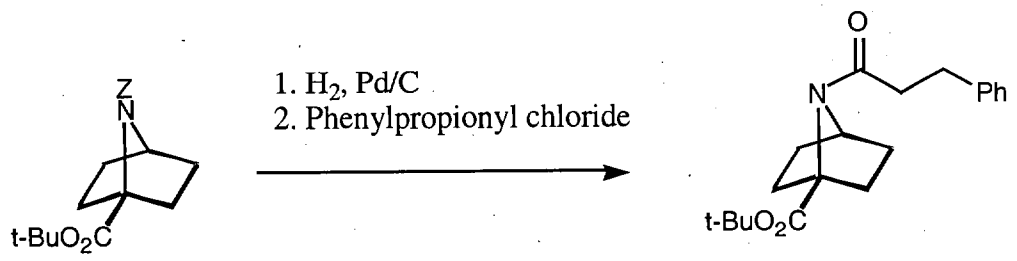
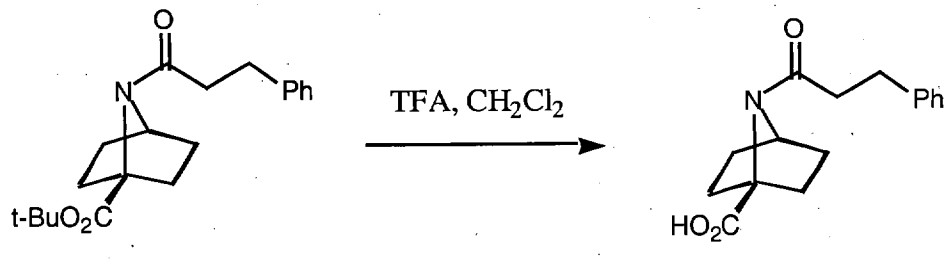
Preparation of (R)-N-(N-(3-Phenylpropionyl)-9-azabicyclo[2.2.1]heptane-1-carboxylboroarginine α-pinenediol ester (**8**)



4 **a**

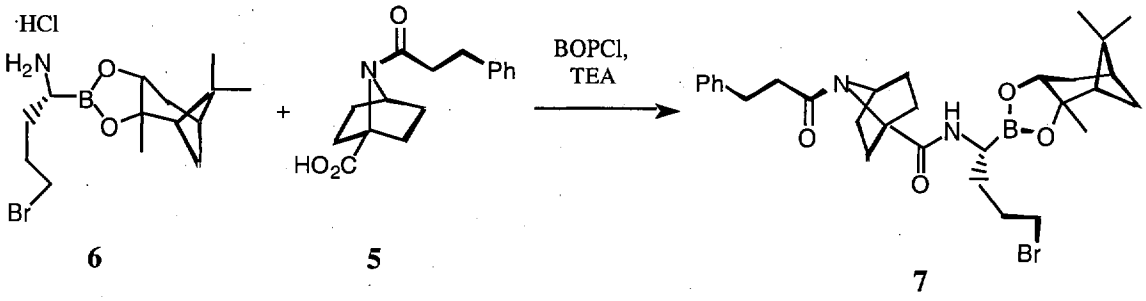
t-Butyl N-(3-phenylpropionyl)-7-azabicyclo[2.2.1]heptane-1-carboxylate (a): A solution of t-butyl N-(carbobenzyloxy)-9-azabicyclo[2.2.1]heptane-1-carboxylate (0.96 g, 2.9 mmol) in methanol (30 mL) was hydrogenated over 10% Pd/C (one atmosphere, 20° C) for 90 minutes. After filtration (celite) and solvent evaporation the resulting light yellow oil (0.56 g, 100% yield) was dissolved in anhydrous ether (30 mL) and N-methylmorpholine (0.35 g, 3.5 mmol) was added. The solution was cooled in an ice bath and treated with 3-phenylpropionyl chloride (0.59 g, 3.5 mmol) dropwise over 5 minutes. The mixture stirred an additional 30 minutes and was then washed with 1N HCl (20 mL) and water (20 mL). The mixture was dried ($MgSO_4$) and evaporated in vacuo. The crude oil was chromatographed on a silica gel column (100 g) eluted with a gradient of 15% to 20% to 25% ethyl acetate in hexanes. The resulting pure, viscous oil weighed 0.80 g (84%). ^{1}H-NMR ($CDCl_3$); δ 7.30–7.13 (m, 5H), 4.16 (t, 1H, J = 4.4 Hz), 2.95 (t, 2H, J = 9.3 Hz), 2.58 (t, 2H, J = 9.3 Hz), 2.13 (m, 2H), 1.58 (m, 6H), 1.55 (s, 9H). ^{13}C-NMR ($CDCl_3$);δ 172.87, 169.71, 141.31, 128.49, 128.40, 126.10, 80.98, 67.99, 59.07, 36.25, 32 .47, 31.28, 30.31, 27.92. IR (Neat); 3026, 1730, 1664 cm^{-1}. HRMS (ESI) calculated for $C_{20}H_{27}NO_3$ 330.206919, found 330.206617.



