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Material. Thin layer chromatography (TLC) was performed on E. Merck silica gel 60 F_{254} glass plates. Compounds with *tert*-butyloxycarbonylamino groups or free amino groups were visualized on TLC plates by first dipping the plates in a ninhydrin solution (0.1% ninhydrin in 95% *n*-butanol, 4.5% water, 0.5% glacial acetic acid) and then heating the plates until color evolved. Column chromatography was performed on E. Merck silica gel 60 (230-240 mesh ASTM) under positive nitrogen pressure. Melting points were determined visually in an open capillary on a Thomas Hoover capillary melting point apparatus. ¹H-NMR and ¹¹B-NMR spectra were performed on a Bruker AC-250 (250 MHz) NMR and on a Bruker AC-200 (200 MHz) NMR, respectively; chemical shifts were expressed in parts per million (ppm) and referenced to either CDCl₃ or CD₃OD. Mass spectrometry (ZAB-E Cl⁺/MS) was conducted by John Dykins and Rakesh K. Kohli of the Mass Spectrometry Center, University of Pennsylvania. Small molecule X-ray crystallographic studies were conducted by Patrick Carroll of the X-ray Diffraction Facility, University of Pennsylvania. 2(S)-N -(tert-butyloxycarbonyl)-glutamic acid *tert*-butyl ester (1) was purchased from Sigma. Triethylamine and DMSO (dimethyl sulfoxide) were purchased from Fisher. All other reagents were purchased from Aldrich.

2(S)-*N*-(*tert*-butyloxycarbonyl)-5-hydroxypentanoic acid, *tert*-butyl ester (2). To a -5°C solution of 2.339 gm (7.71 mmol) of 2(S)-*N*-(*tert*-butyloxycarbonyl)-glutamic acid *tert*-butyl ester in 70 mL of THF was added 7.80 mL (77.1mmol) triethylamine and 7.37 mL (77.1 mmol) ethyl chloroformate. The mixture was stirred at -5°C for ten minutes. The precipitant triethylamine salt was quickly removed by filtration. The filtrate was added to a suspension of sodium borohydride in 10 mL of water and stirred at room temperature overnight. The resulting crude product was purified by column chromatography on silica gel (with 2:1 hexane:ethyl acetate as an eluent).

Following concentration *in vacuo*, 1.010 gm (45%) of product as a colorless oil was obtained. In subsequent preparations, **2** was also obtained as a crystalline solid. TLC (1:1 hexane:ethyl acetate) indicated a single spot at R_f 0.40; ¹H-NMR (CDCl₃) δ 5.10 (d, 1H), 4.20 (m, 1H), 3.65 (t, 2H), 1.9-1.55 (m, 5H), 1.45 (s, 9H), 1.40 (s, 9H).

2(S)-N -(tert-butyloxycarbonyl)-5-oxopentanoic acid, tert-butyl ester (3). To a solution of 0.756 mL (8.67 mmol) of oxalyl chloride in 20 mL CH₂Cl₂ at -78°C was added 1.02 mL (14.4 mmol) of DMSO. The solution was stirred at -78°C for 5 min. A solution of 2.094 gm (7.22 mmol) of 2 dissolved in CH₂Cl₂ was prepared, added by canula to the pre-formed Swern reactant, and stirred at -78°C for 15 min. The Swern oxidation was completed by the addition of 5.03 mL (36.1 mmol) of triethylamine. The mixture was stirred for 5 min at -78°C and then warmed to room temperature. The CH₂Cl₂ was evaporated *in vacuo*. The crude material was taken up in THF. The precipitant triethylamine salt was removed by filtration. The material was purified by column chromatography on silica gel (with 6:1 hexane:ethyl acetate as an eluent). As indicated by TLC (3:1 hexane:ethyl acetate) a single spot at R_f 0.26 was obtained following concentration in vacuo. ¹H-NMR (CDCl₃) revealed a strong tendency for **3** to possibly undergo an intramolecular enamine-type cyclization. In subsequent preparations crude compound 3 was used directly for the synthesis of 4, eventhough the putative, intramolecular enamine-type cyclization seemed not to affect the following Wittig reaction.

