Pergamon © 1997 The DuPont Merck Pharmaceutical Company. Published by Elsevier Science Ltd. All rights reserved.
Tetrahedron: Asymmetry, Vol. 8, No. 9, pp. 1435–1440, 1997
Printed in Great Britain
PII: S0957-4166(97)00135-3
0957-4166/97 $17.00 + 0.00

Resolution of α-aminoboronic esters by diastereoselective crystallization with pinanediols. Confirmation by X-ray analysis

Christian S. Brosz*,[a] Joseph C. Calabrese,[b] Charles A. Kettner[a] and Christopher A. Teleha*[a,*]

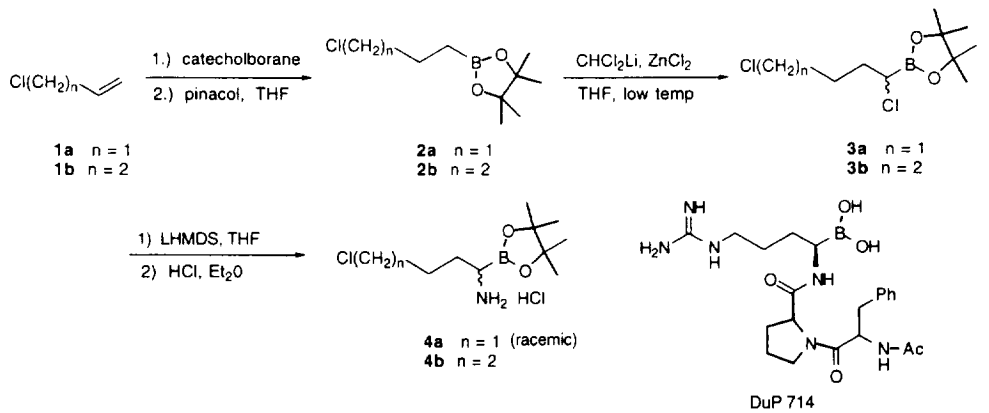
[a] The DuPont Merck Pharmaceutical Co., Chemical and Physical Sciences, Experimental Station, Wilmington, DE 19880-0336, USA

[b] DuPont Co., Central Research and Development Department, Experimental Station, Wilmington, DE 19880-0228, USA

Abstract: A resolution method for α-aminoboronic esters **4a,b** using chiral pinanediol is described. © 1997 The DuPont Merck Pharmaceutical Company. Published by Elsevier Science Ltd

The synthesis of boron-containing mimics of amino acids (referred to as α-aminoboronic acids) has been well established. Matteson and coworkers have extensively developed technology for both racemic[1] and asymmetric[2] preparation of α-haloboronic esters.[3] Additional work has shown that α-aminoboronic esters and acids, when incorporated in a peptide sequence, are extremely potent enzyme inhibitors of serine proteases such as chymotrypsin and thrombin.[4] An alternative route to racemic prolineboronate esters has been developed; further reaction with chiral pinanediol provided diastereomers which were separable using HPLC.[5]

Our studies were focused on the preparation of chiral α-aminoboronic acids intermediates for use in the synthesis of DuP 714 (Ac-D-Phe-Pro-boroArg, Scheme 1), a potent inhibitor of thrombin.[6] Our strategy focused on the resolution of a racemic boronic ester, taking advantage of the facile transesterification properties of pinacol-boronic esters with chiral pinanediols.[7]



Scheme 1.