a **5**

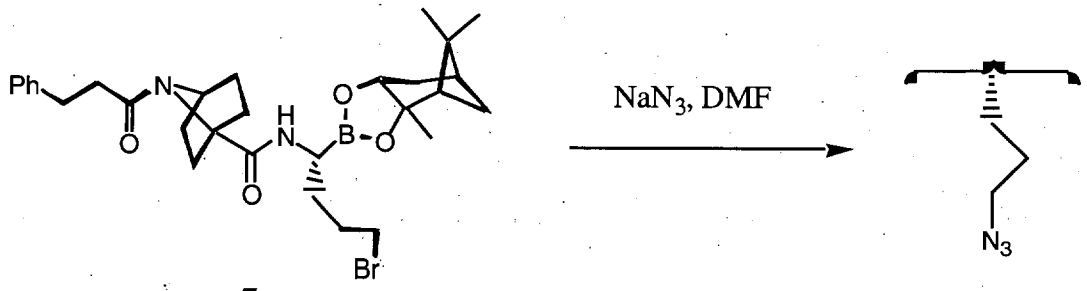
N-(3-Phenylpropionyl)-7-azabicyclo[2.2.1]heptane-1-carboxylic acid (5): A solution of the ester **a** (0.75 g, 2.3 mmol) in trifluoroacetic acid (4 mL) and dichloromethane (10

mL) was stirred for 2.5 h then evaporated in vacuo. The residue was dissolved in toluene (5 mL), evaporated in vacuo and the process was repeated twice. The thick oily residue (0.62 g, 100%) crystallized from 30% ethyl acetate in hexanes. M.p. 98-99° C. ^{1}H-NMR ($CDCl_3$); δ 7.34–7.16 (m, 5H), 4.22 (bs, 1H), 3.00 (t, 1H, J = 7.3 Hz), 2.74 (t, 2H, J = 7.3 Hz), 2.13-2.01 (m, 4H), 1.52-1.47 (m, 4H). ^{13}C-NMR ($CDCl_3$); δ 171.79, 171.00, 140.09, 128.69, 128.44, 126.64, 71.86, 60.29, 36.69, 35.00, 31.40, 28.30. IR (KBr); 2956, 1736, 1716, 1662 cm^{-1}. HRMS (ESI) calculated for $C_{16}H_{19}NO_3$ 274.144319, found 274.144838.



