# 4-Dihydroxyborylphenyl Analogues of 1-Aminocyclobutanecarboxylic Acids: Potential Boron Neutron Capture Therapy Agents

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A series of 4-dihydroxyborylphenyl analogues of an unnatural α-amino acid, 1-aminocyclobutanecarboxylic acid (ACBC), was synthesized. Varying numbers of methylene units were introduced between the 4-boronophenyl and ACBC moieties in order to introduce different degrees of lipophilicity into the molecules. The key step in the syntheses was the preparation of the precursor *p*-boronophenyl-substituted cyclobutanones which were subsequently converted to the desired amino acids via the Bucherer−Strecker reaction.

## Introduction

Boron neutron capture therapy (BNCT) was first proposed as a potential cancer therapy in 1936,[1] but the successful application of BNCT to the treatment of cancer still presents a challenge in modern medical research. Early attempts to cure cancer using BNCT were unsuccessful[2−5] due to vascular damage caused by the nonselective uptake of the boronated agents. Encouraging results obtained in Japan[6] using sodium mercaptoundecahydrodecaborate ($Na_2B_{12}H_{11}SH$, BSH) and 4-dihydroxyborylphenylalanine (BPA, **1**) have led to a resurgence of interest in BNCT. Current clinical trials suggest that BNCT can play an important role in cancer therapy (especially in the treatment of glioblastoma multiforma, which does not respond well to conventional chemotherapy and radiation therapy.)[7,8]

Boron neutron capture therapy (BNCT) is a binary therapy which is dependent on the selective deposition of boron-10 in the tumor prior to irradiation by slow (thermal) neutrons.[9] The interaction of a boron-10 atom with a thermal neutron produces an α-particle and a high energy lithium-7 ion. The linear energy transfer (LET) of these heavy charged particles has a range of approximately one cell diameter and thus they are lethal to the cells in which they are generated. To minimize damage to normal tissues, the quantity of boron in the tumor (∼30 μg of $^{10}$B/g of tumor) must exceed that in the surrounding normal tissues.[9−11] A variety of carrier molecules have been used to deliver boron to tumor cells. These include carbohydrates,[12−14] polyamines,[15] amino acids,[16,17] nucleosides,[18−21] antisence agents,[22] porphyrins,[23,24] antibodies,[25] and liposomes.[26]

Boron-containing amino acid derivatives[16,17] have been examined as potential agents for BNCT. It is believed that amino acids are preferentially taken up by growing tumor cells. In fact, the only drug (BPA) currently in clinical trials in the United States is an amino acid.[27] Carboranyl analogues of phenylalanine[16,17] have also been synthesized and are currently being evaluated as potential BNCT agents.

Large cellular concentrations of boron are required for successful BNCT, which makes it imperative that the carrier molecules be nontoxic. For these reasons, we have focused our efforts on a cyclic α-amino acid, 1-aminocyclobutanecarboxylic acid (ACBC), as a boron carrier.

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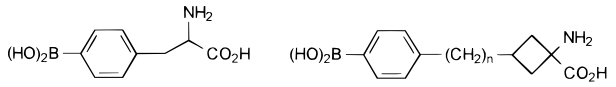
This unnatural amino acid is known to be preferentially retained in intracerebral tumors. In fact, carbon-11-labeled ACBC is used for imaging brain tumors at the University of Tennessee Medical Center.[28,29]

We recently reported the syntheses of a *m*-carborane-containing ACBC derivative and a more lipophilic analogue.[30,31] We now wish to report the syntheses of a new series of boron-containing ACBC molecules, **2**−**5**. These novel boronated unnatural amino acids contain a 4-boronophenyl moiety as the boron source. The syntheses of these molecules were undertaken because of the tumor selectivity of ACBC[29] and their structural similarity to BPA, **1**, a boron-containing amino acid currently in phase II clinical trials in the United States.[27] We introduced varying numbers of methylenes between the boronophenyl and ACBC moieties, **2**−**5**, to create different degrees of lipophilicity in the molecules. It is known that lipophilicity plays an important role in the transport of biologically active molecules.

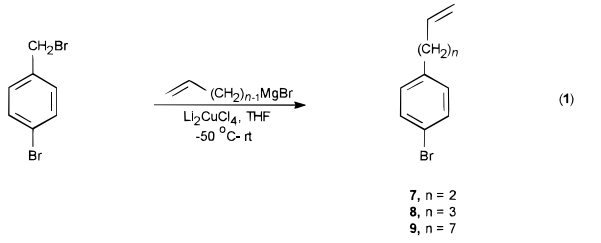


**1**

**2**, n = 0
**3**, n = 2
**4**, n = 3
**5**, n = 7

## Results and Discussion

The key synthetic step in the formation of the desired amino acids involves the preparation of appropriately substituted cyclobutanones followed by a Bucherer−Strecker amino acid synthesis.[32] The syntheses of the boron-containing amino acids were initiated starting with alkenes **6**−**9** (Scheme **1**). While alkene **6** is commercially available, alkenes **7**−**9** were prepared by an $S_N2$ displacement reaction using 4-bromobenzyl bromide and the appropriate Grignard reagent (eq 1). For the syntheses

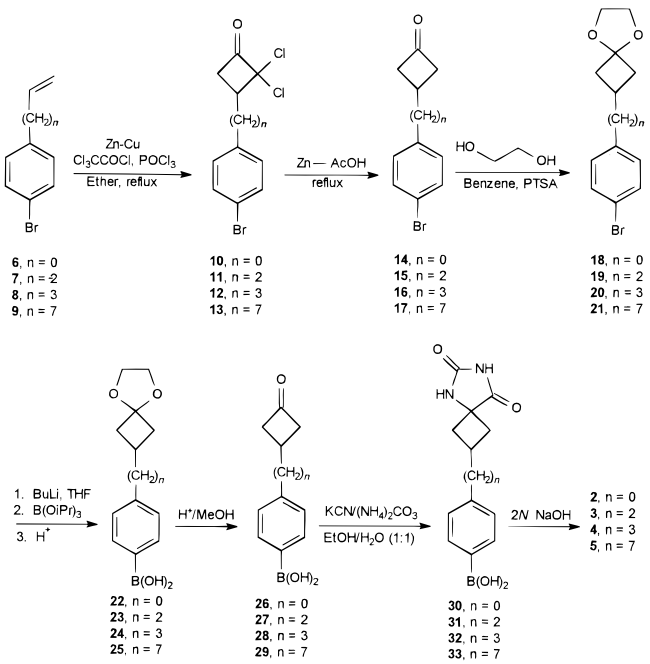


**7**, n = 2
**8**, n = 3
**9**, n = 7

(1)