2(S)-*N*-(*tert*-butyloxycarbonyl)-hex-5-enoic acid, *tert*-butyl ester (4). The Wittig salt triphenylphosphonium methylide was prepared by the addition of 2.244 gm (20.0 mmol) of potassium *tert*-butoxide to a partially dissolved solution of 7.15 gm (20.0 mmol) methyltriphenylphosphonium bromide in 100 mL of THF at 0°C. The mixture was stirred at 0°C for 10 min and then at room temperature for 90 min. The

mixture turned yellow and was cooled to -78°C. The aldehyde **3**, 1.151gm (4.01 mmol) dissolved in THF was added directly to the triphenyl phosphonium methylide solution. The Wittig reaction was stirred and allowed to proceed for 15 min at -78°C and then overnight at room temperature. The olefin **4** was purified by two applications of column chromatography on silica gel (with 10:1 hexane:ethyl acetate as an eluent). Following concentration *in vacuo*, 450 mg (22% over two steps) of product as a colorless oil was obtained. TLC (3:1 hexane:ethyl acetate) indicated a single spot at R_f 0.60; ¹H-NMR (CDCl₃) δ 5.80 (m, 1H), 5.00 (m, 3H), 4.15 (m, 1H), 2.05 (m, 2H), 1.85 (m, 1H), 1.65 (m, 1H), 1.45 (s, 9H), 1.40 (s, 9H).

2(S)-N-(tert-butyloxycarbonyl)-6-[(1S,2S,3R,5S)-(+)-pinanedioxaboranyl]-hexanoic acid, tert-butyl ester (5). To a 0°C chilled, stirred solution of 6.05 mL (6.05 mmol) of 1M BH3. THF in 60 mL THF was added 345 mg (1.21 mmol) of olefin 4. The reaction mixture was stirred for 2 h at room temperature. The reaction was monitored by TLC (3:1 hexane:ethyl acetate) for the disappearance of the olefin. Excess unreacted borane was quenched by the slow addition of methanol until gaseous evolution as indicated by bubbling ceased. The solvent was evaporated in vacuo. The crude material was taken up in CH₂Cl₂. Excess (1S,2S,3R,5S)-(+)-pinanediol (1 gm, 5.87 mmol) was added to the solution of crude material in CH₂Cl₂. Esterification with (+)-pinanediol was allowed to proceed at room temperature over a period of 2 h. Compound 5 was purified by column chromatography on silica gel (with 25:1 hexane:ethyl acetate as an eluent). The product as an oil was obtained in 31% yield (174 mg) following concentration in vacuo. TLC (10:1 hexane:ethyl acetate) indicated a single spot at R_f 0.15; ¹H-NMR (CDCl₃) δ 4.95 (d, 1H), 4.20 (d, 1H), 4.1 (m, 1H), 2.40-2.15 (m, 2H), 2.05 (m, 1H), 1.95-1.65 (m, 4H), 1.60 (s, 3H), 1.42 (2s, 18H), 1.35 (apparent s, 4H), 1.25 (s, 3H), 1.05 (d, 1H), 0.80 (m, 5H); ZAB-E Cl⁺/MS calculated for C₂₅H₄₄NO₆B + H: 466.33; found: 466.25.

2(S)-amino-6-boronohexanoic acid, hydrochloride salt (6). To a -78°C chilled, stirred solution of 174 mg of 5 in CH₂Cl₂ was slowly added 1.49 mL of 1M BCl₃ in CH₂Cl₂ (1.49 mmol). The reaction mixture was stirred for 15 min at -78°C and then for 30 min at 0°C. The solvent CH₂Cl₂ with excess BCl₃ were evaporated by allowing a flow of nitrogen gas to pass over the mixture. Continued drying with N₂ gas afforded crude product as an orange solid. Addition of acetonitrile removed most of the color from the crude material. Vacuum filtration followed by several washings with acetonitrile gave a pale pink-colored solid which upon air-drying had a faint discoloration. Acetone was added to the faint-pink colored solid . Vacuum filtration followed by several washings with acetone removed all discoloration from the solid to afford 33 mg (42%) of pure product as a white solid. TLC (80:10:10 *n*-butanol:acetic acid:water) indicated a single spot at R_f 0.15; mp 148-150 °C, dec. >150°; ¹H-NMR (CD₃OD) δ 3.95 (t, 1H), 1.90 (m, 2H), 1.45 (m, 4H), 0.82 (m, 2H); ¹¹B NMR (CD₃OD) δ 18.86 (s).

Crystallization and X-ray crystal structure determination of 2(S)-amino-6boronohexanoic acid, hydrochloride salt (6). In a 3.7 mL screw-cap glass vial, 11 mg of compound 6 were dissolved in 0.200 mL of ethanol. The screw-cap on the glass vial was not tightened in order to allow for the slow evaporation of ethanol. The vial was placed in a fume hood for two days. Upon inspection, all solvent had evaporated; and 6 had crystallized as needles and plates. A section of one of the plates proved suitable for crystallographic studies. Larger crystals were grown by the slow evaporation of 6 (11 mg) dissolved in 0.200 ml of water over a period of five days.

