

## A Convenient Reduction of Amino Acids and Their Derivatives

Marc J. McKennon and A. I. Meyers\*

Department of Chemistry, Colorado State University,  
Fort Collins, Colorado 80523

Karlheinz Drauz\*<sup>1</sup> and Michael Schwarm

Degussa AG, ZN Wolfgang, Abt. IC-FEO-A, Postfach 1345,  
D-6450 Hanau 1, Germany

Received November 13, 1992

The formation of chiral amino alcohols by reduction of amino acids has been the subject of considerable effort due to their importance in asymmetric synthesis,<sup>2</sup> peptide and pharmaceutical chemistry,<sup>3</sup> resolution of racemic mixtures,<sup>4</sup> synthesis of insecticidal compounds,<sup>5</sup> and others. From the earliest reports by Karrer in 1921, amino alcohols were prepared by reduction of the corresponding amino acid esters with sodium in ethanol.<sup>6a</sup> Subsequently, lithium aluminum hydride<sup>6b</sup> and sodium borohydride<sup>6c</sup> were employed and furthermore, free amino acids were shown to be reduced directly by sodium bis(2-methoxyethoxy)aluminum hydride,<sup>7a</sup> the borane-dimethyl sulfide complex activated by boron trifluoride-etherate,<sup>7b-d</sup> lithium aluminum hydride,<sup>7e</sup> lithium borohydride with trimethylchlorosilane,<sup>7f</sup> sodium borohydride-trimethylchlorosilane,<sup>7g</sup> or boron trifluoride-etherate.<sup>7h</sup> Very recently, while this manuscript was being prepared, a report appeared describing an efficient reduction of amino acids and derivatives using sodium borohydride and sulfuric

acid.<sup>7i</sup> One of the examples briefly mentioned the NaBH<sub>4</sub>-I<sub>2</sub> system, a procedure which we had been already utilizing and now wish to describe in detail. It had been shown some 15 years ago that most of the above hydride reductions proceed without any detectable racemization.<sup>8</sup> The lithium aluminum hydride procedure is one of the most commonly used techniques but on large scale (~1 kg) still suffers from the disadvantage of cost, inflammability, and, in certain cases, laborious isolation procedures resulting in widely varying yields. Therefore, a cheaper, safer, and simpler process was sought, especially when preparations on a larger scale are required.

### Reduction of Free $\alpha$ -Amino Acids

Recently, a study appeared<sup>9</sup> describing the reduction of various aliphatic, aromatic, and  $\alpha,\beta$ -unsaturated carboxylic acids to the corresponding alcohols using sodium borohydride and iodine in THF. We now report that this was found to be an excellent process for the direct reduction of amino acids. The reactions were routinely carried out on a 10-g scale while the reduction of phenylalanine has been successfully performed on a molar scale. Furthermore, this method proved to be convenient both from a safety and cost standpoint, while producing optically pure materials. Treatment of several amino acids with sodium borohydride-iodine in THF afforded the corresponding amino alcohols as crude products which were essentially colorless and in most cases pure enough by <sup>1</sup>H NMR to be of further synthetic utility (Table I). It is of note that reduction of asparagine and glutamine proved difficult owing to the high water solubility of the products.

In order to further evaluate the scope of the reaction, we studied the reduction of phenylalanine under various conditions. When gaseous chlorine was used as the activating agent instead of the iodine solution, the reaction proceeded in a similar fashion producing L-phenylalaninol in ~60% yield after crystallization. Activation of the borohydride with bromine in tetrahydrofuran proved unsuccessful, affording poor mass recovery and extensive decomposition. It is noted that a vigorous exotherm occurred upon addition of bromine to tetrahydrofuran at 25 °C. Lithium borohydride was also shown to be an equally suitable reducing agent. The reduction could also be carried out in dimethoxyethane (monoglyme, DME) while essentially no conversion was observed in methyl *tert*-butyl ether (MTBE). The poor solubility of the reactants in this solvent was probably responsible.

### Reduction of *N*-Acyl- $\alpha$ -amino Acids

Since the earlier report using NaBH<sub>4</sub>-I<sub>2</sub> indicated that carboxylic acids could be reduced to alcohols in the presence of ester groups,<sup>9</sup> we anticipated that the reduction of *N*-acylamino acids would lead to the formation of *N*-acylamino alcohols. Surprisingly, the *N*-acyl group was completely reduced affording *N*-alkylamino alcohols as the only products. A similar observation was made in the analogous NaBH<sub>4</sub>-H<sub>2</sub>SO<sub>4</sub> system.<sup>7i</sup> Decrease in temperature, time, and reducing agent resulted in lower yields of product and the *N*-acylamino alcohols were never observed. This was confirmed by a subsequent study of the NaBH<sub>4</sub>-

(1) Amino Acid Transformations. Part 10. For part 9, see: Drauz, K.; Kottenhahn, M.; Klenk, H. *J. Prakt. Chem.* 1992, 334, 214.