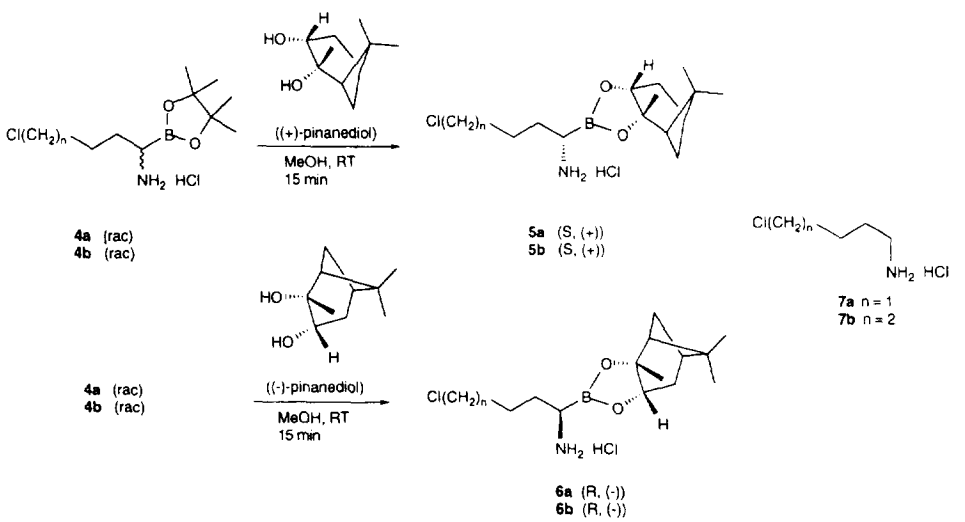
Scheme 1 shows the preparation of the requisite pinacol esters used in this study. This was identical to that previously reported, with the exception being the sidechain chloride was used.[6]

Reaction of catecholborane with allyl or butenyl chloride **1a,b** gave the expected addition products with excellent regioselectivity. Without isolation, direct transesterification of the labile catechol ester

* Corresponding author. Email: telehaca@a1.lldmpc.umc.dupont.com

was affected using pinacol to provide esters **2a,b** as distillable oils. Subjecting **2a,b** to the Matteson homologation protocol (racemic), using the lithium anion of dichloromethane, which was followed by zinc chloride-promoted migration of the tetravalent boronate complex, provided the dichlorides **3a,b** as distillable oils. In the presence of two displaceable chlorides, the amine functionality was incorporated with high selectivity using the previously established protocol of first treating **3a,b** with lithium hexamethyldisilylamide to give the bistrimethylsilyl amines, followed by desilylation using anhydrous HCl. This method provided multigram quantities of racemic α-aminoboronic esters **4a,b**, as their hydrochloride salts, for use in this study.

The racemic **4a** was subjected to similar transesterification conditions used earlier with pinacol, instead substituting (+)-pinanediol and using methanol as solvent (room temp, 30 minutes[8]) (Scheme 2).



Scheme 2.

The viscous residue that was obtained after concentration (*in vacuo*) was triturated with ether to provide a crude solid which was easily filtered. Further purification was carried out by direct recrystallization with ethyl acetate and a trace of ethanol and provided pinanediol ester **5a** in 43% overall yield.[9] Examination of **5a** by NMR (^{1}H, ^{13}C) suggested the material had high diastereomeric purity. Further analysis by HPLC, after derivatization of the amine function to the amide using either benzoyl chloride or Mosher's acid chloride, supported the formation of **5a** as a single diastereomer in >96% d.e. The fine, colorless needles from the crystallization of **5a** proved suitable for X-ray crystallographic analysis (Figure 1[10]) and revealed the 1(*S*) absolute configuration at the α-aminoboronic acid center. The *S*,(+) **5a** was *diastereomeric* in configuration to the *R*,(+) product that would be expected when the Matteson asymmetric homologation protocol was applied using this (+)-pinanediol.[2a,b,6]

When **4a** was subjected to the transesterification procedure using the opposite (−)-pinanediol, **6a** was obtained from the mixture after trituration in 83% yield.[9] Crystallization as above provided crystals of suitable quality for X-ray analysis and confirmed the 1(*R*) absolute configuration of **6a**. This *R*,(−) was enantiomeric to **5a** is likewise *diastereomeric* to the anticipated product isomer (*S*,(−)) that would be produced applying the asymmetric Matteson sequence with the unnatural (−)-pinanediol.[2a,b,6]