2(S)-Amino-6-boronohexanoic acid, hydrochloride salt (6), $C_6H_{15}BNO_4Cl$, crystallizes in the orthorhombic space group $P2_12_12_1$ (systematic absences h00: l=odd;

0k0: k=odd; 001: l=odd) with a=9.914(2)Å, b=20.213(2)Å, c=5.1801(6)Å, V=1038.0(2)Å³, Z=4 and d_{calc}=1.353 g/cm³. X-ray intensity data were collected on an Rigaku R-AXIS IIc area detector employing graphite-monochromated Mo-K_{α} radiation (λ =0.71069 Å) at a temperature of 295°K. Indexing was performed from a series of 1° oscillation images with exposures of 30 minutes per frame. A hemispere of data was collected using 8° oscillation angles with exposures of 60 minutes per frame and a crystal-to-detector distance of 82 mm. Oscillation images were processed using bioteX¹, producing a listing of unaveraged F² and σ (F²) values which were then passed to the teXsan² program package for further processing and structure solution on a Silicon Graphics Indigo R4000 computer. A total of 4539 reflections were measured over the ranges: $5.76 \leq 20 \leq 50.70^\circ$, $-10 \leq h \leq 11$, $-21 \leq k \leq 24$, $-6 \leq l \leq 6$ yielding 1838 unique reflections (R_{int} = 0.0590). The intensity data were corrected for Lorentz and polarization effects but not for absorption.

The structure was solved by direct methods (SIR92³). Refinement was by fullmatrix least squares based on F² using SHELXL-93⁴. All reflections were used during refinement (F²'s that were experimentally negative were replaced by F² = 0). The weighting scheme used was w=1/[$\sigma^2(F_0^2)$ + 0.0537P² + 2.4010P] where P = (F₀² + 2F_c²)/3. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined according to a "riding" model in which the positions of the hydrogen atoms are reidealized before each least squares cycle by applying the co-ordinate shifts of the atom to which each hydrogen is attached. Refinement converged to R₁=0.0768 and wR₂=0.1627 for 1580 reflections for which F > 4 σ (F) and R₁=0.0905, wR₂=0.1756 and GOF = 1.106 for all 1838 unique, non-zero reflections and 122 variables⁵. The maximum Δ/σ in the final cycle of least squares was 0.002 and the two most prominent peaks in the final difference Fourier were +0.351 and -0.514 e/Å³.

Table 1. lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Table 2. Anisotropic thermal parameters are in Table 3. Tables 4. and 5. list bond distances and bond angles. Figure 1. is an ORTEP⁶ representation of the molecule with 30% probability thermal ellipsoids displayed.





Formula:	C ₆ H ₁₅ BNO ₄ Cl		
Formula weight:	211.45		
Crystal class:	Orthorhombic		
Space group:	P2 ₁ 2 ₁ 2 ₁ (#19)		
Z	4		
Cell constants:			
a	9.914(2)Å		
b	20.213(2)Å		
с	5.1801(6)Å		
V	1038.0(2)Å ³		
μ	3.52 cm ⁻¹		
crystal size, mm	0.15 x 0.05 x 0.005		
D _{calc}	1.353 g/cm ³		
F(000)	448		
Radiation:	Mo-K _α (λ=0.71069Å)		
2θ range	5.76–50.70°		
hkl collected:	-10≤ h ≤11; -21≤ k ≤24; -6≤ l ≤6		
No. reflections measured:	4539		
No. unique reflections:	1838 (R _{int} =0.0590)		
No. observed reflections	1580 (F>4σ)		
No. reflections used in refinement	1838		
No. parameters	122		
R indices (F>4 σ)	$R_1 = 0.0768$		
	wR ₂ =0.1627		
R indices (all data)	R1=0.0905		
	wR2=0.1756		
GOF:	1.106		
Final Difference Peaks, e/Å ³	+0.351, -0.514		