(2) (a) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis*; John Wiley & Sons: New York, 1987. (b) Nogradi, M. *Stereoselective Synthesis*; VCH: Weinheim, 1987. (c) Bolm, C. *Angew. Chem. Int. Ed. Engl.* 1991, 30, 542.

(3) (a) TenBrink, R. E. *J. Org. Chem.* 1987, 52, 418. (b) Nicolaidis, E. D.; Tinney, F. J.; Kaltenbronn, J. S.; Repine, J. T.; DeJohn, D. A.; Lunney, E. A.; Roark, W. H.; Marriott, J. G.; Davis, R. E.; Voigtman, R. E. *J. Med. Chem.* 1986, 29, 959. (c) Fincham, C. I.; Higginbottom, M.; Hill, D. R.; Horwell, D. C.; O'Toole, J. C.; Ratcliffe, G. S.; Rees, D. C.; Roberts, E. *J. Med. Chem.* 1992, 35, 1472. (d) Auvin-Guette, C.; Rebuffat, S.; Prigent, Y.; Bodo, B. *J. Am. Chem. Soc.* 1992, 114, 2170. (e) Iida, A.; Okuda, M.; Uesato, S.; Takaishi, Y.; Shingu, T.; Morita, M.; Fujita, T. *J. Chem. Soc. Perkin Trans 1* 1990, 3249. (f) Kashima, C.; Harada, K.; Fujioka, Y.; Maruyama, T.; Omote, Y. *J. Chem. Soc. Perkin Trans 1* 1988, 535. (g) Roemer, D.; Buescher, H. H.; Hill, R. C.; Pless, J.; Bauer, W.; Cardinaux, F.; Clossé, A.; Hauser, D.; Huguenin, R. *Nature* 1977, 268, 547. (h) Rubini, E.; Gilon, C.; Selinger, Z.; Chorev, M. *Tetrahedron* 1986, 42, 6039.

(4) (a) Horiuchi, F.; Matsui, M. *Agr. Biol. Chem.* 1973, 37, 1713. (b) Kawai, M.; Omori, Y.; Yamamura, H.; Butsugan, Y. *Tetrahedron Asym.* 1992, 3, 1019. (c) Sawayama, T.; Tsukamoto, M.; Sasagawa, T.; Naruto, S.; Matsumoto, J.; Uno, H. *Chem. Pharm. Bull.* 1989, 37, 1382. (d) Tsukamoto, M.; Sawayama, T.; Jpn. Kokai Tokkyo Koho JP 6130,572, Feb 12, 1986; *Chem. Abstr.* 1986, 105, 60525w.

(5) Wu, S.; Takeya, R.; Eto, M.; Tomizawa, C. *J. Pestic. Sci.* 1987, 12, 221.

(6) (a) Karrer, P.; Karrer, W.; Thomann, H.; Horlacher, E.; Mäder, W. *Helv. Chim. Acta* 1921, 4, 76. (b) Karrer, P.; Portmann, P.; Suter, M. *Helv. Chim. Acta* 1948, 31, 1617. (c) Seki, H.; Koga, K.; Matsuo, H.; Ohki, S.; Matsuo, I.; Yamada, S. *Chem. Pharm. Bull.* 1965, 13, 995.

(7) (a) Prasad, B.; Saund, A. K.; Bora, J. M.; Mathur, N. K. *Indian J. Chem.* 1974, 12, 290. (b) Lane, C. F.; U.S. Patent 3 935 280, Jan 27, 1976; *Chem. Abstr.* 1976, 84, 135101p. (c) Smith, G. A.; Gawley, R. E. *Org. Synth.* 1985, 63, 136. (d) Gage, J. R.; Evans, D. A. *Org. Synth.* 1989, 68, 77. (e) Dickman, D. A.; Meyers, A. I.; Smith, G. A.; Gawley, R. E. *Organic Syntheses*; Wiley: New York, 1990; Collect Vol. VII, p 530. (f) Giannis, A.; Sandhoff, K. *Angew. Chem. Int. Ed. Engl.* 1989, 28, 218. (g) Dharanipragada, R.; Alarcon, A.; Hruby, V. J. *Org. Prep. Proc. Int.* 1991, 23, 396. (h) Boesten, W. H. J.; Schepers, C. H. M.; Roberts, M. J. A.; Eur. Pat. Appl. EP O 322 982 A2, July 5, 1989; *Chem. Abstr.* 1989, 111, 233669a. (i) Abiko, A.; Masamune, S. *Tetrahedron Lett.* 1992, 33, 5517.