of alkene **8** and **9**, a catalytic amount of lithium tetrachlorocuprate(II) was required (eq 1).[33] Cyclobutanones were obtained (Scheme 1) via a 2 + 2 cycloaddition of the precursor alkenes with dichloroketene, which was generated in situ from the reaction of trichloroacetyl chloride and phosphorus oxychloride in the presence of a Zn−Cu couple.[34] The crude products (dichlorocyclobutanones **10**−**13**) obtained from the ketene additions were subjected to a reductive dechlorination with zinc and acetic acid. The resultant *p*-bromophenyl-substituted cyclobutanones **14**−**17** were then protected as ethylene ketals **18**−**21** by reaction with ethylene glycol.[35] The ethylene ketals were then sequentially reacted with butyllithium and triisopropylborate.[36] The reaction mixtures were quenched by dilute sulfuric acid to obtain ethylene ketal boronic acids **22**−**25**. The ketal group was removed by the action of dilute hydrochloric acid in methanol to regenerate the desired ketones **26**−**29**, which were reacted with ammonium carbonate and potassium cyanide in a pressure tube. Hydantoins **30**−**33** were formed in excellent yields. In the final step of the syntheses, the hydantoins were heated in the presence of sodium hydroxide to generate the desired amino acids **2**−**5** in good yields.

**Scheme 1**



**6**, n = 0
**7**, n = 2
**8**, n = 3
**9**, n = 7

**10**, n = 0
**11**, n = 2
**12**, n = 3
**13**, n = 7

**14**, n = 0
**15**, n = 2
**16**, n = 3
**17**, n = 7

**18**, n = 0
**19**, n = 2
**20**, n = 3
**21**, n = 7

**22**, n = 0
**23**, n = 2
**24**, n = 3
**25**, n = 7

**26**, n = 0
**27**, n = 2
**28**, n = 3
**29**, n = 7

**30**, n = 0
**31**, n = 2
**32**, n = 3
**33**, n = 7

**2**, n = 0
**3**, n = 2
**4**, n = 3
**5**, n = 7

As anticipated, the introduction of varying numbers of methylene groups between the cyclobutane and the aromatic rings influenced the lipophilicities of the resultant boronated amino acids, as reflected in their $R_f$ values. The most lipophilic product, **5**, exhibited an $R_f$ value of 0.61 using acetonitrile:methanol:water as the mobile phase. Whereas, **2** was found to be the least lipophilic with an $R_f$ value of 0.32 in the same mobile phase. Amino acids **3** and **4**, in which the number of methylene units fell between 0 and 7, exhibited intermediate $R_f$ values.

## Conclusion

We report the syntheses of novel boronic acid-containing analogues of a tumor-seeking unnatural cyclic α-amino acid, 1-aminocyclobutanecarboxylic acid. Boronic acid-containing analogues of ACBCs with varying degree of lipophilicities were synthesized, and the agents are being evaluated as potential BNCT agents.

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## Experimental Section

**General Methods.** All solvents were reagent grade and were distilled from appropriate drying agents under a nitrogen atmosphere prior to use. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl; benzene was distilled from calcium hydride and stored under nitrogen. All other chemicals were (Aldrich Chemical Co., Milwaukee, WI) used as received.

Column chromatography was performed using silica gel (60 Å, 230−400 mesh, ICN Biomedicals GmbH, Eschwege, Germany.). Reverse-phase column chromatography was performed by utilizing octadecyl-functionalized silica gel (Aldrich Chemical Co., Milwaukee, WI). Analytical thin-layer chromatography was performed on 250 $\mu$m silica (Analtech Inc., Newark, DE) and were visualized by phosphomolybdic acid, palladium chloride, and silver nitrate solutions.

Melting points are uncorrected. Infrared spectra were obtained either neat or as Nujol mulls. $^1$H NMR and $^{13}$C NMR spectra were recorded at 250.13 and 62.89 Mz, respectively. In cases where more than one isomer formed, we have reported the $^{13}$C NMR of the major isomer. Chemical shifts for $^1$H and $^{13}$C NMR spectra were referenced to $Si(CH_3)_4$ and measured with respect to the residual protons in the deuterated solvents. Microanalysis were performed by Galbraith Laboratories Inc., Knoxville, TN. HR-FAB-MS (M + 1) were obtained on a ZAB-EQ instrument in a glycerol matrix. Positive ion electrospray mass spectra (ES+) were obtained in instances where satisfactory elemental analyses were obtained for carbon and hydrogen but where boron values exceeded acceptable limits (not uncommon for boron-containing molecules).[37]

**4-(4-Bromophenyl)-1-butene (7).** A 500 mL three-necked round-bottomed flask equipped with an addition funnel, reflux condenser, and an argon-filled balloon was charged with 4-bromobenzyl bromide (80 mmol, 20 g) in 50 mL of anhydrous ether. Allylmagnesium bromide (96 mmol, 96 mL of a 1 M solution in ether) was then added via the addition funnel over a period of 30 min, and the reaction mixture was allowed to stir at room temperature for 2 h. The mixture was then refluxed in an oil bath for 3 h. The progress of the reaction was monitored by TLC. After the starting material (aryl bromide) disappeared, the flask was cooled to room temperature and the reaction quenched with water and then transferred to a separatory funnel. The organic layer was washed with water and then brine, dried over anhydrous magnesium sulfate, and concentrated using a rotatory evaporator. After drying under vacuum (50 °C at 1 mmHg), a colorless liquid (16 g) was obtained. The crude product was purified by Kugelrhor distillation to yield **7** as a colorless liquid (14 g, 83% yield): $R_f$ = 0.86 (hexane, thin-layer chromatography); $^1$H NMR ($CDCl_3$) $\delta$ 7.37 (d, $J$ = 8.2 Hz, 2H), 7.06 (d, $J$ = 8.2 Hz, 2H), 5.61 (m, 1H), 5.06 (m, 2H), 2.67 (t, $J$ = 8.2 Hz, 2H), 2.35 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 140.68, 137.52, 131.28, 130.16, 119.49, 115.24, 35.21, 34.69; IR (neat) 1639. Anal. Calcd for $C_{10}H_{11}Br$: C, 56.87; H, 5.21. Found: C, 57.07; H, 5.65.

