8.79 Hz, 1), 4.97 (d, J=0.87 Hz, 1), 5.06 (t, J=1.35 Hz, 1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 17.24, 20.11, 22.75, 24.05, 26.53, 27.10, 28.53, 30.27, 35.78, 38.31, 39.63, 39.71, 48.77, 77.45, 85.61, 115.30, 118.77, 141.79, 170.17; HRMS calcd for $C_{21}H_{31}BO_3N_2$ (M^+) 370.2428, found 370.2400.

*5.13. [(2R,3S,4S)-1-Acetyl-3-cyanomethyl-4-isopropenyl]pyrrolidyl-2-boronic acid **12***

A solution of phenylboronic acid (0.31 g, 2.54 mmol) in water (20 ml) was added to the solution of (*S*)-pinanediol [(2*R*,3*S*,4*S*)-1-acetyl-3-cyanomethyl-4-isopropenyl]pyrrolidyl-2-boronate (**11**) (0.94 g, 2.54 mmol) in diethyl ether (40 ml). The mixture was stirred at room temperature overnight. The organic phase was removed and the aqueous phase was lyophilized to give a powder, [(2*R*,3*S*,4*S*)-1-acetyl-3-

cyanomethyl-4-isopropenyl]pyrrolidyl-2-boronic acid (**12**), 0.50 g, 83%; ^{1}H-NMR (300 MHz, D_2O) δ 1.63 (s, 3), 1.96 (s, 3), 2.36 (m, 2), 2.55 (m, 1), 2.91 (d, *J*=7.62 Hz, 1), 3.01 (q, *J*=6.7 Hz, 1), 3.56 (dd, *J*=6.10 and 11.58 Hz, 1), 3.66 (dd, *J*=7.32 and 11.58 Hz, 1), 4.70 (s, 1), 4.91 (s, 1); ^{13}C-NMR (75 MHz, D_2O) δ 19.70, 21.91, 24.20, 40.90, 50.75, 52.38, 116.47, 123.03, 144.60, 174.80; HRMS calcd for $C_{11}H_{17}BO_3N_2$ (M^+) 236.1332, calcd for trimeric boronic anhydride $C_{33}H_{45}B_3O_6N_6$ (M^+) 654.3680, found 654.3653.

5.14. *Ethylene glycol [(2*R*,3S,4S)-1-acetyl-3-cyanomethyl-4-isopropenyl]pyrrolidyl-2-boronate 13*

A solution of [(2*R*,3*S*,4*S*)-1-acetyl-3-cyanomethyl-4-isopropenyl]pyrrolidyl-2-boronic acid (**12**) (0.54 g, 2.288 mmol) and ethylene glycol (0.142 g, 2.29 mmol) in ethyl acetate (30 ml) was stirred at room temperature overnight. To the solution, sodium sulfate (5 g) and calcium chloride (5 g) were added to remove water and excess ethylene glycol. The ethyl acetate solution was filtered and concentrated to yield ethylene glycol [(2*R*,3*S*,4*S*)-1-acetyl-3-cyanomethyl-4-isopropenyl]pyrrolidyl-2-boronate (**13**); 0.50 g, 83.4%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.83 (d, *J*=0.54 Hz, 3), 2.14 (d, *J*=1.02 Hz, 3), 2.31 (m, 2), 2.57–2.68 (m, 1), 2.91 (d, *J*=10.86 Hz, 1), 3.25 (m, *J*=4.02 and 7.41 Hz, 1), 3.58 (dd, *J*=4.0 and 11.5 Hz, 1), 3.74 (dd, *J*=7.53 and 11.1 Hz, 1), 4.06 (s, 4), 4.89 (s, 1), 5.08 (t, *J*=1.35 Hz, 1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 17.17, 17.57, 22.92, 39.18, 50.06, 50.39, 65.00, 115.88, 118.51, 141.94, 173.25; HRMS calcd for $C_{13}H_{19}BO_3N_2$ (M^+) 262.1488, $C_{13}H_{20}BO_3N_2$ (M^++H) 263.1567, found 263.1588.

