JOC Article

Synthesis of 1-Amino-3-[(dihydroxyboryl)methyl]-cyclobutanecarboxylic Acid as a Potential Therapy Agent

George W. Kabalka* and Min-Liang Yao

Departments of Chemistry and Radiology, The University of Tennessee, Knoxville, Tennessee 37996-1600

kabalka@utk.edu

Received July 12, 2004

A novel boronated aminocyclobutanecarboxylic acid (**1**) was synthesized for potential use in boron neutron capture therapy. Starting from the readily available 3-(bromomethyl)cyclobutanone ketal (**4**), several synthetic routes to **1** were evaluated. After several unsuccessful attempts with traditional synthetic methods, a novel synthetic strategy to generate the new boronated cyclic amino acid was developed. The tolerance of the hydantoin group to the selenoxide elimination reaction conditions in the preparation of alkenyl compound **7** proved to be the key step in the new strategy.

Introduction

In recent years, there has been renewed interest in boron neutron capture therapy[1] (BNCT), a binary approach for cancer treatment. The potential use of boron compounds for the treatment of cancer is based upon the unique nuclear properties of the ^{10}B nucleus. After absorption of a neutron, the high-energy ^{11}B nucleus that is produced undergoes fission and releases an α-particle and a high-energy lithium-7 ion. These heavy charged particles have a range of approximately one cell diameter and thus they are lethal to the cells in which they are generated. To minimize the damage to normal tissues, the selective targeting of tumor cells by boron compounds is the key for the clinical success of BNCT. To date, a variety of molecules have been used to deliver boron to tumor cells. These include carbohydrates,[2] polyamines,[3] amino acids,[4] nucleosides,[5] antisense agents,[6] porphyrins,[7] and peptides.[8] In recent years, encouraging results have been obtained by using 4-dihydroxyborylphenylalanine (BPA) as the tumor-specific boronated agent.[9]

It is believed that the amino acids are preferentially taken up by growing tumor cells. Positron emission tomography (PET) investigations[10] with carbon-11 labeled 1-aminocyclobutanecarboxylic acid (ACBC) demonstrated that this amino acid localizes in tumors more avidly than BPA. Recently Goodman reported that fluorine-18 labeled 1-amino-3-(fluoromethyl)cyclobutanecarboxylic acid also localizes in tumors.[11] For these reasons, we have focused our efforts on the synthesis of boronated

---

* Address correspondence to this author. Fax: 865-974-2997. Phone: 865-974-3260.

(1) For recent reviews, see: (a) Valliant, J. F.; Guenther, K. J.; King, A. S.; Morel, P.; Schaffer, P.; Sogbein, O. O.; Stephenson, K. A. *Coord. Chem. Rev.* **2002**, *232*, 173. (b) Hawthorne, M. F.; Maderna, A. *Chem. Rev.* **1999**, *99*, 3421. (c) Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F.-G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. *Chem. Rev.* **1998**, *98*, 1515. (d) Hawthorne, M. F. *Mol. Med. Today* **1998**, *4*, 174.

(2) (a) Tietze, L. F.; Griesbach, U.; Schuberth, I.; Bothe, U.; Marra, A.; Dondoni, A. *Chem. Eur. J.* **2003**, *9*, 1296. (b) Titze, L. F.; Bothe, U.; Griesbach, U.; Nakaichi, M.; Hasegawa, T.; Nakamura, H.; Yamamoto, Y. *Bioorg. Med. Chem.* **2001**, *9*, 1747. (c) Giovenzana, G. B.; Lay, L.; Monti, D.; Palmisano, G.; Panza, L. *Tetrahedron* **1999**, *55*, 14123. (d) Maurer, J. L.; Serino, A. J.; Hawthorne, M. F. *Organometallics* **1988**, *7*, 2519.

(3) (a) El-Zaria, M. E.; Doerfler, U.; Gabel, D. *J. Med. Chem.* **2002**, *45*, 5817. (b) Bauce, C.; Gabel, D.; Doerfler, U. *Eur. J. Med. Chem.* **2002**, *37*, 649. (c) Martin, B.; Posseme, F.; Le Barbier, C.; Carreaux, F.; Carboni, B.; Seiler, N.; Moulinoux, J.-P.; Delcros, J.-G. *J. Med. Chem.* **2001**, *44*, 3653. (d) Zhuo, J.-C.; Cai, J.; Soloway, A. H.; Barth, R. F.; Adams, D. M.; Ji, W. *J. Med. Chem.* **1999**, *42*, 1282.

(4) (a) Kabalka, G. W.; Das, B. C.; Das, S. *Tetrahedron Lett.* **2001**, *42*, 7145. (b) Diaz, S.; Gonzalez, A.; de Riancho, S. G.; Rodriguez, A. *J. Organomet. Chem.* **2000**, *610*, 25. (c) Lindstroem, P.; Naeslund, C.; Sjoeberg, S. *Tetrahedron Lett.* **2000**, *41*, 751. (d) Nakamura, H.; Fujiwara, M.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 7529. (e) Malan, C.; Morin, C. *J. Org. Chem.* **1998**, *63*, 8019. (f) Kahl, S. B.; Dasar, R. A. *J. Am. Chem. Soc.* **1996**, *118*, 1223. (g) Radel, P. A.; Kahl, S. B. *J. Org. Chem.* **1996**, *61*, 4582.

(5) (a) Tjarks, W. *J. Organomet. Chem.* **2001**, *614–615*, 37. (b) Hurwitz, S. J.; Ma, L.; Eleuteri, A.; Wright, J.; Moravek, J.; Schinazi, R. F. *Nucleosides Nucleotides Nucleic Acids* **2000**, *19*, 691. (c) Lin, J.; Shaw, B. R. *Tetrahedron Lett.* **2000**, *41*, 6701. (d) Zhou, J.-C.; Soloway, A. H.; Beeson, J. C.; Ji, W.; Barnum, B. A.; Rong, F.-G.; Tjarks, W.; Jordan, G. T., IV; Liu, J.; Shore, S. G. *J. Org. Chem.* **1999**, *64*, 9566. (e) Soloway, A. H.; Zhuo, J.-C.; Rong, F.-G.; Lunato, A. J.; Ives, D. H.; Barth, R. F. *J. Organomet. Chem.* **1999**, *581*, 150.

(6) (a) Olejiniczak, A. B.; Koziolkiewcz, M.; Lesnikowski, Z. J. *Antisense Nucleic Acid Drug Dev.* **2002**, *12*, 79. (b) Zhuo, J.-C.; Tjarks, W.; Soloway, A. H.; Cai, J.; Wang, J.; Barth, R. F.; Adams, D. M.; Eriksson, S.; Lunato, A. J.; Ji, W. *Contemporary Boron Chemistry*; Special Publication−Royal Society of Chemistry No. 253; RSC: Cambridge, UK, 2000; p 127. (c) Fulcrand, El.; Kattan, G.; Lesnikowski, Z. J.; Yao, S.; Tanious, F.; Wilson, W. D.; Schinazi, R. F. *J. Am. Chem. Soc.* **1994**, *116*, 7494.