To investigate the generality of this method, the chain-extended compound **4b** was subjected to the same procedure using with (+)- and (−)-pinanediol. Products **5b** and **6b** were obtained in somewhat lower yields from the reactions after trituration (22 and 39% respectively[9]). Crystallization of the higher yielding **6b** provided crystals of suitable quality for X-ray analysis. The 1(*S*) chirality was

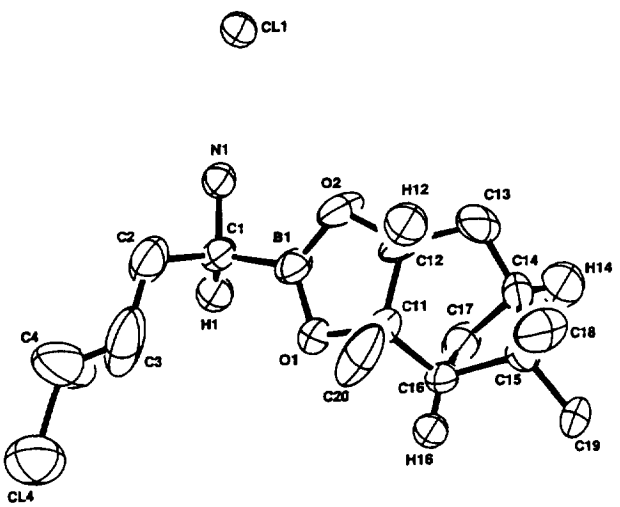


Figure 1.

identical to that seen in n=1 series **6a**. X-Ray quality crystals of **5b** could not be prepared; however, all data supported the absolute stereochemistry to be consistent with that shown.

The yield for the transesterification/crystallization procedure was generally higher for the chloropropyl (n=1) series as compared to the chlorobutyl (n=2) series. Careful analysis of the filtrates (NMR, MS) from the crystallizations of **4a** revealed that de-boronated 4-chlorobutane-1-amine hydrochloride (**7a**) was present. Similarly from the reactions of **4b**, 5-chloropentane-1-amine hydrochloride (**7b**) was detected. Careful inspection of the proton NMR suggested that the diastereomeric isomers of **5** and **6** were present in the filtrate. Attempts to isolate these diastereomers were unsuccessful, in part due to their higher solubility compared to isolated **5a,b** and **6a,b**. The presence of **7** suggests that the decomposition of **4a,b** is competitive with the transesterification of either enantiomer of **4a,b** with pinanediol. Although the rate of decomposition of pinacol esters in deuterochloroform with 'a little ethanol' has been reported to take place over the course of a few hours,[2d] the observation that **7a,b** are formed under these reaction conditions suggests that the rates of transesterification and decomposition for **4a,b** must be comparable when methanol was used as solvent. This interpretation is supported by the observation that when the solvent for the transesterification was changed to diethyl ether or tetrahydrofuran, no de-boronated material **7** was observed (^{1}H NMR) despite the production of the products (both diastereomers).

It was our initial expectation that the product of transesterification of racemic **4a,b** with the (+)-pinanediol would have led to the *R*,(+) diastereomer. This was based on the earlier observation that α-aminoboronic esters of this type were fully characterized stable solids (as hydrochloride salt) and were freely soluble in chlorinated organic solvents like chloroform and dichloromethane.[6] What was unexpected about our results was the *S*,(+) diastereomer as the preferred compound crystallizing from alcoholic solution. Therefore, our procedure constitutes a selective crystallization method for the products **6a,b** and **7a,b**.