5.15. *(2S,3S)-2-Cyanomethyl-3-[(triphenylmethoxy)methyl]-4-methyl-4-pentenal 16*

To a solution of crude (*S*)-pinanediol [(1*S*,2*S*,3*S*)-1-chloro-2-cyanomethyl-3-isopropenyl-4-(triphenylmethoxy)propyl]boronate (**5**) (1.22 g, 2.01 mmol) in THF (20 ml) and phosphate buffer (pH=8.0) (10 ml) was added hydrogen peroxide (0.5 ml, 30%) at 0°C. After the addition of hydrogen peroxide, sodium carbonate (0.5 g, 4.74 mmol) was added to keep the pH between 8 and 9. After 0.5 h, the cold bath was removed. The pH of the aqueous solution was checked frequently. The reaction was complete within 3 h. Sodium iodide (0.2 g, 1.3 mmol) was added at 0°C. The iodine was reduced by sodium thiosulfate (1.5 g, 6 mmol), and the THF solution was separated from aqueous solution. The aqueous layer was extracted with diethyl ether (2×30 ml). The combined organic layer was washed with sodium thiosulfate solution (10%, 5 ml) and dried over magnesium sulfate and concentrated. The crude material contained a 13:1 ratio of **16**:epimer if the reaction was worked up within 1 h, but a 9:1 ratio of **16**:epimer after 3 h. Crude material was chromatographed on silica gel with hexanes:diethyl ether (7:3), which resulted in 40% epimerization; 0.65 g, 79.1%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.70 (m, 3), 2.23 (m, 1), 2.41 (m, 1), 2.89–2.92 (m, 1), 2.92–3.00 (m, 1), 3.21 (m, 1), 3.39 (m, 1), 4.71 (d, *J*=0.72 Hz, 1), 4.97 (m, 1), 7.15–7.55 (m, 15), 9.66 (s, 1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.61, 22.17, 46.07, 47.71, 62.32, 87.52, 114.99, 118.09, 127.26, 127.96, 128.44, 141.57, 143.28, 200.00; HRMS calcd for $C_{28}H_{27}O_2N$ (M+) 409.2042, found 409.2031. Evidence for epimer: Extra peaks in the NMR spectra indicated the chromatographed samples of **16** contained some of the (2*R*,3*S*)-epimer; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.61 (m, 3), 2.28 (m, 1), 2.50 (m, 1), 2.65 (m, 1), 2.82–2.92 (m, 1), 3.28 (m, 1), 3.36 (m, 1), 4.49 (s, 1), 4.97 (m), 7.15–7.55 (m, 15), 9.69 (d, *J*=1.38 Hz, 1, CHO); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 15.04, 21.12, 47.32, 48.23, 63.48, 87.58, 115.31, 117.78, 127.21, 127.94, 128.47, 141.43, 143.38, 200.74.

5.16. [2(R+S),3S,4S]-2-Hydroxy-3-cyanomethyl-4-[(triphenylmethoxy)methyl]-5-methyl-5-hexenenitrile 17