(7) (a) Isaac, M. F.; Kahl, S. B. *J. Organomet. Chem.* **2003**, *680*, 232. (b) Maderna, A.; Huertas, R.; Hawthorne, M. F.; Luguya, R.; Vicente, M. G. H. *Chem. Commun.* **2002**, 1784. (c) Vicente, M. G. H.; Edwards, B. F.; Shetty, S. J.; Hou, Y.; Boggan, J. E. *Bioorg. Med. Chem.* **2002**, *10*, 481. (d) Miura, M.; Micca, P. L.; Fisher, C. D.; Gordon, C. R.; Heinrichs, J. C.; Slatlin, D. N. *Br. J. Radiol.* **1998**, *71*, 773. (e) Kahl, S. B.; Koo, M.-S. *Chem. Commun.* **1990**, 1769.

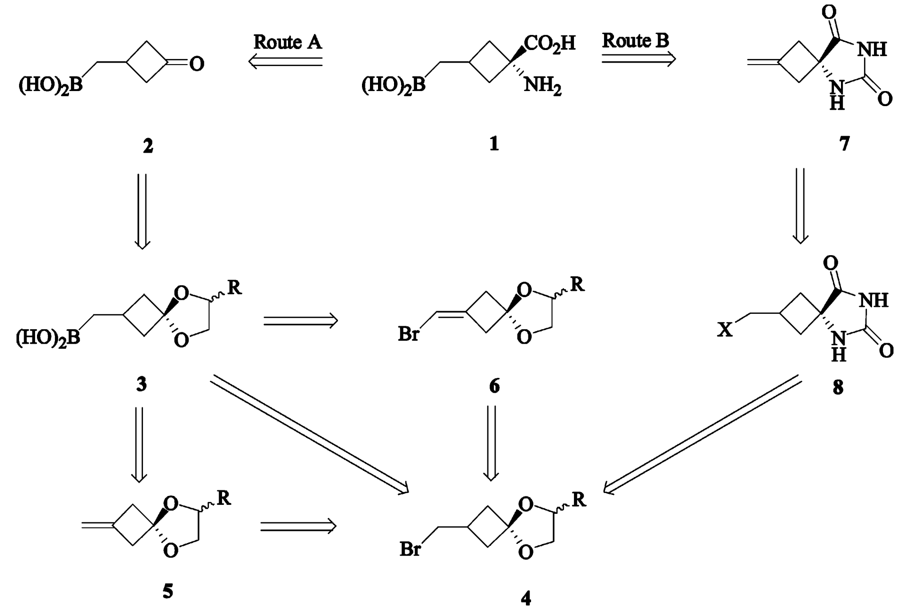
(8) (a) Schirrmacher, E.; Schirrmacher, R.; Beck, C.; Mier, W.; Trautman, N.; Rösch, F. *Tetrahedron Lett.* **2003**, *44*, 9143. (b) Ivanov, D.; Bachovchin, W. W.; Redfield, A. G. *Biochemistry* **2002**, *41*, 1587. (c) Leusch, A.; Jungblut, P. N.; Moroder, L. *Synthesis* **1994**, 305.

(9) (a) Barth R. F.; Yang, W.; Bartus, R. T.; Rotaru, J. H.; Ferketich, A. K.; Moeschberger, M. L.; Nawrocky, M. M.; Coderre, J. A.; Rofstad, E. K. *Int. J. Radiat. Oncol. Biol. Phys.* **2002**, *52*, 858. (b) Kiger, W. S., III; Palmer, M. R.; Riley, K. J.; Zamenhof, R. G.; Busse, P. M. *Radiat. Res.* **2001**, *155*, 611. (c) Mallesch, J. L.; Moore, D. E.; Allen, B. J.; McCarthy, W. H.; Jones, R.; Stening, W. A. *Int. J. Radiat. Oncol. Biol. Phys.* **1994**, *28*, 1183.

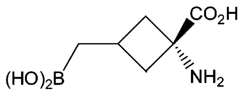
(10) Hubner, K. F.; Thie, J. A.; Smith, G. T.; Kabalka, G. W.; Keller, I. B.; Cliefoth, A. B.; Campbell, S. K.; Buonocore, E. *Clin. Positron Imaging* **1998**, *1*, 165.

10.1021/jo048824c CCC: $27.50

SCHEME 1



ACBC derivatives.[12–14] Herein we wish to report the synthesis of 1-amino-3-[(dihydroxyboryl)methyl]cyclobutanecarboxylic acid **1**.



1

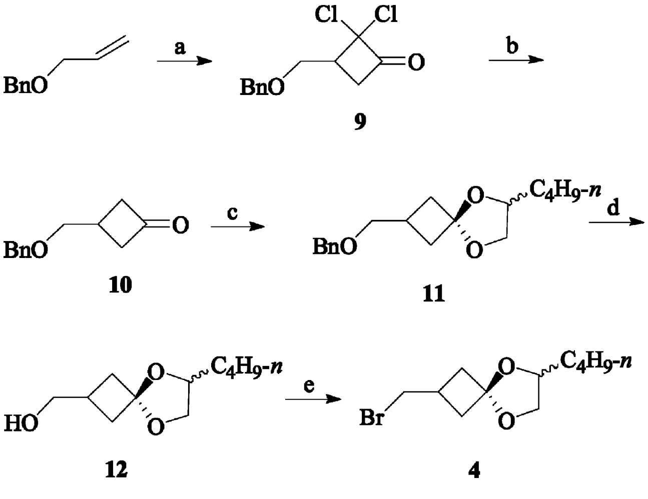
Results and Discussion

The retrosynthetic analyses for **1** are outlined in Scheme 1. There are two reasonable synthetic routes to **1**: initial introduction of the boronic acid function to the target molecule (defined as route A) and initial introduction of the amino acid, or its precursor hydantoin (defined as route B). The key step in route A is the preparation of ketal **3**. With ketal **3** in hand, the amino acid portion can be constructed with use of Bücherer–Strecker methodology. To prepare ketal **3**, three literature methods are available (the reaction of a Grignard reagent derived from **4** with a borate ester,[15] hydroboration of alkene **5**,[16] or Miyaura borylation of alkenyl bromide **6**).[17] The key step in route B is the elimination reaction required to produce terminal alkene **7**. Interestingly both routes use 3-(bromomethyl)cyclobutanone ketal, **4**, as the starting material.