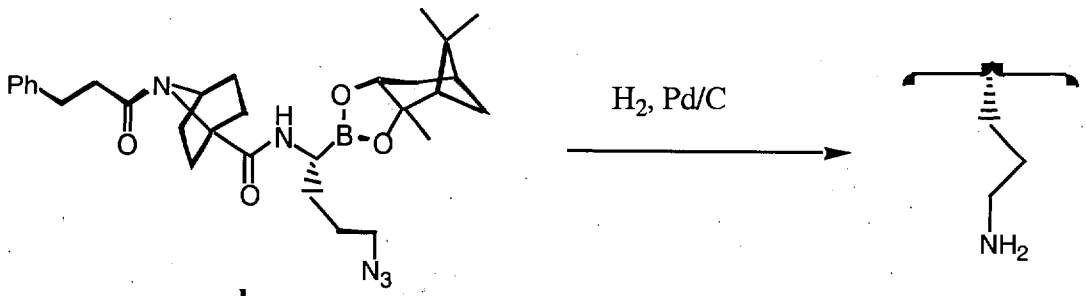
6 **5** **7**

(R)-1-(N-(3-Phenylpropionyl)-7-azabicyclo[2.2.1]heptane-1-carboxamidyl)-4-bromobutyl-1-boronic acid pinenediol ester (7): A solution of the acid **5** (100 mg, 0.37 mmol) and triethylamine (42 mg, 0.41 mmol) in dimethylformamide (3 mL) under a nitrogen atmosphere was cooled to 0° C and treated with BOPCl (104 mg, 0.41 mmol). After 30 minutes the amine **6** (268 mg, 0.74 mmol) and triethylamine (126 mg, 1.2 mmol) were added and the mixture warmed to 20° C over 1.5 h then stirred for 18 h. The mixture was diluted with ethyl acetate (30 mL), washed with 1N HCl (10 mL), water (10 mL), 1N NaOH (2 X 10 mL) and water (10 mL). The organic layer was dried ($MgSO_4$) and evaporated to leave a colorless gum (82 mg, 38%). ^{1}H-NMR ($CDCl_3$); δ 7.29-7.18 (m, 5H), 4.27-4.20 (m, 2H), 3.99 (dd, 1H, J = 9.2 Hz, J = 5.1 Hz), 3.58 (t, 1H, J = 6.6 Hz), 3.29 (bs, 1H), 2.96-2.88 (m, 3H) 2.65-2.58 (m, 2H), 2.52-1.37 (m, 16H), 1.31 (s, 3H), 1.27 (s, 3H), 0.93 (s, 3H), 0.84 (s, 2H). ^{13}C-NMR ($CDCl_3$); δ 141.30, 141.00, 128.44, 126.78, 126.13, 69.21, 60.07, 54.01, 51.86, 45.22, 40.54, 39.88, 38.97, 38.19, 37.01, 36.15, 34.12, 31.30, 30.58, 29.56, 29.30, 28.88, 28.65, 28.01, 27.82, 27.25, 26.49, 24.10. IR (CH_2Cl_2 film) 3378.0, 2956.0, 2922.0, 1816.0 1662.0. LRMS (ESI); 609 (M + 23 (Na^+)).



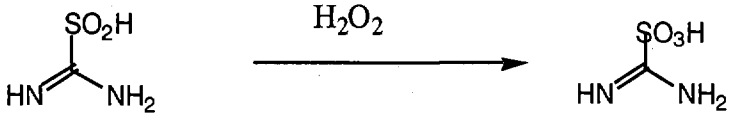
7 **b**

(R)-1-(N-(3-Phenylpropionyl)-7-azabicyclo[2.2.1]heptane-1-carboxamidyl)-4-azidobutyl-1-boronic acid pinenediol ester (b): A mixture of the bromide **7** (80 mg, 0.14 mmol) and sodium azide (18 mg, 0.28 mmol) in dimethylformamide (1.5 mL) was heated to 100° C for 5 h. After cooling to 20° C the mixture was diluted with ethyl acetate (10 mL), washed with water (4 X 5 mL), dried ($MgSO_4$) and evaporated in vacuo to leave the azide **c** as a light tan gum (70 mg, 91%). ^{1}H-NMR ($CDCl_3$); δ 7.30–7.17 (m, 5H), 4.30-4.28 (m, 2H), 3.95 (t, 1H, J = 8.4 Hz), 3.28 (m, 2H), 2.90 (m, 2H), 2.62 (t, 2H, J = 8.1 Hz), 2.50-1.32 (m, 16H), 1.28 (s, 3H), 1.25 (s, 3H), 0.92 (s, 3H), 0.83 (s, 2H). ^{13}C-NMR ($CDCl_3$); δ 141.00, 139.90, 128.50, 128.43, 126.28, 126.14, 69.06, 60.07, 59.36, 53.98, 51.87, 51.52, 40.52, 39.87, 38.90, 38.12, 36.99, 36.17, 34.11, 31.29, 31.00, 29.62, 28.71, 28.05, 27.25, 25.76. IR (Neat); 2094 cm^{-1}. LRMS (ESI); 548 (M + 1).