To a solution of crude (2*S*,3*S*)-2-cyanomethyl-3-[(triphenylmethoxy)methyl]-4-methyl-4-hexenal (**16**) (1.07 g, 2.62 mmol) in diethyl ether (5 ml), aqueous ammonium chloride [0.16 g, 3 mmol in H_2O (5 ml)] was added at 0°C, followed by an ice-cold solution of potassium cyanide [0.182 g, 2.8 mmol in H_2O (4 ml)]. The mixture was stirred at room temperature for 4 h, and the ether solution was separated from aqueous solution. The aqueous layer was extracted with diethyl ether (2×10 ml). The combined organic layer was dried over magnesium sulfate and concentrated. Two diastereomers were separated by chromatography on silica gel with hexanes:diethyl ether (2:1); 0.68 g, 59.5%. Diastereomer A: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.75 (d, *J*=0.51 Hz, 3), 2.19–2.32 (m, 2), 2.45–2.51 (m, 1), 2.68 (dt, *J*=5.30 and 10.59 Hz, 1), 3.21 (dd, *J*=5.1 and 10.0 Hz, 1), 3.32 (dd, *J*=5.6 and 10.0 Hz, 1), 3.39 (d, *J*=5.82 Hz, 1), 4.72 (dd, *J*=3.96 and 5.52 Hz, 1), 4.87 (s, 1), 5.04 (t, *J*=1.35 Hz, 1), 7.28–7.61 (m, 15); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 15.23, 21.64, 39.65, 45.90, 62.53, 62.70, 87.42, 115.04, 117.95, 118.91, 127.27, 128.01, 128.47, 143.24. Diastereomer B: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.75 (d, *J*=0.57 Hz, 3), 2.18 (dd, *J*=9.99 and 17.16 Hz, 1), 2.29–2.36 (m, 2), 2.81 (m, 1), 3.03 (dd, *J*=8.31 and 10.23 Hz, 1), 3.42 (dd, *J*=4.02 and 10.29 Hz, 1), 4.56 (d, *J*=0.72 Hz, 1), 4.61 (d, *J*=8.97 Hz, 1), 4.71 (dd, *J*=3.93 and 8.95 Hz, 1), 4.92 (m, 1), 7.21–7.54 (m, 15); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.92, 22.16, 40.52, 45.67, 62.37, 62.42, 88.78, 114.13, 117.76, 118.05, 127.55, 128.22, 128.37, 142.57, 142.94.

5.17. [2(R+S),3(R+S),4S]-2-(Trimethylsilyloxy)-3-cyanomethyl-4-[(triphenylmethoxy)methyl]-5-methyl-5-hexenenitrile, trimethylsilyl derivative of 17

To a solution of trimethylsilyl cyanide (0.27 g, 2.74 mmol) and epimerized **16**, [2(*R*+*S*),3*S*]-2-cyanomethyl-3-[(triphenylmethoxy)methyl]-4-methyl-4-hexenal (1.12 g, 2.74 mmol) in THF (12 ml) was added a catalytic amount of triethylamine (0.028 g, 0.274 mmol, 10%) at 0°C. The mixture was stirred at the same temperature for 2 h, and the solvent was removed under reduced pressure. The residue was pure enough for usual use. The ^{13}C-NMR spectrum indicated that there were four diastereomers of trimethylsilylated **17**; 1.02 g, 73.3%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.70–1.80 (m, 3), 2.07–2.68 (m, 4), 3.00–3.46 (m, 2), 4.23–4.83 (d, 1), 4.82–5.02 (s, 1), 5.04–5.16 (t, 1), 7.18–7.61 (m, 15); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 15.29, 15.17, 16.85, 16.56; 21.86, 20.50, 21.68, 21.35; 40.06, 40.97, 39.63, 42.25; 45.41, 47.41, 45.92, 47.78; 62.46, 62.95, 61.82, 61.66; 63.02, 63.45, 63.08, 64.84; 87.25, 87.23, 86.85, 87.51; 114.79, 115.38, 115.64, 115.43; 117.75, 117.29, 117.88, 117.80; 119.38, 118.10, 118.92, 118.48; 127.27, 127.21; 128.02, 127.99, 127.97; 128.55, 128.51, 128.46; 142.95, 142.42, 142.60, 142.38; 143.35, 143.51, 143.56, 143.32. HRMS calcd for $C_{32}H_{36}O_2N_2Si$ (M^+) 508.2546, found 508.2533.