3-(Bromomethyl)cyclobutanone ketal, **4**, could be obtained in 51% overall yield by using the sequence outlined in Scheme 2. The synthesis of **11** and **12** was described earlier.[18] As noted in the earlier report, the use of 1,2-hexanediol in place of ethanediol stabilizes the ketal during the subsequent debenzylation reaction. The use of the unsymmetrical diol does result in the formation of a new chiral center and leads to the formation of a mixture (1:1) of diastereomers (readily observable in the ^{13}C NMR spectra). Starting from **4**, the two synthetic routes (Scheme 1) were evaluated and the results are presented below.

Evaluation of Route A. The preparation of the prerequisite boronic acid with use of Grignard methodology was investigated.[15] The reaction of ketal **4** with 1.2

SCHEME 2[a]



[a] Reagents and conditions: (a) Cl_3CCOCl, $POCl_3$, Zn–Cu, Et_2O; (b) Zn, HOAc; (c) hexane-1,2-diol, PTSA, benzene, reflux; (d) Pd/C, CH_3OH, H_2 (1 atm), rt; (e) CBr_4, PPh_3, DCM, rt.

---

(11) Martarello, L.; McConathy, J.; Camp, V. M.; Malveaux, E. J.; Simpson, N. E.; Simpson, C. P.; Olson, J. J.; Bowers, G. D.; Goodman, M. M. *J. Med. Chem.* **2002**, *45*, 2250.

(12) (a) Das, B. C.; Das, S.; Li, G.; Bao, W.; Kabalka, G. W. *Synlett* **2001**, 1419. (b) Das, B. C.; Kabalka, G. W.; Srivastava, R. R.; Bao, W.; Das, S.; Li, G. *J. Organomet. Chem.* **2000**, *614–615*, 255. (c) Srivastava, R. R.; Singhaus, R.; Kabalka, G. W. *J. Org. Chem.* **1997**, *62*, 4476.

(13) Srivastava, R. R.; Singhaus, R.; Kabalka, G. W. *J. Org. Chem.* **1999**, *64*, 8495.

(14) (a) Kabalka, G. W.; Yao, M.-L. *Appl. Organomet. Chem.* **2003**, *17*, 398. (b) Kabalka, G. W.; Yao, M.-L. *Synthesis* **2003**, 2890.

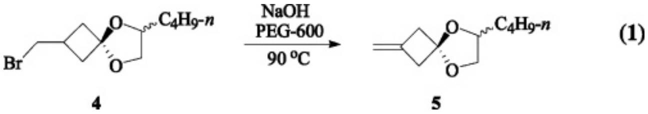
(15) (a) Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316. (b) Washburn, R. M.; Levens, E.; Albright, C. F.; Billig, F. A. *Org. Synth.* **1959**, *39*, 3.

(16) (a) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1996**, 2073. (b) Wang, K.-K.; Liu, C.; Gu, Y.-G.; Burnett, F. N. *J. Org. Chem.* **1991**, *56*, 1914.

(17) (a) Giroux, A. *Tetrahedron Lett.* **2003**, *44*, 233. (b) Furstner, A.; Seidel, G. *Org. Lett.* **2002**, *4*, 541. (c) Takahashi, K.; Takagi, J.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, 127. (d) Ishyiyama, T.; Ahiko, T.-A.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447. (e) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508.

equiv of magnesium powder in THF proceeded smoothly to generate the corresponding Grignard reagent.[19] Surprisingly the reaction of this Grignard reagent with the borate esters was unsuccessful.

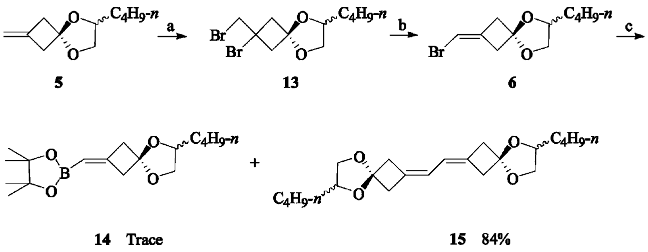
Dehydrobromination of **4** with NaOH in PEG-600 generated 3-methylenecyclobutanone ketal, **5**, in 67% yield[20] (eq 1). Hydroboration of **5** to generate **3** with either catecholborane or diisopinocampheylborane (Ipc_2BH) proved problematic due to reduction of the ketal group.



(1)

We then evaluated the Miyaura borylation reaction,[17] a palladium-catalyzed coupling of an alkenyl halide with bis(pinacolato)diboron. Alkenyl bromide **6** was prepared from alkene **5** in two steps [21] (Scheme 3). Under typical Miyaura conditions (5 mol % of $PdCl_2(PPh_3)_2$·$2PPh_3$ and 1.5 equiv of PhOK in toluene at 50 °C),[17c] the reaction of **6** with 1.1 equiv of bis(pinacolato)diboron afforded only a trace of the anticipated alkenylboronic ester **14**. However, dicyclobutylideneethane **15** was obtained in 84% isolated yield.

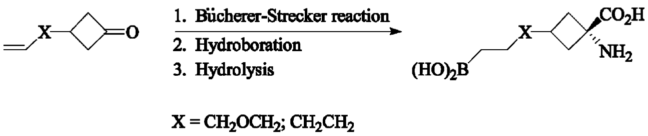
SCHEME 3 [a]



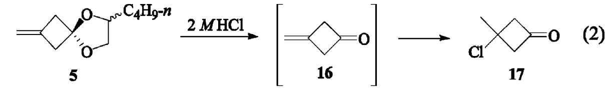
[a] Reagents and conditions: (a) Br_2, DCM, 0 °C to rt; (b) KOH, EtOH, reflux; (c) di(pinacolato)diboron, PhOK, $Pd(PPh_3)_2Cl_2$, PPh_3.

Evaluation of Route B. We then turned our attention to route B, in which the hydantoin group is introduced first. This synthetic strategy proved quite efficient in the synthesis of ACBC derivatives bearing long alkylboronic acid side chains (Scheme 4).[14]

SCHEME 4



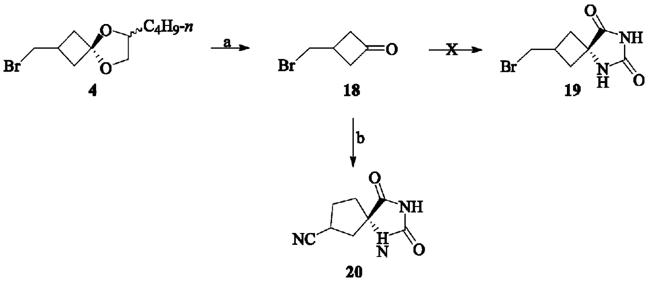
As part of our study, we attempted to remove the ketal group in **5** using dilute HCl. The reaction generated undesired ketone **17**, resulting from addition of HCl to the highly strained methylenecyclobutanone **16** (eq 2).[22]



(2)

Thus, generation of the alkene moiety, after construction of the hydantoin group, was the only remaining route for the preparation of **1**. Removal of the ketal group from 3-(bromomethyl)cyclobutanone ketal, **3**, regenerated ketone **18**, but the Bücherer−Strecker reaction did not produce the anticipated hydantoin **19**. A mixture was obtained with hydantoin **20** being the main product (Scheme 5).[23]

SCHEME 5 [a]



[a] Reagents and conditions: (a) HCl (2 M), EtOH/H_2O, reflux; (b) $(NH_4)_2CO_3$, KCN, EtOH/H_2O (1:1), 60 °C.