In conclusion, a method for the preparation of diastereomerically pure α-aminoboronic esters has been described, wherein racemic α-aminoboronic pinacol esters **4a,b** were resolved by transesterification with chiral pinanediols under selective crystallization conditions. For the compounds examined above, (+)-pinanediol was used to the separate the 1(*S*) isomers, and (−)-pinanediol provided diastereomers with the 1(*R*) configuration. Unfortunately, for purposes of further development, this approach was unattractive since the unnatural (and more expensive) (−)-pinanediol was required to crystallize the biologically active 1(*R*)-α-aminoboronic esters. Nonetheless, method is useful for direct

isolation of the diastereomeric pairs of chiral pinanediol esters of α-aminoboronic acids which can not be accessed using the two-step homologation technology.

Experimental section

General

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ and were referenced to TMS. Mass spectra were obtained on either VG 70-VSE (High res DCI) or Finnigan MAT 8230 (DCI) mass spectrometers. Optical rotations were measured on a Perkin Elmer model 241 polarimeter. 4-Chloro-1-butene was obtained from Wiley Organics and used without purification. Pinanediol was obtained from Aldrich Chemical Co. and recrystallized from petroleum ether.

*Pinacol 4-chlorobutane-1-boronate (**2b**)*

To a 250 mL flask containing catecholborane (43.31 mL, 0.406 mol) was added dropwise 4-chloro-1-butene (36.79 g, 0.406 mol) and slowly heated to 100°C over 35 min. The heating was continued for 4 h and allowed to cool to RT overnight. The reaction was transferred via cannula over 1.5 h to a −4°C solution of pinacol (49.18 g, 0.415 mol) in THF (285 mL). After warming to RT overnight, the reaction was concentrated, diluted with hexane (660 mL), and extracted with aq. Na_2CO_3 (10%, 220 mL), $NaHCO_3$ (satd., 3×220 mL), water (220 mL) and brine (275 mL). The organics were filtered through silica gel (250 g) using hexane followed by toluene (3000 mL ea). The product was collected in fractions 6–48 (125 mL ea), concentrated and distilled (44–47°C, 100 mm) to give the product (59.7 g) as an oil in 67% yield. ^{1}H NMR δ: 3.52 (d, *J*=7 Hz, 1H), 3.49 (d, *J*=7 Hz, 1H), 1.81–1.71 (m, 2H), 1.51–1.41 (m, 2H), 1.22 (s, 12H), 0.78 (t, *J*=7 Hz, 2H); Mass spec (NH_3–CI): m/e 236 $(M+NH_4)^+$.

*Pinacol 1,5-dichloropentane-1-boronate (**3b**)*

A solution of LDA (prepared from 180 mL of 1.6 M n-BuLi in hexane, 38.54 mL diisopropylamine and 200 mL THF) was added to a −60°C solution of **2b** (54.63 g, 0.250 mol), CH_2Cl_2 (19.6 mL, 0.305 mol), THF (283 mL) and cyclohexane (385 mL), followed immediately by the addition of $ZnCl_2$ (1.0 M in ether, 400 mL) at −45 to −55°C. After allowing the reaction to warm to RT overnight, hexane (615 mL) was added and the reaction stirred for 20 min. The mixture was transferred to a separatory funnel (12 L) with additional hexane (1575 mL) and the organic layer washed with aq. H_2SO_4 (1 N, 1575 mL). The aqueous layer was washed with fresh hexane (473 mL) and the combined organics were washed with water (2365 mL), $NaHCO_3$ (satd., 2×2760 mL) and brine (3875 mL). The organic layer was directly concentrated and filtered through silica gel (315 g, wetted with 10% EtOAc in hexane) using EtOAc in hexane (10%, 25%). After evaporation of the product containing fractions, the product was distilled (70–85°C, 92 mm) to give the product (44.72 g) as an oil in 67% yield. ^{1}H NMR δ: 3.54 (t, *J*=7 Hz, 2H), 3.42 (dd, *J*=7Hz, 8Hz, 1H), 1.75–1.92 (m, 4H), 1.48–1.75 (m, 2H), 1.29 (s, 12H); HRMS (NH_3–CI/DEP) calculated for $C_{11}H_{21}BCl_2O_2$ $(M+NH_4)^+$: 284.135540, found: 284.126271.