5.18. [2(R+S),3S,4S]-[2-Hydroxy-3-cyanomethyl-4-isopropenyl]tetrahydrofuran 18

[2(*R*+*S*),3*S*,4*S*]-2-Hydroxy-3-cyanomethyl-4-[(triphenylmethoxy)methyl]-5-methyl-5-hexenenitrile (**17**) (1.03 g, 2.36 mmol) was dissolved in a mixture of formic acid (4.5 ml) and diethyl ether (4.5 ml). The mixture was stirred at room temperature for 2 h, and was diluted with diethyl ether (10 ml), washed successively with brine and saturated aqueous sodium bicarbonate until neutral, dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica gel with hexanes:diethyl ether (7:3); 0.34 g, 86.3%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.80 (t, *J*=0.63 Hz, 3), 2.18 (m, 2), 2.54–2.64 (m, 1), 2.76 (d, *J*=2.85 Hz, 1), 3.33 (m, 1), 3.95 (t, *J*=8.94 Hz, 1), 4.18 (dd, *J*=8.04 and 8.79 Hz, 1), 4.76 (s, 1), 5.02 (d, *J*=1.32 Hz), 5.46 (d, *J*=2.07 Hz, 1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 15.21, 23.41, 44.78, 45.39, 68.46, 101.26, 113.49, 118.53, 139.88.

*5.19. (S)-Pinanediol [(1*R*,2S,3S)-1-(2,2,5,5-tetramethyl-2,5-disila-1-azacyclopentyl)-2-cyanomethyl-3-isopropenyl-4-(triphenylmethoxy)butyl]boronate* ***19***

A solution of 1-lithio(2,2,5,5-tetramethyl-2,5-disila-1-azacyclopentane) (5.19 mmol) was prepared by the addition of 2,2,5,5-tetramethyl-2,5-disila-1-azacyclopentane (0.827 g, 5.19 mmol) in THF (4 ml) to the solution of LDA (2.85 ml, 2 M, 5.68 mmol) in THF (4 ml) with stirring at −78°C. To the lithio(2,2,5,5-tetramethyl-2,5-disila-1-azacyclopentane) solution, a solution of (*S*)-pinanediol [(1*S*,2*S*,3*S*)-1-chloro-2-cyanomethyl-3-isopropenyl-4-(triphenylmethoxy)propyl]boronate (**5**) (3.0 g, 4.94 mmol) in THF (20 ml) was added at −78°C. The mixture was allowed to warm to room temperature and stirred overnight. The solvents were removed under reduced pressure. The residue was redissolved in pentane and filtered through a column of Celite and magnesium sulfate. Concentration in a rotary evaporator gave (*S*)-pinanediol [(1*R*,2*S*,3*S*)-1-(2,2,5,5-tetramethyl-2,5-disila-1-azacyclopentyl)-2-cyanomethyl-3-isopropenyl-4-(triphenylmethoxy)butyl]boronate (**19**); 3.15 g, 63.8%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6), 0.12 (s, 6), 0.55–0.73 (m, 4), 0.84 (s, 3), 1.23–1.33 (m, 4), 1.42 (s, 3), 1.71 (s, 3), 1.80–2.70 (m, 9), 3.01 (d, *J*=5.07 Hz, 1), 3.14 (m, 1), 3.35 (m, 1), 4.31 (dd, *J*=1.59 and 8.58 Hz, 1), 4.95 (s, 1), 5.03 (t, *J*=1.5 Hz, 1), 7.15–7.60 (m, 15); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 0.96, 1.79, 8.76, 16.81, 21.38, 24.03, 26.62, 27.06, 28.23, 34.95, 38.22, 39.41, 42.40, 48.31, 51.24, 63.58, 78.06, 86.03, 86.75, 113.71, 120.58, 126.96, 127.72, 128.73, 143.92, 145.13; MS m/e calcd for $C_{44}H_{59}BO_3N_2Si_2$ (M^+) 730.4, found 730.4.