Generation of alkene **7** by selenoxide elimination appeared to be a reasonable approach (Scheme 6). Treatment of 3-(bromomethyl)cyclobutanone ketal, **4**, with benzeneselenolate anion (generated from either benzeneselenol[24] or diphenyl diselenide[25]) provided selenide **21** in high yield. Removal of the ketal group with dilute HCl in refluxing ethanol produced 3-(phenylselanylmethyl)-cyclobutanone, **22**. It should be pointed out that the preparation of ketone **22** from allylbenzylselane via a [2+2] cycloaddition reaction with dichloroketene was reported to be unsuccessful.[26] The reaction of ketone **22** with ammonium carbonate and potassium cyanide in an Ace pressure tube afforded hydantoin **23** in a 3:1 ratio of stereoisomers with the cis-isomer being the major product.[27] Oxidation of **23** with $NaIO_4$ in aqueous methanol produced **24** in quantitative yield.[28] In the presence of sodium bicarbonate, selenoxide elimination occurred in refluxing methanol[29] to produce **7** in moderate yield (45%).

---

[18] Kabalka, G. W.; Yao, M.-L. *Tetrahedron Lett.* **2003**, *44*, 1879.

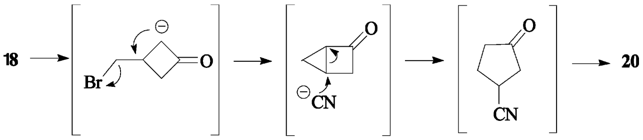
[19] To verify formation of the Grignard reagent derived from **4**, we quenched a reaction with D_2O (separate experiment). ^1H NMR analysis revealed the presence of the monodeuterated product: appearance of a new multiplet at 1.11 ppm ($-CH_2D$) and disapperance of the multiplet at 3.49 ppm ($-CH_2Br$).

[20] Kimura, Y.; Regen, S. L. *J. Org. Chem.* **1982**, *47*, 2493.

[21] Du, Z.-M.; Haglund, M. J.; Pratt, L. A.; Erickson, K. L. *J. Org. Chem.* **1998**, *63*, 8880.

[22] (a) Jennings, L. D.; Rayner, D. R.; Jordan, D. B.; Okonya, J. F.; Basarab, G. S.; Amorose, D. K.; Anaclerio, B. M.; Lee, J. K.; Schwartz, R. S.; Whitemore, K. A. *Bioorg. Med. Chem.* **2000**, *8*, 897. (b) Hoz, S.; Livneh, M. *J. Am. Chem. Soc.* **1987**, *109*, 7483.

[23] The unanticipated ring expansion reaction presumably proceeds via a bicyclic intermediate under basic conditions.



[24] Miyashita, M.; Yoshikoshi, A. *Synthesis* **1980**, 664.

[25] Liotta, D.; Sunay, U.; Santiesteban, H.; Markiewicz, W. *J. Org. Chem.* **1981**, *46*, 2605.

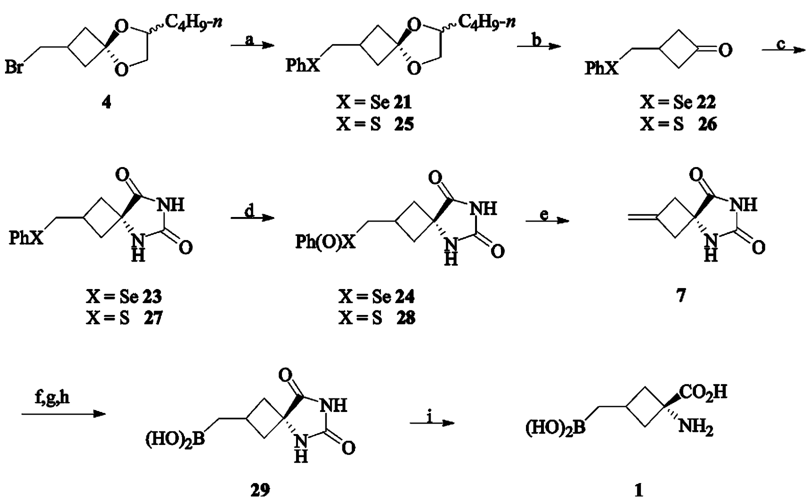
[26] Johnston, B. D.; Czyzewska, E.; Oehlschlager, A. C. *J. Org. Chem.* **1987**, *52*, 3693.

[27] Rammeloo, T.; Stevens, C. *Chem. Commun.* **2002**, 250.

[28] (a) Zhu, Y.; van der Donk, W. A. *Org. Lett.* **2001**, *3*, 1189. (b) Evans, P. A.; Holmes, A. B.; Russell, K. *Tetrahedron: Asymmetry* **1990**, *1*, 593.

[29] Selenoxide elimination reactions are generally carried out in 1,2-dichloroethane. In our case, this proved problematic due to the NH group in hydantoin **24**. In the presence of base, a S_N2 reaction between 1,2-dichloroethane and **24** took place.

SCHEME 6[a]



[a] Reagents and conditions: (a) PhSeNa (or PhSNa), CH_3OH, rt; (b) HCl (2 M), EtOH/H_2O, reflux; (c) KCN, $(NH_4)_2CO_3$, EtOH/H_2O (1:1), 60 °C; (d) $NaIO_4$, CH_3OH, rt; (e) $NaHCO_3$, CH_3OH, 70 °C; (f) $(Ipc)_2BH$, THF, 0 °C to rt; (g) CH_3CHO, THF, 0 °C to rt; (h) HCl (2 M) rt; (i) HCl (12 M) HCl, 150 °C.

Considering both the toxicity and the expense of selenium compounds, a similar synthetic route, using sulfur in place of selenium, was examined. However, the synthetic route was hampered by the resistance of sulfoxide **28** to elimination.

The hydroboration of **7** was realized by treatment of **7** with 3.0 equiv of diisopinocampheylborane (Ipc_2BH) in THF at room temperature.[30] The hydrolysis of **29** in the presence of concentrated HCl gave **1** in good yield.