**5-(4-Bromophenyl)-1-pentene (8).** A 250 mL three-necked round-bottomed flask, equipped with an addition funnel and an argon-filled balloon was charged with 4-bromobenzyl bromide (44 mmol, 11 g) in 25 mL of anhydrous THF. 3-Butenylmagnesium bromide (37 mmol, 74 mL of 0.5 M solution in THF) was then added via the addition funnel over a period of 20 min while the reaction was maintained at −70 °C using a dry ice−acetone bath. Following addition of the Grignard reagent, a solution of dilithium tetrachlorocuprate(II) (0.18 mmol, 1.9 mL of a 0.1 M solution in THF) was added while the reaction was maintained at −50 °C. The resultant solution was stirred overnight while the reaction was allowed to reach room temperature. The reaction was quenched with saturated aqueous ammonium chloride and the solvent removed under reduced pressure. The residue was then taken into ether and washed sequentially with water and brine, dried over anhydrous magnesium sulfate, concentrated using a rotatory evaporator, and then dried under vacuum (50 °C at 1 mmHg) to obtain a colorless liquid (3.6 g). The crude reaction mixture was purified using chromatography (silica gel, hexane) to obtain **8** as a colorless liquid (2.8 g, 33% based on 4-bromobut-1-ene): $R_f$ = 0.87 (hexane, thin-layer chromatography); $^1$H NMR ($CDCl_3$) $\delta$ 7.36 (d, $J$ = 8.2 Hz, 2H), 7.02 (d, $J$ = 8.2 Hz, 2H), 5.78 (m, 1H), 5.01 (m, 2H), 2.54 (t, $J$ = 7.75 Hz, 2H), 2.05 (m, 2H), 1.66 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 141.26, 138.23, 131.25, 130.16, 119.36, 114.89, 34.60, 33.08, 30.35.

**9-(4-Bromophenyl)-1-nonene (9).** This alkene was prepared using the procedure described to prepare **8**. 4-Bromobenzyl bromide (28.8 mmol, 7.19 g) in THF (20 mL) was added to 7-octenylmagnesium bromide (26 mmol, 52 mL of a 0.5 M solution in THF) in the presence of dilithium tetrachlocuprate (0.29 mL, 2.9 mL of 0.1 M solution in THF) to obtain compound **9** as a colorless liquid (3.1 g, 42% based on 8-bromocten-1-ene): $R_f$ = 0.85 (hexane, thin-layer chromatography); $^1$H NMR ($CDCl_3$) $\delta$ 7.36 (d, $J$ = 8.2 Hz, 2H), 7.02 (d, $J$ = 8.2 Hz, 2H), 5.78 (m, 1H), 4.96 (m, 2H), 2.53 (t, $J$ = 7.5 Hz, 2H), 2.01 (m, 2H), 1.56 (m, 2H), 1.29 (m, 8H); $^{13}$C NMR ($CDCl_3$) $\delta$ 141.71, 139.04, 131.19, 130.09, 119.21, 114.14, 35.29, 33.73, 31.24, 29.26, 29.08, 28.99, 28.85; IR (neat) 1641; HRMS calcd for $C_{15}H_{21}Br$ 280.083, found 280.085. Anal. Calcd for $C_{15}H_{21}Br$: C, 64.06; H, 7.53. Found: C, 64.13; H, 7.73.

**3-(4-Bromophenyl)cyclobutanone (14).** A 500 mL three-necked, round-bottomed flask equipped with an addition funnel, reflux condenser, and argon-filled balloon was charged with 4-bromostyrene (**6**) (137 mmol, 25.0 g) and diethyl ether (200 mL) along with a freshly prepared Zn−Cu couple (273 mmol, 17.9 g). A solution of trichloroacetyl chloride (205 mmol, 22.9 mL) and phosphorus oxychloride (205 mmol, 19.1. mL) in ether (100 mL) was placed in the addition funnel and added dropwise over a period of 60 min. After the addition, the reaction mixture was stirred at room temperature for 1 h and then refluxed for 3 h under an argon atmosphere. The reaction mixture was then cooled to room temperature and filtered through a pad of Celite. Additional ether was used to wash the Celite. The combined organic extract was neutralized with saturated sodium bicarbonate, washed with water and then brine, dried over anhydrous magnesium sulfate, and concentrated on a rotatory evaporator to obtain **10** as a light yellow liquid.

Crude **10** was dissolved in glacial acetic acid (50 mL) along with zinc dust (20 g, excess). The reaction mixture was stirred at room temperature for 30 min and then heated at 120 °C (oil bath) for 2 h. TLC indicated disappearance of the starting material. The mixture was cooled to room temperature and passed through a pad of Celite. Additional ethyl acetate was used to wash the Celite pad and to transfer the material from the flask. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate, washed with water and then brine, dried over anhydrous magnesium sulfate, and concentrated to obtain a light yellow thick liquid (28 g). The crude product was purified by Kugelrhor distillation to obtain 3-(4-bromophenyl)cyclobutanone (**14**) as a colorless liquid (24 g, 78% yield based on alkene **6**): $R_f$ = 0.19 (5% ethyl acetate in hexane, thin-layer chromatography); $^1$H ($CDCl_3$) $\delta$ 7.43 (d, $J$ = 8.4 Hz, 2H), 7.16 (d, $J$ = 8.4 Hz, 2H), 3.62 (m, 1H), 3.44 (m, 2H), 3.17 (m, 2H); $^{13}$C ($CDCl_3$) $\delta$ 205.52, 142.32, 131.49, 128.07, 119.97, 54.29, 27.69; IR (neat) 1747; HRMS calcd for $C_{10}H_9BrO$ 223.984, found 223.982.

**3-[2-(4-Bromophenyl)ethyl]cyclobutanone (15).** The synthesis of **15** was carried out as described for **14**. A solution of trichloroacetyl chloride (71 mmol, 7.9 mL) and phosphorus oxychloride (71 mmol, 6.6 mL) in ether (20 mL) was allowed to react with with **7** (47 mmol, 10 g) in ether (100 mL) in the presence of Zn−Cu couple (118 mmol, 7.7 g) to obtain 2,2-dichloro-3-[2-(4-bromophenyl)ethyl]cyclobutanone (**11**). The dichloro ketone **11** was subjected to a reductive dechlorination with zinc (7.7 g, excess) and acetic acid (30 mL) to yield a light yellow liquid (14 g). The crude product was purified by column chromatography using silica gel (30 × 4 cm, 10% ethyl acetate in hexane) to yield **15** as a colorless liquid (10 g, 84% yield based on olefin **7**): $R_f$ = 0.26 (10% ethyl acetate in hexane, thin-layer chromatography); $^1$H NMR ($CDCl_3$) $\delta$ 7.33 (d, $J$ = 8.0 Hz, 2H), 6.98 (d, $J$ = 8.0 Hz, 2H), 3.06 (m, 2H), 2.58 (m,

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4H), 2.28 (m, 1H), 1.79 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 207.59, 140.29, 131.38, 130.02, 119.62, 52.32, 37.64, 33.90, 23.25; IR (neat) 1785. Anal. Calcd for $C_{12}H_{13}BrO$: C, 56.92; H, 5.14. Found: C, 56.92; H, 5.29.