*5.20. (S)-Pinanediol [(4S,5S)-3-isopropenyl]valerolactone-4-(*R*)-(acetamidomethyl)boronate* ***21***

(*S*)-Pinanediol [(1*R*,2*S*,3*S*)-1-acetamido-2-cyanomethyl-3-isopropenyl-4-(triphenylmethoxy)butyl]-boronate (**7**) (1.52 g, 2.41 mmol) and $ZnBr_2$ (4.342 g, 19.28 mmol) were dissolved in dichloromethane (60 ml) and diethyl ether (2.5 ml). To this solution, methanesulfonyl chloride (0.466 ml, 0.697 g, 6.025 mmol) was added dropwise at 0°C. The mixture was stirred at 0°C for 20 h, and then at room temperature for another 20 h. The solvents were removed under reduced pressure. The residue was treated with saturated aqueous ammonium chloride and diethyl ether. The ether layer was dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica gel with diethyl ether:methanol (97:3), and **21** was the major product; 0.35 g, 37.3%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 3), 1.27–1.36 (m, 4), 1.40 (s, 3), 1.78 (d, *J*=0.57 Hz, 3), 1.85–1.95 (m, 1), 1.95–2.03 (m, 1), 2.06 (s, 3), 2.10–2.31 (m, 4), 2.58 (dd, *J*=5.88 and 16.2 Hz, 1), 2.68 (td, *J*=5.58 and 8.7 Hz, 1), 2.82 (dd, *J*=10.74 and 16.17 Hz, 1), 2.96 (dd, *J*=3.18 and 4.29 Hz, 1), 4.16 (dd, *J*=6.21 and 11.52 Hz, 1), 4.24 (dd, *J*=2.13 and 8.7 Hz, 1), 4.40 (dd, *J*=2.1 and 11.52 Hz, 1), 4.91–4.93 (t and d overlap, *J*=1.47 and 0.63 Hz, 2), 7.33 (br s, conc. dependent, 1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.49, 20.13, 24.20, 26.68, 27.19, 29.08, 32.07, 36.23, 36.62, 38.12, 39.91, 43.97, 51.87, 70.72, 76.87, 83.86, 114.22, 143.93, 173.11, 174.02; HRMS calcd for $C_{21}H_{32}BO_5N$ (M^+) 389.2374, found 389.2390.

*5.21. [(2*R*,3S,4S)-1-Acetyl-3-cyanomethyl-4-isopropenyl]pyrrolidyl-2-boron difluoride* ***20***

To the solution of (*S*)-pinanediol [(2*R*,3*S*,4*S*)-1-acetyl-3-cyanomethyl-4-isopropenyl]pyrrolidyl-2-boronate (**11**) (0.64 g, 1.73 mmol), trimethylboroxine (0.434 g, 3.46 mmol) in diethyl ether (20 ml), KF·HF solution [0.27 g, 3.46 mmol in water (20 ml)] was added dropwise at room temperature. The mixture was stirred at room temperature for 18 h, and the ether solution was separated from aqueous solution. The aqueous layer was extracted with ethyl acetate (2×20 ml). The ethyl acetate layer was dried over sodium sulfate and concentrated to give **20**; 0.28 g, 67.4%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.83 (d, J=0.51 Hz, 3), 2.21 (d, J=1.23 Hz, 3), 2.29 (m, 2), 2.56–2.65 (m, 1), 2.82 (d, J=11.52 Hz, 1), 3.31 (m, 1), 3.59 (m, 1), 3.78 (m, 1), 4.90 (s, 1), 5.10 (t, J=1.26 Hz, 1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 15.95, 16.95, 22.85, 38.21, 50.15, 50.74, 116.31, 118.36, 141.85, 174.59; HRMS calcd for $C_{11}H_{15}BON_2F_2$ (M^+) 240.1245, calcd for $C_9H_{13}BONF_2$ (M^+-CH_2CN), 200.1058, found 200.1049.

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