Conclusion

We report the synthesis of a novel 1-aminocyclobutanecarboxylic acid containing an alkylboronic acid. Several synthetic routes to **1** starting from 3-(bromomethyl)cyclobutanone ketal, **4**, were evaluated. A novel synthetic strategy to boronated cyclic amino acid was developed after failures encountered with traditional synthetic methods. The generation of the alkenyl group via a selenoxide elimination in the presence of a hydantoin group proved to be the key step in the novel strategy. The new agent is currently being evaluated as a BNCT agent.

Experimental Section

General Methods. All reagents were used as received. Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl. Column chromatography was performed with silica gel (60 Å, 230−400 mesh). Analytical thin-layer chromatography was performed with 250-μm silica and was visualized by phosphomolybdic acid.

^{1}H NMR and ^{13}C NMR spectra were recorded at 250.13 and 62.89 MHz, 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 NMR and ^{13}C NMR spectra were referenced to TMS and measured with respect to the residual protons in the deuterated solvents. HR-FAB-MS (M + 1) were obtained in a glycerol matrix.

3-Benzyloxymethyl-2,2-dichlorocyclobutanone (9). A 250-mL, three-necked, round-bottomed flask, equipped with an addition funnel and reflux condenser, was charged with allyl benzyl ether (30 mmol, 4.4 g), freshly prepared zinc−copper couple (100 mmol, 6.5 g), and anhydrous diethyl ether (50 mL). A solution of trichloroacetyl chloride (60 mmol, 6.7 mL) and phosphorus oxychloride (60 mmol, 5.6 mL) in diethyl ether (100 mL) was placed in the addition funnel and the solution added dropwise over a period of 30 min. After the addition was complete, the mixture was refluxed at 55 °C (oil bath) for 2 days under an argon atmosphere, cooled to room temperature, and filtered through a pad of Celite. Additional diethyl ether was used to wash the Celite. The solvent from the combined filtrates was removed in vacuo and the residue dissolved in petroleum ether (3 × 100 mL). The clear yellow solution was decanted into a separatory funnel, washed with water (2 × 50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator to obtain **9** as a light yellow liquid. Compound **9** was unstable on silica gel and was therefore used directly for the next step.

3-(Benzyloxymethyl)cyclobutanone (10). Crude **9** was dissolved in glacial acetic acid (20 mL) and zinc dust (10 g, excess) was added in portions. The mixture was stirred at room temperature for 30 min and then heated at 120 °C (oil bath) for 12 h. Thin-layer chromatography indicated the disappearance of the starting material. The mixture was cooled to room temperature, neutralized with saturated sodium bicarbonate at 0 °C, and passed through a pad of Celite. Ethyl acetate was used to wash the Celite. The combined filtrate was then extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with water (2 × 20 mL) and brine (20 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to obtain a thick light yellow liquid. The crude product was purified by column chromatography (EtOAc:hexanes = 1:15). 3-Benzyloxymethylcyclobutanone, **10**, was obtained as a colorless liquid (3.2 g, 56%, yield based on allyl benzyl ether). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.22−7.42 (m, 5H), 4.55 (s, 2H), 3.58 (d, J = 6.68 Hz, 2H), 3.05−3.17 (m, 2H), 2.78−2.94 (m, 2H), 2.62−2.71 (m, 1H). ^{13}C NMR δ 207.2, 138.0, 128.3, 127.6, 127.5, 73.1, 72.8, 50.0, 23.6.

3-(Benzyloxymethyl)cyclobutanone Ketal (11). A 250-mL, round-bottomed flask equipped with a Dean−Stark apparatus and a reflux condenser was charged with **10** (7.6 g, 40 mmol), hexane-1,2-diol (6.2 g, 44 mmol), and p-toluenesulfonic acid (500 mg) in benzene (150 mL). The mixture was refluxed at 120 °C (oil bath) for 14 h and the progress of the

---

[30] Petter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: New York, 1988; p 427.

reaction was monitored by TLC. After 14 h the flask was cooled to room temperature and saturated aqueous $NaHCO_3$ (20 mL) was added. The mixture was transferred to a separatory funnel, washed with H_2O (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a colorless oil. The product was purified by column chromatography (EtOAc:hexanes = 1:20) to yield 11.2 g (97%) of **11** as a colorless liquid. ^1H NMR (250 MHz, $CDCl_3$) δ 7.25−7.41 (m, 5 H), 4.50 (s, 2 H), 3.90−4.02 (m, 2 H), 3.48 (d, J = 6.26 Hz, 2 H), 3.42 (dd, J = 12.3, 6.7 Hz, 1 H), 2.18−2.46 (m, 3 H), 2.05−2.17 (m, 2 H), 1.17−1.65 (m, 6 H), 0.90 (t, J = 6.49 Hz, 3 H). ^{13}C NMR δ 138.4, 128.2, 127.5, 106.8, 106.7, 75.8, 75.5, 74.2, 72.8, 68.9, 68.6, 39.1, 38.7, 33.3, 33.0, 27.8, 24.7, 24.5, 22.6, 14.0. Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45, H, 9.02. Found: C, 74.23; H, 9.08.

3-(Hydroxymethyl)cyclobutynone Ketal (12). To a 100-mL, round-bottomed flask fitted with a septum cap were added compound **11** (11.2 g, 38.6 mmol), 10% Pd/C (1.12 g), and MeOH (60 mL). The air in the flask was removed under vacuum and H_2 was introduced by using a H_2-filled balloon. After being stirred for 24 h at room temperature, the mixture was filtered and the residual Pd/C was washed with MeOH. Concentration of the filtrate and washings under reduced pressure yielded the colorless product **12** (7.6 g, 99%). ^1H NMR (250 MHz, $CDCl_3$) δ 3.93−4.05 (m, 2 H), 3.63 (d, J = 6.18 Hz, 2 H), 3.45 (dd, J = 12.4, 6.7 Hz, 1 H), 3.68 (s, 1 H), 2.23−2.47 (m, 3 H), 2.00−2.17 (m, 2 H), 1.16−1.64 (m, 6 H), 0.91 (t, J = 6.48 Hz, 3 H). ^{13}C NMR δ 106.7, 106.5, 75.9, 75.7, 69.0, 68.8, 66.7, 66.6, 38.6, 38.5, 38.3, 33.3, 33.1, 27.8, 26.8, 26.6, 22.6, 13.9. HRMS *m/z* calcd for $C_{11}H_{20}O_3$ + 1 201.1491, found 201.1490. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.44; H, 10.09.