(8) Poindexter, G. S.; Meyers, A. I. *Tetrahedron Lett.* 1977, 3527.

(9) Bhaskar Kanth, J. V.; Periasamy, M. *J. Org. Chem.* 1991, 56, 5964.

Table I. Reduction of  $\alpha$ -Amino Acids with  $\text{NaBH}_4\text{-I}_2$ 

| entry <sup>a</sup> | config | structure | yield, % <sup>b</sup> | $[\alpha]_D^{20}$ , deg (lit.)                              |
|--------------------|--------|-----------|-----------------------|---|
| a                  | L      |           | 84                    | +37 (+37 <sup>10</sup> )<br>(1, EtOH)                       |
| b                  | L      |           | 94                    | +17 (+17 <sup>11</sup> )<br>(10, EtOH)                      |
| c                  | D      |           | 67                    | -32 (-31.7 <sup>11</sup> )<br>(0.75, 1 M HCl)               |
| d                  | L      |           | 72                    | -22 (-22.8 <sup>11</sup> )<br>(1.2, 1 M HCl) <sup>c</sup>   |
| e                  | L      |           | 58                    | +30 (+31 <sup>11</sup> )<br>(1.6, toluene)                  |
| f                  | L      |           | 75                    | +3.5 (+5.4, <sup>11</sup> -3.6 <sup>6c</sup> )<br>(1, EtOH) |
| g                  | L      |           | 65                    | -14 (-12.7 <sup>11</sup> )<br>(1, EtOH)                     |
| h                  | L      |           | 45                    | -13.6<br>(2, H <sub>2</sub> O)                              |

<sup>a</sup> Compounds 2a, 2b, 2e, 2f, and 2g were distilled bulb-to-bulb; 2c and 2d were recrystallized from toluene. 2h was isolated as hydroiodide and recrystallized from ethanol. <sup>b</sup> Isolated, purified yields. <sup>c</sup>  $[\alpha]_D$  in EtOH ( $c = 1$ ) gave  $-24.1^\circ$ .

Table II. Reduction of *N*-Acyl- $\alpha$ -amino Acids to *N*-Alkylamino Alcohols

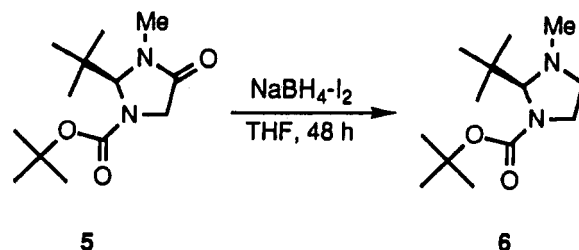
| entry <sup>a</sup> | config | R                                  | R' | R'' | yield (%) <sup>b</sup> |
|--------------------|--------|------------------------------------|----|-----|------------------------|
| a                  | L      | PhCH <sub>2</sub>                  | H  | H   | 73                     |
| b                  | D      | PhCH <sub>2</sub>                  | H  | Me  | 83                     |
| c                  | L      | -(CH <sub>2</sub> ) <sub>3</sub> - |    | Me  | 57                     |
| d                  |        | H                                  | H  | Ph  | 64                     |

<sup>a</sup> Compound 4a was recrystallized from toluene and ethyl acetate, respectively, and 4b from *n*-hexane. 4c and 4d were bulb-to-bulb distilled. <sup>b</sup> Isolated, purified yields.

$\text{I}_2$  system describing the reduction of carboxylic acids, esters, amides, and nitriles.<sup>12</sup>

The results of reduction of several *N*-acylamino acids to *N*-alkylamino alcohols are given in Table II.

In assessing further the efficacy of the  $\text{NaBH}_4\text{-I}_2$  system, we observed that glycine derivative 5 was smoothly reduced to the *N*-*t*-Boc-imidazolidine 6 in 61% yield. The latter is known to be a useful template in asymmetric routes to 2,3-diaminopropanoic acids.<sup>13</sup>



It is noteworthy that the Boc group in 5 was resistant to reduction. This fact may hold true for other urethane protecting groups since it was already shown for other reducing agents.<sup>7i,14</sup>

The reduction of *N*-acylamino acids (3) is probably due to the presence of a proton in the free carboxylic acid which results in the formation of an (acyloxy)borohydride,<sup>15</sup> previously shown to be suitable for the reduction of amides to amines.<sup>16</sup> The reduction of esters of *N*-(aryloxy)- or *N*-(alkoxycarbonyl)-protected amino acid esters to the corresponding alcohols has also been described.<sup>14c</sup>

## Experimental Section

**General Procedures.** <sup>1</sup>H NMR spectra were recorded at 250 or 500 MHz and <sup>13</sup>C NMR spectra at 62.9 MHz, respectively. Polarimetric measurements were taken on an automatic polarimeter. Melting points are not corrected. All chemicals and solvents were of technical or ACS reagent grade and used as received unless otherwise stated.