*Pinacol 1-amino-4-chlorobutane-1-boronate hydrochloride (**4a**)*

A 2 L round-bottom flask was charged with **3a** (73.03 g, 0.289 mol), THF (383 mL) and cooled to −78°C. A solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 310 mL) was added dropwise, stirred for 45 min and warmed to RT overnight. The reaction was concentrated *in vacuo*, followed by the addition of hexane (940 mL) and re-evaporation *in vacuo*. Fresh hexane (940 mL) caused the precipatation of a white solid (LiCl) which was filtered using a sintered funnel. The hexane filtrate was cooled to −24°C and treated with HCl in ether (1 M, 930 mL) over 2.5 h, followed by stirring at RT overnight. The slurry was carefully filtered, limiting exposure to moisture, and gave the product (69.47 g) as a cream-colored solid, mp 140–5°C, in 89% yield. Although this material was sufficiently pure enough for use in the next reaction, a 2 g sample was purified by dissolution in $CHCl_3$, filtered

(removed ca. 50 mg of a white solid — LiCl) and evaporated, followed by recrystallization from EtOAc to give 1.38 g of a white solid, mp 147–8.5°C. ^{1}H NMR δ: 8.29 (br s, 3H), 3.59 (d, *J*=6 Hz, 1H), 3.57 (d, *J*=6 Hz, 1H), 2.11–1.93 (m, 4H), 1.29 (s, 12H); Mass spec (NH_3–DCI): m/e 234 $(M+H-HCl)^+$.

*Pinacol 1-amino-5-chloropentane-1-boronate hydrochloride (**4b**)*

Prepared from **3b** in a similar manner to **4a**, 86% yield; white solid, mp 162–3°C; ^{1}H NMR δ: 8.25 (br s, 3H), 3.55 (t, *J*=7 Hz, 2H), 2.92 (m, 1H), 1.75–1.93 (m, 4H), 1.59–1.74 (m, 2H), 1.29 (s, 12H); HRMS (NH_3–CI/DEP) calculated for $C_{11}H_{24}BClNO_2$ $(M+H-HCl)^+$: 248.158862, found: 248.159369.

Diastereoselective crystallization of pinanediol esters. Representative procedure

*(+)-Pinanediol (1S)-1-amino-4-chlorobutane-1-boronate hydrochloride (**5a**)*

To a mixture of **4a** (1.08 g, 4.0 mmol) in MeOH (8 mL) was added (+)-pinanediol (0.68 g, 4.00 mmol) for 30 min at RT. The clear mixture was concentrated on a rotary evaporator, and the viscous oil was triturated with ether (3×25 mL). Ether (10 mL) was added and the slurry was filtered. The crude solid was recrystallized from EtOAc/EtOH (20 mL/1 mL) to give the product as fine needles (0.131 g), mp 192–4°C, in 20% isolated yield. $[\alpha]_D^{25}$=+14.81 (c 1.0, EtOH); ^{1}H NMR δ: 8.36 (br s, 3H), 4.40 (dd, *J*=2 Hz, 9 Hz, H), 3.59 (t, *J*=6 Hz, 2H), 2.98 (m, 1H), 1.92–2.35 (m, 9H), 1.42 (s, 3H), 1.29 (s, 3H), 1.16 (d, *J*=11.0 Hz, 1H), 0.83 (s, 3H); HRMS (NH_3–CI/DEP) calculated for $C_{14}H_{26}BCl_2NO_2$ $(M+H-HCl)^+$: 286.174512, found: 286.174198; IR (KBr, cm^{-1}): 2930, 1594, 1392, 1078. Anal. Calcd for $C_{14}H_{26}BCl_2NO_2$: C, 52.21; H, 8.14; N, 4.35; B, 3.36; Cl, 22.01. Found: C, 51.83; H, 8.09; N, 4.29; B, 3.26; Cl, 21.73.