3-(Bromomethyl)cyclobutanone Ketal (4). To a 250-mL, round-bottomed flask fitted with a septum cap were added compound **12** (6.0 g, 30.0 mmol), CBr_4 (12.5 g, 37.5 mmol), and CH_2C1_2 (50 mL). The solution was cooled with an ice−water bath. Then Ph_3P (11.8 g, 45.0 mmol) in CH_2C1_2 (70 mL) was added dropwise via syringe. After addition was complete, the bath was removed and the mixture stirred for an additional 6 h. The solvent was removed under reduced pressure and the residue extracted into ether (5 × 40 mL). The ether layer was concentrated in vacuo and the residue purified by column chromatography (EtOAc:hexanes = 1:30) to yield 7.4 g (94%) of **4** as a colorless liquid. ^1H NMR (250 MHz, $CDCl_3$) δ 3.93−4.06 (m, 2H), 3.49 (d, J = 7.02 Hz, 2H), 3.42−3.48 (m, 1H), 2.42−2.54 (m, 3H), 2.03−2.15 (m, 2H), 1.16−1.58 (m, 6H), 0.91 (t, J = 6.78 Hz, 3H). ^{13}C NMR δ 105.4, 105.2, 76.0, 75.8, 69.1, 68.8, 41.2, 41.1, 40.9, 38.4, 33.2, 33.0, 27.8, 27.7, 27.6, 22.6, 13.9. Anal. Calcd for $C_{11}H_{19}O_2Br$: C, 50.20; H, 7.28. Found: C, 50.23; H, 7.30.

3-(Methylene)cyclobutanone Ketal (5). A 100-mL, round-bottomed flask equipped with a reflux condenser was charged with **4** (6.6 g, 25 mmol), PEG-600 (1.5 g), 50% NaOH aqueous solution (15 mL), and benzene (20 mL). The mixture was refluxed at 90 °C (oil bath) and the progress of the reaction was monitored by TLC. After 16 h, the flask was cooled to room temperature and water (20 mL) added. The mixture was transferred to a separatory funnel, the product extracted with ether (3 × 20 mL), and the combined ether layer washed with H_2O (2 × 15 mL) and then brine (15 mL). After the solution was dried over anhydrous $MgSO_4$, the solvent was removed by distillation (**Caution**: compound **5** is volatile). The product was purified by column chromatography (Et_2O: hexanes = 1:20) to afford **5** as a colorless liquid (3.1 g, 67%). ^1H NMR (250 MHz, $CDCl_3$) δ 4.94−4.98 (m, 2H), 3.98−4.06 (m, 2H), 3.47−3.52 (m, 1H), 3.03−3.04 (m, 2H), 2.95−2.97 (m, 2H), 1.12−1.61 (m, 6H), 0.91 (t, J = 6.33 Hz, 3H). ^{13}C NMR δ 138.5, 107.9, 105.7, 76.2, 69.2, 45.7, 45.5, 33.1, 27.2, 22.6, 14.0. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.60; H, 9.78.

3-Bromo-3-(bromomethyl)cyclobutanone Ketal (13). To a 100-mL, round-bottomed flask were added **5** (2.5 g, 13.7 mmol) and dry CH_2C1_2 (30 mL). The solution was cooled to 0 °C, and bromine (2.5 g, 15.6 mmol) in dry CH_2C1_2 (10 mL) was added dropwise. After the addition was complete, the mixture was stirred for an additional 4 h while warming slowly to room temperature. The mixture was transferred to a separatory funnel and washed sequentially with aqueous saturated $NaHSO_3$ (10 mL), H_2O (10 mL) and then brine (10 mL). After the solution was dried over anhydrous $MgSO_4$, the solvent was removed under reduced pressure. The residue was purified by column chromatography (EtOAc:hexanes = 1:30) to yield 3.3 g (71%) of **13** as a colorless liquid. ^1H NMR (250 MHz, $CDCl_3$) δ 3.92−4.05 (m, 4H), 3.44−3.53 (m, 1H), 2.69−3.13 (m, 4H), 1.27−1.62 (m, 6H), 0.91 (t, J = 6.75 Hz, 3H). ^{13}C NMR δ 104.0, 76.4, 76.2, 69.4, 69.0, 52.9, 52.5, 51.4, 51.2, 43.9, 39.1, 33.0, 32.7, 27.7, 22.6, 13.9. Anal. Calcd for $C_{11}H_{18}O_2Br_2$: C, 38.62; H, 5.30. Found: C, 38.51; H, 5.23.

3-(Bromomethylene)cyclobutanone Ketal (6). Compound **13** (3.1 g, 9.0 mmol) was dissolved in aqueous ethanol (95% ethanol in water, 10 mL), the solution treated with KOH (1.12 g, 20 mmol), and the mixture refluxed for 1 h. The mixture was diluted with EtOAc (50 mL), washed with brine (10 mL), and dried over anhydrous $MgSO_4$ and the solvent was removed by distillation (**Caution**: compound **6** is volatile). The residue was purified by chromatography (EtOAc:hexanes = 1:30) to give 1.5 g (64%) of **6** as a colorless liquid. ^1H NMR (250 MHz, $CDCl_3$) δ 5.98 (m, 1H), 3.99−4.06 (m, 2H), 3.47−3.51 (m, 1H), 2.97−3.00 (m, 2H), 2.89−2.93 (m, 2H), 1.16−1.63 (m, 6H), 0.91 (t, J = 6.38 Hz, 3H). ^{13}C NMR δ 135.5, 104.5, 98.9, 76.5, 69.4, 46.3, 46.0, 45.0, 44.7, 33.0, 27.8, 22.6, 14.0. HRMS calcd for M + 1 261.0446, found 261.0430.

Diene 15. Compound **6** (260 mg, 1.0 mmol), bis(pinacolato)diboron (280 mg, 1.1 mmol), $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol), PPh_3 (26 mg, 0.10 mmol), and PhOK (200 mg, 1.5 mmol) were placed in a flask under argon atmosphere. Toluene (5 mL) was added, the mixture was stirred at 50 °C, and the reaction was monitored by TLC. On completion, the mixture was diluted with ether (25 mL) and filtered through a short pad of silica gel, and the solvent was evaporated. Purification of the residue by column chromatography (EtOAc:hexanes = 1:20) yielded 152 mg (84%) of diene **15**. ^1H NMR (250 MHz, $CDCl_3$) δ 5.84 (s, 2H), 3.97−4.06 (m, 4H), 3.46−3.52 (m, 2H), 3.05 (m, 4H), 2.96 (m, 4H), 1.16−1.60 (m, 12H), 0.91 (t, J = 6.36 Hz, 6H). ^{13}C NMR δ 130.0, 120.0, 106.2, 76.2, 69.2, 45.2, 44.9, 43.7, 43.4, 33.1, 27.8, 22.6, 13.9. HRMS calcd for $C_{22}H_{34}O_4$ 362.2457, found 362.2449.