**3-[3-(4-Bromophenyl)propyl]cyclobutanone (16).** The synthesis of **16** was carried out as described for **14**. A solution of trichloroacetyl chloride (18.8 mmol, 2.08 mL) and phosphorus oxychloride (18.8 mmol, 1.70 mL) in ether (15 mL) was allowed to react with **8** (12.5 mmol, 2.82 g) in 25 mL of ether in the presence of Zn−Cu couple (25 mmol, 2.16 g) to obtain dichlorocyclobutanone **12**. The dichloroketone **12** was subjected to dechlorination in the presence of Zn (2.16 g, excess) and acetic acid (20 mL) to obtain a light yellow thick liquid that was purified by Kugelrhor distillation to obtain **16** as a colorless liquid (2.89 g, 86.5% yield based on olefin **8**): $R_f$ = 0.35 (5% ethyl acetate in hexane thin-layer chromatography); $^1$H NMR ($CDCl_3$) $\delta$ 7.39 (d, $J$ = 7.75 Hz, 2H), 7.04 (d, $J$ = 7.75 Hz, 2H), 3.11 (m, 2H), 2.64 (m, 4H), 2.35 (m, 1H), 1.61 (br s, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 208.04, 140.93, 131.29, 130.01, 119.45, 52.39, 35.62, 34.95, 29.76, 23.66; IR (neat) 1788. Anal. Calcd for $C_{13}H_{15}BrO$: C, 58.44; H, 5.66. Found: C, 58.65; H, 5.88.

**3-[7-(4-Bromophenyl)heptyl]cyclobutanone (17).** The synthesis of **17** was carried out as described for **14**. A solution of trichloroacetyl chloride (16.4 mmol, 1.82 mL) and phosphorus oxychloride (16.4 mmol, 1.52 mL) in ether (10 mL) was allowed to react with alkene **9** (10.9 mmol, 3.09 g) in ether (25 mL) in the presence of Zn−Cu couple (21.8 mmol, 1.43 g). The dichloro ketone **13** (4.98 g, crude) thus obtained was reacted with Zn (1.50 g) in acetic acid (20 mL) to obtain a thick liquid that was purified via silica gel chromatography using 10% ethyl acetate in hexane to obtain **17** as a colorless liquid (2.59 g, 73% yield based on starting alkene): $R_f$ = 0.73 (10% ethyl acetate in hexane thin-layer chromatography); $^1$H NMR ($CDCl_3$) $\delta$ 7.36 (d, $J$ = 8.2 Hz, 2H), 7.03 (d, $J$ = 8.2 Hz, 2H), 3.11 (m, 2H), 2.59 (m, 4H), 2.31 (m, 1H), 1.56 (br s, 4H), 1.29 (br s, 8H); $^{13}$C NMR ($CDCl_3$) $\delta$ 208.31, 141.54, 131.07, 130.01, 119.09, 52.34, 36.14, 35.14, 31.09, 29.18, 28.92, 28.07, 23.66; IR (neat) 1784. Anal. Calcd for $C_{17}H_{23}BrO$: C, 63.16; H, 7.17. Found: C, 63.26; H, 7.22.

**3-(4-Bromophenyl)cyclobutanone Ethylene Ketal (18).** A 500 mL three-necked round-bottomed flask equipped with a Dean−Stark apparatus and a reflux condenser was charged with ketone **14** (78.2 mmol, 17.6 g), ethylene glycol (391 mmol, 21.8 mL), and *p*-toluenesulfonic acid (3.91 mmol, 0.743 g) in benzene (250 mL). The reaction mixture was refluxed at 120 °C (oil bath) for 20 h and the reaction was monitored by thin-layer chromatography. After 20 h, the flask was cooled to room temperature and NaOH (2 mL of 3 N aqueous solution) was added to make the reaction mixture basic. The mixture was transferred to a separatory funnel, washed with water and then brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to yield a colorless oil. The product was purified by Kugelrhor distillation to obtain **18** as a colorless liquid (19.3 g, 82.5% yield): $R_f$ = 0.29 (5% ethyl acetate in hexane, thin-layer chromatography); $^1$H NMR ($CDCl_3$) $\delta$ 7.38 (d, $J$ = 8.3 Hz, 2H), 7.11 (d, $J$ = 8.3 Hz, 2H), 3.89 (m, 4H), 3.24 (m, 1H), 2.71 (m, 2H), 2.41 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 143.73, 131.29, 128.37, 119.69, 105.74, 64.23, 63.69, 43.10, 29.44; IR (Nujol) 1297. Anal. Calcd for $C_{12}H_{13}BrO_2$: C, 53.53; H, 4.83; Br, 29.74. Found: C, 53.39; H, 4.99; Br, 29.84.

**3-[2-(4-Bromophenyl)ethyl]cyclobutanone Ethylene Ketal (19).** The synthesis was carried out as described for **18**. A solution of **15** (33 mmol, 8.3 g) and ethylene glycol (330 mmol, 18.4 mL) in benzene (180 mL) was refluxed in the presence of *p*-toluenesulfonic acid (3.3 mmol, 0.6 g). The compound was purified by Kugelrohr distillation to obtain **19** as a colorless thick oil that solidified upon standing at room temperature (8.9 g, 91% yield): $R_f$ = 0.26 (10% ethyl acetate in hexane, thin-layer chromatography); $^1$H NMR ($CDCl_3$) $\delta$ 7.30 (d, $J$ = 8.2 Hz, 2H), 6.95 (d, $J$ = 8.2 Hz, 2H), 3.77 (s, 4H), 2.43 (t, $J$ = 7.4 Hz, 2H), 2.33 (m, 1H), 1.90 (m, 4H), 1.69 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 140.99, 131.19, 130.04, 119.30, 106.48, 63.89, 63.45, 40.92, 37.88, 33.42, 24.46; IR (neat) 1293. Anal. Calcd for $C_{14}H_{17}BrO_2$: C, 56.57; H, 5.72. Found: C, 56.81; H, 5.90.