*(−)-Pinanediol (1R)-1-amino-4-chlorobutane-1-boronate hydrochloride (**6a**)*

From **4a** and (−)-pinanediol, 42% isolated yield; white solid, mp 193–5°C (2×from 14% EtOH in EtOAc); $[\alpha]_D^{25}$=−15.20 (c 1.0, EtOH); ^{1}H NMR δ: 8.36 (br s, 3H), 4.40 (dd, *J*=2 Hz, 9 Hz, 1H), 3.59 (t, *J*=5 Hz, 2H), 2.98 (m, 1H), 1.92–2.35 (m, 9H), 1.42 (s, 3H), 1.29 (s, 3H), 1.16 (d, *J*=11 Hz, 1H), 0.83 (s, 3H); HRMS (NH_3–CI/DEP) calculated for $C_{14}H_{26}BCl_2NO_2$ $(M+H-HCl)^+$: 286.174512, found: 286.173629.

*(+)-Pinanediol (1S)-1-amino-5-chloropentane-1-boronate hydrochloride (**5b**)*

From **4b** and (+)-pinanediol, 18% isolated yield; white solid, mp 177–8°C; $[\alpha]_D^{25}$=+11.90 (c 1.0, EtOH); ^{1}H NMR δ: 8.33 (br s, 3H), 4.39 (dd, *J*=2 Hz, 9 Hz, 1H), 3.55 (t, *J*=2 Hz, 7H), 2.95 (m, 1H), 1.59–2.35 (m, 11H), 1.42 (s, 3H), 1.28 (s, 3H), 1.17 (d, *J*=11 Hz, 1H), 0.83 (s, 3H); HRMS NH_3–CI/DEP calc. for $C_{15}H_{28}BClNO_2$ $(M+H-HCl)^+$: 300.190162, found 300.189385. Anal. Calcd for $C_{15}H_{28}BCl_2NO_2$: C, 53.60; H, 8.41; N, 4.18; B, 3.23; Cl, 21.10. Found: C, 53.36; H, 8.30; N, 4.01; B, 3.26; Cl, 20.97.

*(−)-Pinanediol (1R)-1-amino-5-chloropentane-1-boronate hydrochloride (**6b**)*

From **4b** and (−)-pinanediol, 11% isolated yield; white solid, mp 175–6°C; $[\alpha]_D^{25}$=−13.12 (c 1.0, EtOH); ^{1}H NMR δ: 8.30 (br s, 3H), 4.39 (dd, *J*=2 Hz, 9 Hz, 1H), 3.55 (t, *J*=2 Hz, 7H), 2.95 (m, 1H), 1.59–2.35 (m, 11H), 1.42 (s, 3H), 1.28 (s, 3H), 1.17 (d, *J*=11 Hz, 1H), 0.83 (s, 3H); HRMS NH_3–CI/DEP calc. for $C_{15}H_{28}BClNO_2$ $(M+H-HCl)^+$: 300.190162, found 300.190326. Anal. Calcd for $C_{15}H_{28}BCl_2NO_2$: C, 53.60; H, 8.41; N, 4.18; B, 3.23; Cl, 21.10. Found: C, 53.64; H, 8.09; N, 4.07; B, 3.13; Cl, 21.38.

*4-Chlorobutane-1-amine hydrochloride (**7a**)*

^{1}H NMR δ: 8.22 (br s, 3H), 3.61 (t, *J*=6 Hz, 2H), 3.10 (t, *J*=7 Hz, 2H), 1.87–2.04 (m, 4H); HRMS (NH_3–CI/DEP) calculated for $C_4H_{11}BClN$ $(M+H-HCl)^+$: 108.058002, found: 108.058093.