3-(Bromomethyl)cyclobutanone (18). A 100-mL, round-bottomed flask was charged with compound **4** (526 mg, 2.0 mmol) dissolved in a mixture of ethanol (10 mL) and aqueous hydrochloric acid (3 mL, 2 M). The mixture was refluxed overnight at which time TLC indicated complete disappearance of the starting ketal. After cooling to room temperature, the mixture was extracted with ether (3 × 20 mL), the combined organic phases dried over anhydrous $MgSO_4$, and the solvent removed by distillation (**Caution**: compound **18** is volatile). The residue was purified with silica gel column chromatography (Et_2O:pentane = 1:20) to give 283 mg (87%) of product **18**. ^1H NMR (250 MHz, $CDCl_3$) δ 3.62 (d, J = 5.90 Hz, 2H), 3.14−3.27 (m, 2H), 2.68−2.98 (m, 3H). ^{13}C NMR δ 204.8, 51.9, 37.2, 26.2. Anal. Calcd for C_5H_7OBr: C, 36.84; H, 4.33. Found: C, 36.63; H, 4.33.

3-(Phenylselanylmethyl)cyclobutanone ketal (21). Method A:[24] Diphenyl diselenide (4.7 g, 15 mmol) was suspended in methanol (50 mL), and solid sodium borohydride was added in small amounts until the yellow color disappeared (about 650 mg of $NaBH_4$ was added). Compound **4** (5.3 g, 20 mmol) was added dropwise to the mixture at room temperature. After the addition was complete, the mixture was stirred for an additional 1.5 h. The volatile components were removed under reduced pressure, and the residue was taken up in methylene chloride (60 mL) and then washed with 10% aqueous K_2CO_3 solution (2 × 20 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc−hexanes, 1:30) to give **21** as a colorless oil (6.1 g, 90%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.46−7.50 (m, 2H), 7.21−7.26 (m, 3H), 3.93−4.00 (m, 2H), 3.40−3.46 (m, 1H), 3.04 (d, J = 5.91 Hz, 2H), 2.33−2.53 (m, 3H), 1.94−2.06 (m, 2H), 1.23−1.65 (m, 6H), 0.90 (t, J = 6.67 Hz, 3H). ^{13}C NMR δ 132.7, 129.7, 129.0, 126.9, 105.7, 69.0, 68.7, 42.3, 42.0, 34.4, 33.3, 27.8, 25.4, 22.6, 14.1. HRMS calcd for $C_{17}H_{24}O_2Se$ 340.0942, found 340.0950. **Method B:**[25] Benzeneselenol (1.0 g, 6.4 mmol) was treated with NaH (168 mg, 7.0 mmol) in THF (15 mL) under nitrogen at room temperature. After 30 min, compound **4** (1.7 g, 6.4 mmol) in THF (10 mL) was added dropwise to the mixture, and the mixture was stirred for another hour. The workup procedure was identical with that described in method A (yield 88%).

3-(Phenylselanylmethyl)cyclobutanone (22). The synthesis was carried out as described for compound **18**. A solution of **21** (6.1 g, 17.9 mmol) and aqueous hydrochloric acid (8 mL, 2 M) in ethanol (30 mL) was refluxed for 19 h. The product was purified by silica gel chromatography (EtOAc:hexanes = 1:30) to obtain **22** as a colorless liquid (3.8 g, 88% yield). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43−7.47 (m, 2H), 7.18−7.21 (m, 3H), 3.03−3.12 (m, 4H), 2.67−2.76 (m, 2H), 2.50−2.65 (m, 1H). ^{13}C NMR δ 206.4, 133.3, 129.1, 127.3, 52.8, 33.8, 24.3. HRMS calcd for $C_{10}H_{12}OSe$ 240.0054, found 240.0060.

Hydantoin 23 of 3-(Phenylselanylmethyl)cyclobutanone (22). A 50-mL Ace pressure tube was charged with ketone **22** (3.6 g, 15 mmol), aqueous ethanol (50%, 20 mL), potassium cyanide (2.0 g, 30 mmol), and ammonium carbonate (7.2 g, 75 mmol). The reaction vessel was sealed and heated at 60 °C (oil bath) for 8 h. A faint yellow precipitate formed. The mixture was cooled to room temperature and the vessel carefully opened in a fume hood. The mixture was concentrated under reduced pressure and the solid obtained was purified by column chromatography (EtOAc:hexanes = 2:1) to afford 3.1 g of **23** as a white solid (yield: 67%). ^{1}H NMR (250 MHz, CD_3OD) δ 7.60−7.65 (m, 2H), 7.37−7.45 (m, 3H), 3.14 (d, J = 6.62 Hz, 2H), 2.63−2.76 (m, 3H), 2.12−2.19 (m, 2H). ^{13}C NMR δ 180.4, 158.2, 133.7, 131.0, 130.3, 128.1, 58.7, 38.7, 34.7, 28.3. HRMS calcd for $C_{13}H_{14}N_2O_2Se$ 310.0221, found 310.0217.

Selenoxide (24). Hydantoin **23** (2.8 g, 9.0 mmol) was dissolved in methanol (30 mL) and cooled in an ice bath prior to the dropwise addition of a solution of sodium metaperiodate (1.9 g, 9.0 mmol) in a minimum amount of water (about 4.5 mL). When addition was complete, the ice bath was removed and the reaction was stirred at room temperature. TLC analysis showed complete disappearance of the starting material after 24 h. The mixture was filtered and the precipitate washed several times with methanol. The combined filtrate and washings were concentrated in vacuo to quantitatively yield a pale yellow solid. The crude selenoxide was essentially pure and was utilized directly for the next step. ^{1}H NMR (250 MHz, CD_3OD + DMSO-d_6) δ 7.69−7.78 (m, 2H), 7.43−7.55 (m, 3H), 3.14−3.16 (m, 2H), 2.43−2.72 (m, 3H), 1.97−2.19 (m, 2H). ^{13}C NMR δ 177.2, 155.2, 138.8, 130.1, 128.4, 124.8, 57.4, 37.8, 36.4, 20.5.

3-(Methylene)cyclobutanone Hydantoin (7). To a 100-mL round-bottomed flask were added **25** (3.9 g, 9.0 mmol), $NaHCO_3$ (756 mg, 9.0 mmol), and CH_3OH (20 mL). The mixture was stirred at 70 °C (oil bath) for 14 h. After the reaction was complete, the solvent was removed under reduced pressure. The residue was purified by column chromatography (EtOAc:hexanes = 2.5:1) to yield 620 mg (45%) of **7** as a colorless solid. ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.37 (s, 1H), 6.65 (s, 1H), 4.88 (s, 2H), 2.88−3.11 (m, 4H). ^{13}C NMR δ 177.5, 158.1, 137.9, 107.4, 57.2, 41.8. HRMS calcd for $C_7H_8N_2O_2$ 152.0586, found 152.0580. Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 54.83; H, 5.38; N, 18.02.