**3-[3-(4-Bromophenyl)propyl]cyclobutanone Ethylene Ketal (20).** The synthesis was carried out as described for **18**. A solution of **16** (10.5 mmol, 2.80 g) and ethylene glycol (105 mmol, 5.85 mL) in benzene (50 mL) was refluxed in the presence of *p*-toluenesulfonic acid (1.05 mmol, 0.199 g). The product was purified by Kugelrhor distillation to obtain **20** as a colorless liquid (2.96 g, 91% yield). $R_f$ = 0.44 (5% ethyl acetate in hexane, thin-layer chromatography); $^1$H NMR ($CDCl_3$) $\delta$ 7.34 (d, $J$ = 8.2 Hz, 2H), 6.99 (d, $J$ = 8.2 Hz, 2H), 3.83 (s, 4H), 2.53 (t, $J$ = 6.9 Hz, 2H), 2.36 (m, 2H), 1.98 (m, 1H), 1.87 (m, 2H), 1.45 (br s, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 141.47, 131.28, 130.11, 119.34, 106.66, 63.96, 63.51, 41.05, 35.91, 35.14, 29.37, 24.91; IR (neat) 1292. Anal. Calcd for $C_{15}H_{19}BO_2$: C, 57.89; H, 6.15. Found: C, 58.02; H, 6.48.

**3-[7-(4-Bromophenyl)heptyl]cyclobutanone Ethylene Ketal (21).** The synthesis was carried out as described for **18**. A solution of **17** (7.23 mmol, 2.34 g) and ethylene glycol (72.3 mmol, 4.00 mL) in benzene (40 mL) was refluxed in the presence of *p*-toluenesulfonic acid (0.723 mmol, 0.137 g). The crude material was purified using a silica gel column to obtain **21** as a thick liquid (2.42 g, 90.9% yield). $R_f$ = 0.67 (10% ethyl acetate in hexane, thin-layer chromatography); $^1$H NMR ($CDCl_3$) $\delta$ 7.36 (d, $J$ = 8.2 Hz, 2H), 7.02 (d, $J$ = 8.2 Hz, 2H), 3.86 (s, 4H), 2.53 (t, $J$ = 7.4 Hz, 2H), 2.39 (m, 2H), 1.94 (m, 3H), 1.56 (m, 2H), 1.42 (br s, 2H), 1.28 (m, 8H); $^{13}$C NMR ($CDCl_3$) $\delta$ 141.65, 131.13, 130.04, 119.13, 106.66, 63.84, 63.37, 40.98, 36.37, 35.22, 31.18, 29.30, 29.03, 27.57, 24.97; IR (neat) 1294. Anal. Calcd for $C_{19}H_{27}BrO_2$: C, 61.96; H, 7.66. Found: C, 62.23; H, 7.44.

**3-(4-Boronophenyl)cyclobutanone Ethylene Ketal (22).** A 250 mL three-necked round-bottomed flask equipped with an argon-filled balloon was charged with **18** (15.0 mmol, 4.00 g) in anhydrous tetrahydrofuran (80 mL). The flask was cooled to −78 °C using a dry ice−acetone bath. Butyllithium (17.8 mmol, 11.2 mL of a 1.60 M solution in hexane) was added dropwise via a syringe. The resultant yellow solution was stirred at −70 °C for 30 min and then triisopropyl borate (17.8 mmol, 4.12 mL) was added dropwise via syringe. The reaction mixture was allowed to stir overnight (during this time the bath temperature was allowed to rise to room temperature). The flask was then cooled to 0 °C and the reaction quenched with $H_2SO_4$ (6 mL of 2 N aqueous sulfuric acid). The mixture was stirred for an additional 30 min at the 0 °C and then transferred to a separatory funnel. The product was extracted into ether and the organic layer was washed sequentially with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to obtain a faint yellow solid (4.02 g). The product was purified by column chromatography using silica gel (22 × 1.5 cm, 30% ethyl acetate in hexane) to obtain **22** as a white solid (2.89 g, 83% yield): $R_f$ = 0.46 (50% ethyl acetate in hexane, thin-layer chromatography); mp 158−160 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.17 (d, $J$ = 7.8 Hz, 2H), 7.40 (d, $J$ = 7.8 Hz, 2H), 3.96 (m, 4H), 3.41 (m, 1H), 2.78 (m, 2H), 2.59 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 149.63, 135.83, 126.34, 106.01, 64.35, 63.78, 43.12, 30.34; IR (Nujol) 3370. Anal. Calcd for $C_{12}H_{15}BO_4$: C, 61.58; H, 6.46; B, 4.62. Found C, 63.40; H, 6.56; B, 4.62.

**3-[2-(4-Boronophenyl)ethyl]cyclobutanone Ethylene Ketal (23).** The synthesis of **23** was carried out as described for **22**. A solution of **19** (6.7 mmol, 2.0 g) in anhydrous tetrahydrofuran (40 mL) was treated with butyllithium (8.0 mmol, 5.0 mL of a 1.6 M solution in hexane) followed by triisopropyl borate (8.0 mmol, 1.9 mL) to obtain a colorless thick liquid (1.9 g). The product was purified by column chromatography using silica gel (25 × 2 cm, 30% ethyl acetate in hexane) to obtain **23** as a white solid (1.5 g, 87% yield): $R_f$ = 0.56 (50% ethyl acetate in hexane, thin-layer chromatography); mp 78−80 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.06 (d, $J$ = 7.5 Hz, 2H), 7.23 (d, $J$ = 7.5 Hz, 2H), 3.81 (s, 4H), 2.53 (m, 2H), 2.36 (m, 1H), 1.95 (m, 4H), 1.74 (m, 2H); $^{13}$C ($CDCl_3$) $\delta$ 147.14, 135.74, 128.12, 106.66, 63.96, 63.50, 40.99, 37.96, 34.47, 24.71; IR (Nujol) 3370. Anal. Calcd for $C_{10}H_{11}B$: C, 64.15; H, 7.31; B, 4.12. Found: C, 63.47; H, 7.08; B, 4.26.

**3-[3-(4-Boronophenyl)propyl]cyclobutanone Ethylene Ketal (24).** The synthesis of **24** was carried out as described

for **22**. A solution of **20** (8.39 mmol, 2.60 g) in anhydrous tetrahydrofuran (50 mL) was treated with butyllithium (10.1 mmol, 6.30 mL of a 1.6 M solution in hexane) followed by triisopropyl borate (10.1 mmol, 2.32 mL) to obtain a white solid (2.64 g). The product was purified by column chromatography using silica gel to obtain **24** as a white solid (1.76 g, 76% yield): $R_f$ = 0.51 (50% ethyl acetate in hexane, thin-layer chromatography); mp 128−130 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 7.99 (s, 2 H, disappears upon addition of $D_2O$), 7.74 (d, $J$ = 7.8 Hz, 2H), 7.2 (d, $J$ = 7.8 Hz, 2H), 3.31 (s, 4H), 2.03 (m, 2H), 1.86 (m, 1H), 1.45 (m, 4H), 1.24 (m, 2H); $^{13}$C (DMSO-$d_6$) $\delta$ 144.22, 134.21, 127.41, 105.88, 63.37, 62.91, 40.71, 35.56, 35.10, 29.01, 24.46; IR (Nujol) 3239; HR-FAB-MS (M + H; glycerol matrix) calcd for $C_{18}H_{26}O_4B$: 333.188, found: 333.189. Anal. Calcd for $C_{15}H_{21}BO_4$: C, 66.24; H, 7.67. Found: C, 69.45; H, 7.60.