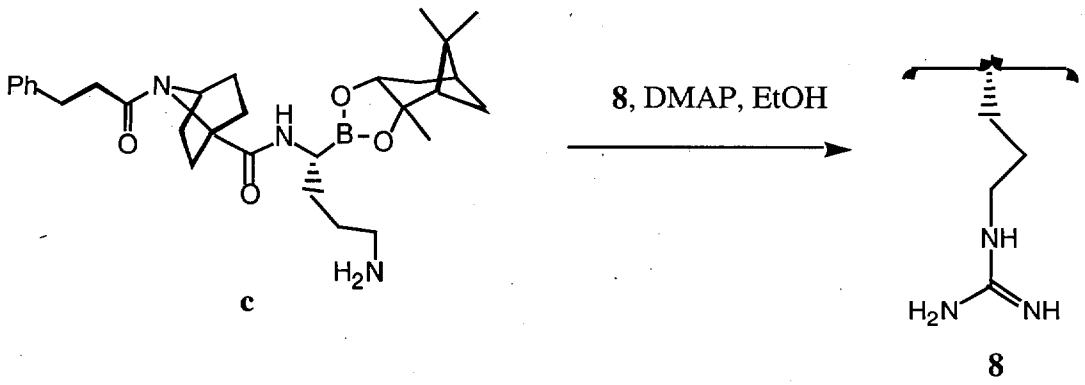
b **c**

(R)-1-(N-(3-Phenylpropionyl)-7-azabicyclo[2.2.1]heptane-1-carboxamidyl)-4-aminobutyl-1-boronic acid pinenediol ester (c): A solution of the azide **b** (62 mg, 0.11mmol) in ethyl acetate (3 mL) was hydrogenated over 10% Pd/C (1 atm., 20° C) for 16 h. After filtration of the catalyst and evaporation of the solvents the residue was redissolved in dichloromethane (3 mL), treated with anhydrous, ethereal hydrogen chloride (1.0 M, 0.10 mL) and evaporated in vacuo. The thick gum was dissolved in ethyl acetate (2 mL) and hexane (10 mL) was added dropwise to the mixture. The powdery precipitate was isolated by decanting the solvents, swirling with hexane (2 mL), decanting and drying in vacuo (21 mg, 31%). ^{1}H-NMR ($CDCl_3$); δ 8.11 (bs, 1H), 7.25-7.07 (m, 5H), 4.14 (m, 2H), 2.97-1.40 (m, 25H), 1.30 (s, 3H), 1.19 (s, 3H), 0.77 (bs, 5H). ^{13}C-NMR ($CDCl_3$); δ 141.00, 140.67, 128.58, 126.30, 83.22, 76.16, 65.51, 59.73, 52.26, 40.10, 39.81, 38.12, 36.72, 36.47, 33.33, 32.87, 31.57, 31.41, 30.20, 29.32, 27.55, 26.67, 25.51, 24.20, 22.64, 14.11. (ESI); 522 (M + 1).



d

Iminoaminomethanesulfonic acid (d): A suspension of iminoaminomethanesulfinic acid (5.0 g, 46 mmol) in water (10 mL) was stirred rapidly and cooled to 5° C. The mixture was treated with 30% hydrogen peroxide solution (5.2 mL, 51 mmol) dropwise over five minutes, warmed to 20° C over 2 h. and allowed to stir for an additional 20 h. After filtration to remove unreacted starting material the filtrate was evaporated in vacuo to near dryness and the residue was triturated with acetic acid (10 mL). The resulting white, crystalline solid was filtered, washed (acetic acid, cold methanol) and dried to leave 2.3 g (40%). M.p. 113-114° C (dec.).



c **8**

(R)-1-(N-(3-Phenylpropionyl)-7-azabicyclo[2.2.1]heptane-1-carboxamidyl)-4-guanidinobutyl-1-boronic acid pinenediol ester (8): A solution of amine **c** (21 mg, 40 μmol), iminoaminomethanesulfonic acid **d** (15.0 mg, 120 μmol) and dimethylaminopyridine (15.0 mg, 120 μmol) in absolute ethanol (1 mL) was heated to 80° C for 3 h. After evaporation of the solvents the product was purified by size exclusion chromatography eluted with methanol to provide 5.2 mg (23%) of pure **8**. ^{1}H-NMR (CD_3OD); δ 7.30-7.11 (m, 5H), 4.36 (bs, 1H), 4.18 (d, 1H, J = 9.2Hz), 4.04 (q, 1H, J = 7.0 Hz), 2.88 (t, 2H, J = 7.0 Hz), 2.67 (t, 2H, J = 7.0 Hz), 2.55 (m, 1H), 2.33 (m, 1H), 2.18-1.45 (m, 16H), 1.37 (s, 3H), 1.29 (s, 3H), 0.85 (bs, 5H). HRMS (ESI) calculated for $C_{31}H_{46}BN_5O_4$ 564.371241; found 564.372111.