3-(Phenylsulfanylmethyl)cyclobutanone Ketal (25). Compound **4** (4.0 g, 15 mmol) in 50 mL of THF was added dropwise to 1 M NaSPh in MeOH (24 mL, 24 mmol) at 0 °C. After completion of the addition, the mixture was warmed slowly to room temperature and stirred for another 16 h. The mixture was then poured into water (50 mL), the products extracted with ether (3 × 20 mL), and the combined ether extracts washed with brine (2 × 10 mL), dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography (EtOAc:hexanes = 1:25) to give 3.7 g (85%) of **25** as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.16−7.34 (m, 5H), 3.92−4.00 (m, 2H), 3.42−3.46 (m, 1H), 3.04 (d, J = 6.40 Hz, 2H), 2.39−2.49 (m, 2H), 2.23−2.38 (m, 1H), 1.97−2.15 (m, 2H), 1.23−1.66 (m, 6H), 0.90 (t, J = 6.64 Hz, 3H). ^{13}C NMR δ 136.2, 130.5, 129.5, 128.8, 126.0, 106.3, 106.1, 76.1, 69.0, 41.6, 40.0, 33.5, 33.3, 27.8, 24.7, 22.6, 13.9. Anal. Calcd for $C_{17}H_{24}O_2S$: C, 69.82; H, 8.27. Found: C, 69.83; H, 8.28.

3-(Phenylsulfanylmethyl)cyclobutanone (26). The synthesis was carried out as described for compound **18**. A solution of **25** (3.7 g, 12.7 mmol) and aqueous hydrochloric acid (6 mL, 2 M) in ethanol (20 mL) was refluxed for 20 h. The product was purified by silica gel chromatography (EtOAc: hexanes = 1:30) to obtain **26** as a colorless liquid (2.3 g, 94% yield). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.21−7.40 (m, 5H), 3.10−3.23 (m, 4H), 2.76−2.88 (m, 2H), 2.53−2.64 (m, 1H). ^{13}C NMR δ 206.3, 135.3, 130.0, 129.0, 126.5, 52.2, 39.9, 23.5. Anal. Calcd for $C_{11}H_{12}OS$: C, 68.71; H, 6.29. Found: C, 68.74; H, 6.29.

Hydantoin 27 of 3-(Phenylsulfanylmethyl)cyclobutanone (26). The synthesis was carried out as described for **23**. Compound **26** (960 mg, 5.0 mmol), aqueous ethanol (50%, 12 mL), potassium cyanide (650 mg, 10 mmol), and ammonium carbonate (2.4 g, 25 mmol) were sealed in a 25-mL Ace pressure tube and heated at 60 °C (oil bath) for 8 h. The product was purified by column chromatography (EtOAc: hexanes = 2:1) to afford 920 mg of **27** as a white solid (yield: 70%). ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.99 (s, 1H), 7.15−7.67 (m, 6H), 2.99 (d, J = 7.52 Hz, 2H), 2.56−2.74 (m, 3H), 1.94−2.16 (m, 2H). ^{13}C NMR δ 180.5, 158.2, 137.4, 130.5, 130.1, 127.2, 59.3, 37.9, 37.4, 27.5. Anal. Calcd for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38. Found: C, 59.05; H, 5.39.

Sulfoxide (28). The synthesis was carried out as described for **24**. The crude sulfoxide was sufficiently pure for NMR analysis. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.42 (s, 1H), 7.49−7.68 (m, 6H), 3.04−3.15 (m, 2H), 2.53−2.78 (m, 2H), 2.03−2.29 (m, 3H). ^{13}C NMR δ 177.8, 156.7, 142.8, 131.5, 129.4, 124.2, 60.6, 59.5, 38.6, 21.9.

Boronohydantoin (29). Diisopinocampheylborane, $(Ipc)_2BH$, was prepared according to the literature procedure.[30] A 100-mL, round-bottomed flask was fitted with a septum and a magnetic stirring bar and connected to a nitrogen bubbler. The flask was flushed with nitrogen and held at a positive static pressure of nitrogen. Borane−THF (50 mmol, 50 mL, 1.0 M) was added to the flask, which was cooled to 0 °C, then α-pinene (18.4 mL, 115 mmol) was added slowly and the mixture stirred at 0 °C for 1 h. The reaction was maintained at 0 °C for 3 days to give the required crystalline product. Compound **7** (380 mg, 2.5 mmol) was placed in a 150-mL round-bottomed flask and dissolved in THF (10 mL) at 0 °C. $(Ipc)_2BH$ (7.5 mmol) in THF (10 mL) was added dropwise via a syringe. The mixture was allowed to warm to room temperature and stirred for 16 h. Freshly distilled acetaldehyde (12 mmol) was added and the mixture was stirred for an additional 12 h. Excess acetaldehyde was removed under vacuum and the mixture was hydrolyzed with aqueous hydrochloric acid (5 mL, 2 M). The mixture was extracted with EtOAc (3 × 30 mL) and the combined organic phase dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (methanol) to afford **29** as a white solid (302 mg, yield: 61%). ^{1}H NMR (DMSO-d_6) δ 8.49 (s, 1H), 7.44 (s, 1H), 1.74−2.48 (m, 5H), 0.72−0.88 (m, 2H). ^{13}C NMR δ 177.5, 156.3, 59.5, 34.2, 25.7. HR-FAB-MS (M + H + gly − $2H_2O$; obtained in a glycerol matrix) calcd for $C_{10}H_{16}BN_2O_5$ 255.1154, found 255.1148.

1-Amino-3-[(dihydroxyboryl)methyl]cyclobutanecarboxylic Acid (1). Boronohydantoin **29** (297 mg, 1.5 mmol) was placed in a 25-mL Ace pressure tube along with hydrochloric acid (4 mL, 12 M). The tube was sealed and heated to 150 °C (oil bath) for 40 h. It was then cooled to room temperature and carefully opened (Hood!), charcoal was added, and the resulting mixture was filtered through a pad of Celite. The Celite pad was washed with water. Removal of the water under reduced pressure gave a white solid (210 mg, yield: 81%). ^{1}H NMR (D_2O) δ 1.84−2.62 (m, 5H), 0.73−0.89 (m, 2H). ^{13}C NMR δ 179.5, 59.4, 41.2, 35.4, 16.7. HR-FAB-MS (M + H + gly − $2H_2O$; obtained in a glycerol matrix) calcd for $C_9H_{17}BNO_5$ 230.1201, found 230.1202

Acknowledgment. The authors wish to thank the U.S. Department of Energy and the Robert H. Cole Foundation for support of this research.

JO048824C