**3-[7-(4-Boronophenyl)heptyl]cyclobutanone Ethylene Ketal (25).** The synthesis of **25** was carried out as described for **22**. A solution of **21** (5.94 mmol, 2.19 g) in anhydrous tetrahydrofuran (50 mL) was treated with butyllithium (7.12 mmol, 4.46 mL of a 1.60 M solution in hexane) followed by triisopropyl borate (7.12 mmol, 1.64 mL) to obtain a solid that was purified by column chromatography using silica gel to obtain **25** as a white solid (1.58 g, 80% yield): $R_f$ = 0.61 (50% ethyl acetate in hexane, thin-layer chromatography); mp 76−80 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 7.92 (s, 2 H, disappears by the addition of $D_2O$), 7.68 (d, $J$ = 7.7 Hz, 2H), 7.12 (d, $J$ = 7.7 Hz, 2H), 3.75 (s, 4H), 2.53 (t, $J$ = 7.3 Hz, 2H), 2.28 (m, 2H), 1.81 (m, 3H), 1.53 (m, 2H), 1.34 (m, 2H), 1.23 (m, 8H); $^{13}$C (DMSO-$d_6$) $\delta$ 144.33, 134.21, 127.39, 105.91, 63.37, 62.89, 40.74, 35.95, 35.25, 30.86, 28.89, 28.65, 27.22, 24.61; IR (Nujol) 3382; HR-FAB-MS (M + H; glycerol matrix) calcd for $C_{22}H_{34}O_5B$ 389.250, found 389.253. Anal. Calcd for $C_{19}H_{29}BO_4$: C, 68.69; H, 8.8. Found: C, 69.00; H, 8.50.

**3-(4-Boronophenyl)cyclobutanone (26).** A 100 mL round-bottomed flask was charged with ketal **22** (12.8 mmol, 3.00 g) in methanol (30 mL) along with concentrated hydrochloric acid (0.5 mL). The contents of the flask were stirred overnight at room temperature. TLC indicated complete disappearance of the starting ketal. The solvent was removed under reduced pressure and the residue dissolved in ether and washed with water and then brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to yield a faint yellow viscous material (2.6 g). The product was purified using a silica gel chromatography (20 × 2 cm, 30% ethyl acetate in hexane) to obtain **26** as a white solid (1.92 g, 79% yield): $R_f$ = 0.46 (50% ethyl acetate in hexane, thin-layer chromatography); mp 94−98 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.63 (d, $J$ = 7.3 Hz, 2H), 7.20 (d, $J$ = 7.3 Hz, 2H), 3.56 (m, 1H), 3.30 (m, 2H), 3.08 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 208.81, 147.25, 135.29, 126.76, 55.19, 29.57; IR (Nujol) 3358, 1768. Anal. Calcd for $C_{10}H_{11}BO_3C$: 63.21; H, 5.84; B, 5.69. Found: C, 63.50; H, 6.05; B, 6.12.

**3-[2-(4-Boronophenyl)ethyl]cyclobutanone (27).** The synthesis was carried out as described for **26**. A solution of ketal **23** (6.90 mmol, 1.80 g) in methanol (30 mL) was stirred with concentrated hydrochloric acid (0.5 mL) to obtain a faint yellow viscous material (1.7 g) which was purified by silica gel chromatography to yield **27** as a white solid (1.2 g, 78% yield): $R_f$ = 0.56 (50% ethyl acetate in hexane, thin-layer chromatography); mp 93−95 °C; $^1$H ($CDCl_3$) $\delta$ 8.12 (d, $J$ = 7.8 Hz, 2H), 7.27 (d, $J$ = 7.8 Hz, 2H), 3.09 (m, 2H), 2.69 (m, 4H), 2.35 (m, 1H), 1.93 (m, 2H); $^{13}$C ($CDCl_3$) $\delta$ 208.07, 146.37, 135.86, 128.07, 52.43, 37.69, 34.91, 23.45; IR (Nujol) 3340, 1761. Anal. Calcd for $C_{12}H_{15}BO_3$: C, 66.10; H, 6.93; B, 4.96. Found: C, 65.95; H, 6.94; B, 5.12.

**3-[3-(4-Boronophenyl)propyl]cyclobutanone (28).** The synthesis was carried out as described for **26**. A solution of ketal **24** (3.62 mmol, 1.00 g) in methanol (30 mL) was stirred with concentrated hydrochloric acid (0.5 mL) to obtain a faint yellow viscous material (0.86 g) which was purified by silica gel chromatography to yield **28** as a white solid (0.69 g, 83% yield): $R_f$ = 0.52 (50% ethyl acetate in hexane, thin-layer chromatography); mp 105−110 °C; $^1$H (DMSO-$d_6$) $\delta$ 8.1 (s, 2 H, disappear by adding $D_2O$), 7.87 (d, $J$ = 7.8 Hz, 2H), 7.33 (d, $J$ = 7.8 Hz, 2H), 3.25 (m, 2H), 2.75 (m, 4H), 2.49 (m, 1H), 1.72 (m, 4H); $^{13}$C (DMSO-$d_6$) $\delta$ 208.19, 144.12, 134.23, 127.41, 51.99, 35.13, 35.01, 29.48, 23.15; IR (Nujol) 3364, 1765. Anal. Calcd for $C_{13}H_{17}BO_3$: C, 67.28; H, 7.38; B, 4.66. Found: C, 66.90; H, 7.90; B, 4.64.