*5-Chloropentane-1-amine hydrochloride (**7b**)*

White solid, mp 153–4°C; ^{1}H NMR δ: 8.28 (br s, 3H), 3.56 (t, *J*=6 Hz, 2H), 3.03 (t, *J*=7 Hz, 2H), 1.77–1.89 (m, 4H), 1.52–1.64 (m, 2H); HRMS (NH_3–CI/DEP) calculated for $C_5H_{13}BClN$ $(M+H-HCl)^+$: 122.073652, found: 122.073283.

Acknowledgements

We thank the Physical Sciences group for mass spectroscopy, NMR and HPLC support. We also would like to thank Thomas Maduskuie for the preparation of pinacol 1,4-dichorobutane-1-boronate.

References

1. Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc.* **1980**, *102*, 7588
2. (a) Matteson, D. S.; Ray, R. *J. Am. Chem. Soc.* **1980**, *102*, 7590. (b) Matteson, D. S.; Sadhu, K. M. *Organometallics* **1984**, *3*, 614. (c) Matteson, D. S.; Sadhu, K.M. *J. Am. Chem. Soc.* **1983**, *105*, 2077. (d) Matteson, D. S.; Jesthi, P. K.; Sadhu, K. M. *Organometallics* **1984**, *3*, 1284.
3. Matteson, D. S. *Chem Rev.* **1989**, *89*, 1535.
4. Kettner, C. A.; Mersinger, L.; Knabb, R. *J. Biol. Chem.* **1990**, *265*, 18289.
5. Kelly, T. A.; Fuchs, V. U.; Perry, C. W.; Snow, R. J. *Tetrahedron* **1993**, *49*, 1009.
6. Wityak, J.; Earl, R. A.; Abelman, M. A.; Bethel, Y. B.; Fisher, B. N.; Kauffman, G. S.; Kettner, C. A.; Ma, P.; McMillan, J. L.; Mersinger, L. J.; Pesti, J.; Pierce, M. E.; Rankin, F. W.; Chorvat, R. J.; Confalone, P. N. *J. Org. Chem.* **1995**, *60*, 3717.
7. Kettner, C. A.; Shenvi, A. B. *J. Biol Chem.* **1984**, *259*, 15106. Shenvi, A. B. *Biochemistry* **1986**, *25*, 1286. Snow, R.J.; Bachovchin, W. W.; Barton, R. W.; Campbell, S. J.; Coutts, S. J.; Freeman, D. M.; Guthell, W. G.; Kelly, T. A.; Kennedy, C. A.; Krolokowski, D. A.; Leonard, S. F.; Pargellis, C. A.; Tong, L.; Adams, J *J. Am. Chem. Soc.* **1994**, *116*, 10860.
8. ^{1}H NMR of the reaction, when conducted in $CDCl_3$, indicated complete disappearance of the starting material, appearance of product and by-product (pinacol) within 5 minutes of mixing.
9. Yield based on one enantiomer of the racemate reacting to give the isolated product.
10. Crystal data: $Cl_2O_2NC_{14}BH_{26}$, from ethyl acetate/ethanol cooling, colorless, thin needle, ~0.08×0.08×0.44 mm, monoclinic, $P2_1$ (No. 4), a=11.212(1), b=5.921(1), c=14.009(2) Å, β=113.396(5)°, T=−55°C. V=853.5 A^3, Z=2, FW=322.08, Dc=1.253 g/cc, μ(Mo)=3.80 cm^{-1}, 1087 unique reflections with I≥3.0σ(I), MoKa radiation, 4.0°≤2Θ≤48.3°, refinement by full-matrix least squares on F, refined anisotropic: all non-hydrogens atoms, fixed atoms: H 180 parameters, data/parameter ratio=5.99, R=0.052, Rw=0.049, error of fit=1.58, max Δ/σ=0.00 [two atoms in the butyl chain show some disorder, but were modeled successfully with high thermal parameters], largest residual density=0.26 e/A^3 (near C17). Details of the crystal structure for this structure, as well as **6a** and **6b**, are available on request from the director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, UK.

(Received in USA 3 February 1997)