Table 1. Summary of Structure Determination of Compound 9020

				
Atom	x	у	Z	U _{eq} , Å ²
				
Cl	0.5824(2)	0.58210(8)	0.7367(3)	0.0481(4)
O1	0.5795(5)	0.8844(2)	0.4197(8)	0.0503(11)
H1	0.614(3)	0.898(3)	0.286(8)	0.075
O2	0.4088(5)	0.9503(2)	0.2973(7)	0.0462(11)
O3	0.3464(5)	0.5523(2)	1.3516(8)	0.0451(11)
H3	0.394(6)	0.5711(6)	1.457(8)	0.068
O4	0.2110(5)	0.5741(2)	0.9914(8)	0.0428(10)
H4	0.206(6)	0.5337(4)	1.002(9)	0.064
N1	0.2768(5)	0.9342(2)	0.7515(9)	0.0377(11)
H1a	0.238(3)	0.923(2)	0.900(5)	0.056
H1b	0.218(2)	0.929(2)	0.623(5)	0.056
H1c	0.3019(8)	0.9765(3)	0.759(9)	0.056
C1	0.4592(6)	0.9135(3)	0.4522(10)	0.0351(13)
C2	0.3974(6)	0.8919(2)	0.7051(10)	0.0336(13)
H2	0.4628(6)	0.8988(2)	0.8444(10)	0.045
C3	0.3579(7)	0.8183(2)	0.6964(10)	0.043(2)
H3a	0.2711(7)	0.8142(2)	0.6113(10)	0.057
H3b	0.4237(7)	0.7946(2)	0.5930(10)	0.057
C4	0.3491(8)	0.7856(3)	0.9608(11)	0.043(2)
H4a	0.2794(8)	0.8072(3)	1.0617(11)	0.058
H4b	0.4342(8)	0.7912(3)	1.0506(11)	0.058
	Atom Cl O1 H1 O2 O3 H3 O4 H4 N1 H1a H1b H1c C1 C1 C1 C1 C1 H1a H1b H1c C1 H1a H1b H1c C1 C1 C1 C1 C1 H1a H1b H1c C1 C1 H1a H1b H1a H1b H1a H1b H1a H1b H1c C1 C1 H2 C3 H3a H3a H3a H3b C4 H3a H3b C4 H3a H3b C4 H3a H3b	Atom x Cl 0.5824(2) O1 0.5795(5) H1 0.614(3) O2 0.4088(5) O3 0.3464(5) H3 0.394(6) O4 0.2110(5) H4 0.206(6) N1 0.2768(5) H1a 0.238(3) H1b 0.218(2) H1c 0.3019(8) C1 0.4592(6) C2 0.3974(6) H2 0.4628(6) C3 0.2711(7) H3a 0.2711(7) H3b 0.4237(7) C4 0.3491(8) H4a 0.2794(8)	AtomxyCl0.5824(2)0.58210(8)O10.5795(5)0.8844(2)H10.614(3)0.898(3)O20.4088(5)0.9503(2)O30.3464(5)0.5523(2)H30.394(6)0.5711(6)O40.2110(5)0.5741(2)H40.206(6)0.5337(4)N10.2768(5)0.9342(2)H1a0.238(3)0.923(2)H1b0.218(2)0.929(2)H1c0.3019(8)0.9765(3)C10.4592(6)0.8919(2)H20.4628(6)0.8988(2)C30.3579(7)0.8183(2)H3a0.2711(7)0.8142(2)H3b0.4237(7)0.7946(2)C40.3491(8)0.7856(3)H4a0.2794(8)0.8072(3)	AtomxyzCl0.5824(2)0.58210(8)0.7367(3)O10.5795(5)0.8844(2)0.4197(8)H10.614(3)0.898(3)0.286(8)O20.4088(5)0.9503(2)0.2973(7)O30.3464(5)0.5523(2)1.3516(8)H30.394(6)0.5711(6)1.457(8)O40.2110(5)0.5741(2)0.9914(8)H40.206(6)0.5337(4)1.002(9)N10.2768(5)0.9342(2)0.7515(9)H1a0.238(3)0.923(2)0.900(5)H1b0.218(2)0.929(2)0.623(5)H1c0.3019(8)0.9765(3)0.759(9)Cl0.4592(6)0.9135(3)0.4522(10)C20.3974(6)0.8919(2)0.7051(10)H20.4628(6)0.8988(2)0.8444(10)C30.3579(7)0.8183(2)0.6964(10)H3a0.2711(7)0.8142(2)0.6113(10)H3b0.4237(7)0.7946(2)0.5930(10)C40.3491(8)0.7856(3)0.9608(11)H4a0.2794(8)0.8072(3)1.0617(11)H4b0.4342(8)0.7912(3)1.0506(11)

Table 2. Refined Positional Parameters for Compound 9020

 			·	-
B1	0.2987(7)	0.5974(3)	1.1782(12)	0.036(2)
H6b	0.4231(7)	0.6784(3)	1.2520(11)	0.057
H6a	0.2722(7)	0.6932(3)	1.3179(11)	0.057
C6	0.3312(7)	0.6732(3)	1.1906(11)	0.043(2)
H5b	0.3767(8)	0.6922(3)	0.8120(13)	0.065
H5a	0.2255(8)	0.7068(3)	0.8771(13)	0.065
C5	0.3171(8)	0.7117(3)	0.9396(13)	0.049(2)