**3-[7-(4-Boronophenyl)heptyl]cyclobutanone (29).** The synthesis was carried out as described for **26**. A solution of ketal **25** (5.80 mmol, 1.94 g) in methanol (30 mL) was stirred with concentrated hydrochloric acid (0.5 mL) to obtain a solid which upon purification (silica gel chromatography) yielded **29** as a white solid (1.26 g, 75% yield): $R_f$ = 0.57 (50% ethyl acetate in hexane, thin-layer chromatography); mp 70−76 °C; $^1$H ($CDCl_3$) $\delta$ 8.13 (d, $J$ = 7.4 Hz, 2H), 7.30 (d, $J$ = 7.4 Hz, 2H), 3.10 (m, 2H), 2.64 (m, 4H), 2.32 (m, 1H), 1.66 (br s, 2H), 1.55 (m, 2H), 1.33 (br s, 8H); $^{13}$C ($CDCl_3$) $\delta$ 208.71, 147.69, 135.63, 128.07, 52.44, 36.23, 31.16, 29.27, 29.15, 28.16, 23.78; IR (Nujol) 3304, 1765; FAB-MS (M + H; glycerol matrix) calcd for $C_{20}H_{30}O_4B$ 345.224, found 345.223. Anal. Calcd for $C_{17}H_{25}BO_3$: C, 70.85; H, 8.74; B, 3.75. Found: C, 72.50; H, 7.65; B, 4.03.

**Hydantoin 30 of 3-(4-Boronophenyl)cyclobutanone (26).** A 15 mL Ace pressure tube was charged with **26** (3.70 mmol, 0.700 g), aqueous ethanol (50% ethanol in water, 12.0 mL), potassium cyanide (7.4 mmol, 0.48 g), and ammonium carbonate (18.5 mmol, 1.78 g). The reaction vessel was sealed and heated at 60 °C (oil bath) for 4 h. A faint yellow precipitate formed. The reaction vial was cooled to room temperature and carefully opened in a fume hood. The reaction mixture was acidified using dilute aqueous hydrochloric acid. The solvent was removed under reduced pressure and the solid obtained was recrystallized from water (containing 5% ethanol) to yield **30** as a faint yellow solid (0.748 g, 77.8% yield): $R_f$ = 0.65 (10% methanol in methylene chloride, thin-layer chromatography); mp 248−250 °C (dec); $^1$H NMR (DMSO-$d_6$) $\delta$ 7.59 (d, $J$ = 7.5 Hz, 2H), 7.10 (d, $J$ = 7.5 Hz, 2H), 2.62 (m, 2H), 2.22 (m, 2H), benzylic protons (2H) are covered by $H_2O$ of DMSO. $^{13}$C NMR (DMSO-$d_6$) $\delta$ 178.87, 155.98, 146.24, 134.35, 125.65, 57.32, 30.79; IR (Nujol) 3313, 1728, 1718; FAB-MS (M + H; glycerol matrix) calcd for $C_{15}H_{17}O_5BN_2$ 317.1, found 317.1. Anal. Calcd for $C_{12}H_{13}BN_2O_4$ C, 55.42; H, 5.04; N, 10.77. Found C, 53.85; H, 5.06; N, 10.10.

**Hydantoin 31 of 3-[2-(4-Boronophenyl)ethyl]cyclobutanone (27).** The synthesis was carried out as described for **30**. A solution of **27** (1.1 mmol, 0.28 g) in aqueous ethanol (50%, 7.0 mL) was allowed to react with potassium cyanide (3.0 mmol, 0.19 g) and ammonium carbonate (5.0 mmol, 0.48 g) to obtain a faint yellow solid that was recrystallized by water (containing 5% ethanol) to yield **31** as a faint yellow solid (0.23 g, 62% yield): $R_f$ = 0.39 (5% methanol in methylene chloride, thin-layer chromatography); mp 224−226 °C (dec); $^1$H (DMSO-$d_6$) $\delta$ 7.68 (d, $J$ = 7.7 Hz, 2H), 7.12 (d, $J$ = 7.7 Hz, 2H), 2.45 (m, 4H), 2.19 (m, 1H), 1.86 (m, 2H), 1.65 (m, 2H); $^{13}$C (DMSO-$d_6$) $\delta$ 178.78, 155.89, 143.70, 134.18, 127.32, 57.76, 38.11, 32.74, 25.89; IR (Nujol) 3296, 1738, 1713; ES+ (M + H; obtained in MeOH−$H_2O$ solvent mixture containing 1% formic acid) calcd for $C_{16}H_{22}O_4N_2B$ 317.1, found: 317.0. Anal. Calcd for $C_{14}H_{17}BN_2O_4$: C, 58.36; H, 5.96; N, 9.72; B, 3.75. Found: C, 57.54; H, 6.15; N, 9.17, B, 1.49.

**Hydantoin 32 of 3-[3-(4-Boronophenyl)propyl]cyclobutanone (28).** The synthesis was carried out as described for **30**. A solution of **28** (3.71 mmol, 0.862 g) in aqueous ethanol (50% ethanol in water, 12.0 mL) was allowed to react with potassium cyanide (7.4 mmol, 0.48 g) and ammonium carbonate (18.6 mmol, 1.78 g) to obtain a faint yellow solid that was purified using silica gel chromatography (10% methanol in methylene chloride) to obtain **32** as a white solid (0.74 g, 66% yield): $R_f$ = 0.46 (5% methanol in methylene chloride, thin-layer chromatography); mp 220−224 °C; $^1$H (DMSO-$d_6$) $\delta$ 7.89 (s, 2 H, disappears by the addition of $D_2O$), 7.88 (d, $J$ = 7.7 Hz, 2H), 7.36 (d, $J$ = 7.7 Hz, 2H), 2.68 (m, 3H), 2.50−2.29 (m, 3H), 2.08 (m, 1H), 1.62 (m, 4H); $^{13}$C (DMSO-$d_6$) $\delta$ 178.99, 156.04, 144.16, 134.29, 127.48, 57.88, 38.28, 37.07, 35.14, 28.25, 26.32; IR (Nujol) 3168, 1776, 1733; ES+ (M + H; obtained in MeOH−$H_2O$ solvent mixture containing 1% formic acid) calcd for $C_{17}H_{24}O_4N_2B$ 331.1, found 330.9. Anal. Calcd

for $C_{15}H_{19}BN_2O_4$: C, 59.63; H, 6.34; B, 3.58; N, 9.27. Found: C, 59.67; H, 6.30; N, 8.67; B, 3.31.

**Hydantoin 33 of 3-[7-(4-Boronophenyl)heptyl]cyclobutanone (29).** The synthesis was carried out as described for **30**. A solution of **29** (3.67 mmol, 1.06 g) in aqueous ethanol (50%, 12.0 mL) was allowed to react with potassium cyanide (7.34 mmol, 0.479 g) and ammonium carbonate (18.4 mmol, 1.76 g) to obtain a faint yellow solid that was purified using silica gel chromatography (10% methanol in methylene chloride) to obtain **33** as a white solid (0.261 g, 40% yield): $R_f$ = 0.72 (10% methanol in methylene chloride, thin-layer chromatography); mp 206−208 °C (dec); $^1$H (DMSO-$d_6$ with 10% $D_2O$) $\delta$, 8.13 (d, $J$ = 7.7 Hz, 2H), 7.59 (d, $J$ = 7.7 Hz, 2H), 2.99 (t, $J$ = 6.5 Hz, 2H), 2.88 (m, 2H), 2.73−2.55 (m, 2H), 2.32 (m, 1H), 1.97 (br s, 2H), 1.79 (m, 2H), 1.67 (bs, 8H); $^{13}$C (DMSO-$d_6$) $\delta$ 178.84, 155.92, 144.25, 134.16, 127.33, 57.76, 38.25, 37.02, 36.48, 35.22, 28.85, 28.62, 26.43, 26.31; IR (Nujol) 3169, 1779, 1733; HR-FAB-MS (M + H; glycerol matrix) calcd for $C_{22}H_{32}BN_2O_5$ 415.241, found 415.241. Anal. Calcd for $C_{19}H_{27}BN_2O_4$: C, 63.70; H, 7.60; B, 3.02; N, 7.82. Found: C, 65.88; H, 7.65; N, 7.46; B, 2.92.

**1-Amino-3-(4-boronophenyl)cyclobutanecarboxylic Acid (2).** The hydantoin of 3-(4-boronophenyl)cyclobutanone, **30** (1.54 mmol, 0.400 g), was placed in a 15 mL Ace pressure tube along with a solution of aqueous sodium hydroxide (2 N, 4.0 mL). The tube was sealed and then heated at 160 °C (oil bath) for 40 min. After cooling to room temperature, it was carefully opened. TLC indicated disappearance of the starting hydantoin. The reaction mixture was decolorized with charcoal (0.2 g) and filtered. The filtrate was neutralized with dilute aqueous hydrochloric acid and concentrated under reduced pressure. The crude material was purified using a reverse phase column (2 × 16 cm, using 50% methanol water with 2% acetic acid) to obtain **2** as a white solid (0.188 g, 52% yield): $R_f$ = 0.32 (mixture of acetonitrile, methanol, and water in the ratio of 10:2:1.5); compound turns brown (without melting) at 262−265 °C; $^1$H NMR (DCl) $\delta$ 7.54 (d, $J$ = 6.1 Hz, 2H), 7.16 (d, $J$ = 6.1 Hz, 2H), 3.69 (m, 1H), 2.85 (m, 2H), 2.42 (m, 2H); $^{13}$C NMR (DCl) $\delta$ 174.91, 147.05, 134.89, 126.74, 54.46, 37.79, 32.85; IR (Nujol) 3361, 1607; HR-FAB-MS (M + H; obtained in glycerol matrix) calcd for $C_{14}H_{19}O_5BN$ 292.136, found 292.136.

**1-Amino-3-[2-(4-boronophenyl)ethyl]cyclobutanecarboxylic Acid (3).** The synthesis was carried out as described for **2**. A solution of **31** (0.63 mmol, 0.18 g) and aqueous sodium hydroxide (2 N, 4.0 mL) was heated at 160 °C. The crude material was purified to obtain **3** as a white solid (0.18 g, 69% yield): $R_f$ = 0.41 (mixture of acetonitrile, methanol and water, in the ratio of 10:2:1.5); compound turns brown (without melting) at 224−228 °C; $^1$H NMR (DCl) $\delta$ 6.96 (d, $J$ = 7.7 Hz, 2H), 6.56 (d, $J$ = 7.7 Hz, 2H), 1.96 (m, 2H), 1.84 (m, 2H), 1.72 (m, 1H), 1.38 (m, 2H), 1.09 (m, 2H); $^{13}$C (DCl) $\delta$ 174.77, 146.35, 134.72, 129.04, 54.65, 38.43, 36.68, 33.22, 28.24; IR (Nujol) 3404, 1608; HR-FAB-MS (M + H; obtained in glycerol matrix) calcd for $C_{16}H_{23}O_5BN$ 320.167, found 320.167.

**1-Amino-3-[3-(4-boronophenyl)propyl]cyclobutanecarboxylic Acid (4).** The synthesis was carried out as described for **2**. A solution of hydantoin **32** (0.662 mmol, 0.200 g) and aqueous sodium hydroxide (2 N, 2 mL) was heated at 160 °C in a pressure tube. The crude material was purified to obtain **4** as a white solid (0.112 g, 61% yield): $R_f$ = 0.46 (mixture of acetonitrile, methanol, and water in the ratio of 10:2:1.5); compound turns brown (without melting) at 228−232 °C; $^1$H NMR (DMSO-$d_6$ with 5% $D_2O$) $\delta$ 7.84 (d, $J$ = 7.5 Hz, 2H), 7.39 (d, $J$ = 7.5 Hz, 2H), 2.90−2.38 (m, 6H), 2.22 (m, 1H), 1.63 (br s, 4H); $^{13}$C ($CD_3OD$) $\delta$ 176.31, 145.79, 134.93, 128.67, 57.24, 39.23, 38.02, 36.67, 29.53, 26.47; IR (Nujol) 3352, 1610; HR-FAB-MS (M + H; obtained in glycerol matrix) calcd for $C_{17}H_{25}O_5BN$ 334.183, found 334.182.

**1-Amino-3-[7-(4-boronophenyl)heptyl]cyclobutanecarboxylic Acid (5).** The synthesis was carried out as described for **2**. A solution of **33** (1.03 mmol, 0.369 g) and aqueous sodium hydroxide (2 N, 7 mL) was heated at 160 °C. The crude material was purified to obtain **5** as a white solid (0.288 g, 84% yield). $R_f$ = 0.61 (mixture of acetonitrile, methanol, and water in the ratio of 10:2:1.5); compound soften and turns brown (without clear melting) at 204−208 °C; $^1$H NMR ($CD_3OD$ with 5% $D_2O$) $\delta$ 7.05 (d, $J$ = 7.5 Hz, 2H), 6.88 (d, $J$ = 7.5 Hz, 2H), 2.33 (m, 4H), 2.06 (m, 2H), 1.61 (br s, 1H), 1.33 (br s, 2H), 1.19 (br s, 2H), 1.05 (br s, 8H); $^{13}$C ($CD_3OD$) $\delta$ 177.36, 144.02, 134.16, 128.21, 55.93, 38.32, 36.93, 36.76, 32.51, 30.52, 30.25, 29.62, 27.87; IR (Nujol) 3504, 3147, 1636, 1611; HR-FAB-MS (M + H; obtained in glycerol matrix) calcd for $C_{21}H_{33}O_5BN$ 390.246, found 390.245

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