 $U_{eq} = \frac{1}{3} [U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*cos\gamma + 2U_{13}aa^*cc^*cos\beta + 2U_{23}bb^*cc^*cos\alpha]$

						·
Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
C1	0.0505(9)	0.0562(8)	0.0377(7)	-0.0026(8)	-0.0056(8)	0.0058(7)
O1	0.044(3)	0.062(3)	0.044(3)	0.013(2)	0.013(2)	0.015(2)
O2	0.053(3)	0.048(2)	0.037(2)	0.010(2)	0.007(2)	0.002(2)
O3	0.053(3)	0.035(2)	0.047(3)	0.008(2)	-0.013(2)	-0.003(2)
O4	0.055(3)	0.033(2)	0.041(2)	-0.001(2)	-0.012(2)	-0.005(2)
N1	0.044(3)	0.037(2)	0.032(2)	0.003(2)	0.006(2)	-0.003(2)
C1	0.046(3)	0.033(3)	0.027(3)	0.000(3)	0.003(2)	-0.005(3)
C2	0.044(3)	0.032(2)	0.025(3)	0.000(2)	0.004(3)	0.004(2)
C3	0.070(4)	0.028(3)	0.030(3)	0.004(2)	0.004(3)	-0.003(3)
C4	0.072(4)	0.027(3)	0.032(3)	0.004(2)	0.001(3)	-0.002(3)
C5	0.074(5)	0.034(3)	0.038(3)	0.006(3)	-0.007(3)	-0.004(3)
C6	0.057(4)	0.033(3)	0.040(4)	0.003(3)	-0.004(3)	-0.007(3)
B1	0.047(4)	0.029(3)	0.033(3)	0.002(3)	-0.003(3)	-0.001(3)

Table 3. Refined Thermal Parameters (U's) for Compound 9020

The form of the anisotropic displacement parameter is: $exp[-2\pi^{2}(a^{*2}U_{11}h^{2}+b^{*2}U_{22}k^{2}+c^{*2}U_{33}l^{2}+2b^{*}c^{*}U_{23}kl+2a^{*}c^{*}U_{13}hl+2a^{*}b^{*}U_{12}hk)].$

	Table 4. DU	nu Distant	es in comp	ounu 9020,	A
O1-C1	1.342(7)	O2-C1	1.203(6)	O3-B1	1.363(7)
O4-B1	1.383(8)	N1-C2	1.491(7)	C1-C2	1.511(7)
C2-C3	1.539(7)	C3-C4	1.523(7)	C4-C5	1.530(7)
C5-C6	1.522(8)	C6-B1	1.568(8)		

Table 4. Bond Distances in Compound 9020, Å

Table 5. Bond Angles in Compound 9020, °

O2-C1-O1	123.9(5)	O2-C1-C2	126.1(5)	O1-C1-C2	110.0(5)
N1-C2-C1	107.4(4)	N1-C2-C3	110.8(5)	C1-C2-C3	111.0(4)
C4-C3-C2	114.1(5)	C3-C4-C5	111.7(5)	C6-C5-C4	114.8(5)
C5-C6-B1	116.5(5)	O3-B1-O4	116.9(5)	O3-B1-C6	123.7(5)
O4-B1-C6	119.3(5)				

References

1. <u>bioteX</u>: A suite of Programs for the Collection, Reduction and Interpretation of Imaging Plate Data, Molecular Structure Corporation (1995).

2. <u>teXsan</u>: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

3. <u>SIR92</u>: Altomare, A., Burla, M.C., Camalli, M., Cascarano, M., Giacovazzo, C., Guagliardi, A., Polidoro, G. (1994). J. Appl. Cryst., 27, 435.

4. <u>SHELXL-93</u>: Program for the Refinement of Crystal Structures, Sheldrick, G.M. (1993), University of Göttingen, Germany.

5. $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$

 $wR_2 = \{ \sum w \ (F_o^2 - F_c^2)^2 \ / \ \sum w (F_o^2)^2 \}^{1/2}$

GOF = { $\sum w (F_o^2 - F_c^2)^2 / (n - p)$ }^{1/2} where n = the number of reflections and p = the number of parameters refined.

6. "ORTEP-II: A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations". C.K. Johnson (1976) ORNL-5138.