**L-tert-Leucinol (2a).** A 1-L three-neck round-bottom flask was fitted with a magnetic stirbar, a reflux condenser, and an addition funnel. The flask was charged with 6.92 g (183 mmol) sodium borohydride and 200 mL of THF (predried over sodium). *L*-tert-Leucine (1a) (10.00 g, 76 mmol) was added in one portion. The remaining neck was sealed with a septum and an argon line attached, and the flask was cooled to 0 °C in an ice bath. A solution of 19.30 g (76 mmol of iodine dissolved in 50 mL of THF) was poured into the addition funnel and added slowly and dropwise over 30 min resulting in vigorous evolution of hydrogen. After addition of the iodine was complete and gas evolution had ceased, the flask was heated to reflux for 18 h and then cooled to room temperature, and methanol was added cautiously until the mixture became clear. After stirring 30 min, the solvent was removed by rotary evaporation leaving a white paste which was dissolved by addition of 150 mL of 20% aqueous KOH. The solution was stirred for 4 h and extracted with 3 × 150 mL of methylene chloride. The organic extracts were dried over sodium sulfate and concentrated in vacuo, affording a white semisolid (100%) which was bulb-to-bulb distilled to yield 7.53 g (84%) of 2a as a white solid: mp 30 °C, bp 90 °C/0.2 mm (lit.<sup>10</sup> 117–120 °C/57 mm).

**L-Valinol (2b).** Prepared from *L*-valine (1b) by the same procedure in 94% yield as a colorless solid: mp 32 °C, bp 75 °C/6 mm (lit.<sup>11</sup> 8 °C/8 mm).

(13) Pfammatter, E.; Seebach, D. *Liebigs Ann. Chem.* 1991, 1323.

(14) (a) Rodriguez, M.; Linares, M.; Doulot, S.; Heitz, A.; Martinez, J. *Tetrahedron Lett.* 1991, 32, 923. (b) Kokotos, G. *Synthesis* 1990, 299. (c) Soucek, M.; Urban, J.; Saman, D. *Collect. Czech. Chem. Commun.* 1990, 55, 761. (d) Freeman Stanfield, C.; Parker, J. E.; Kanellis, P. *J. Org. Chem.* 1981, 46, 4797.

(15) Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* 1960, 82, 681.

(16) Umino, N.; Iwakuma, T.; Itoh, N. *Tetrahedron Lett.* 1976, 763.

(10) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* 1989, 8, 846.

(11) Aldrich Chemical Catalog, 1990–1991.

(12) Bhanu Prasad, A. S.; Bhaskar Kanth, J. V.; Periasamy, M. *Tetrahedron* 1992, 48, 4623.

**D-Phenylglycinol (2c)** was prepared from D-phenylglycine (1c) by the same procedure, with the exception that the amino acid was added after addition of the iodine was completed. The crude material (91%) was recrystallized from toluene to afford 67% 2c as colorless crystals: mp 69–71 °C (lit.<sup>11</sup> 75–77 °C).

**L-Phenylalaninol (2d). Iodine Procedure.** 2d was prepared from 82.60 g (500 mmol) L-phenylalanine (1d) by the same procedure. The crude material was recrystallized from toluene to yield 72% of 2d as colorless crystals: mp 90–92 °C (lit.<sup>11</sup> 92–94 °C).

**Chlorine Procedure.** A 500-mL three-neck round-bottom flask equipped with a magnetic stirbar, reflux condenser, thermometer, and gas inlet was flushed with argon and charged with 250 mL of THF, 16.52 g (100 mmol) of 1d, and 9.10 g (240 mmol) of NaBH<sub>4</sub>. Then, 7.09 g (100 mmol) of chlorine,<sup>17</sup> diluted with argon, was bubbled into the suspension over a period of 1 h with external cooling with an ice bath. Vigorous gas evolution and a strongly exothermic reaction were observed. Afterwards, the flask was heated to reflux overnight. The reaction mixture was then hydrolyzed by dropwise addition of 30 mL of MeOH at room temperature. The solvent was removed in vacuo, the residue taken up in 150 mL of 20% aqueous KOH, and the product extracted three times with 150 mL of methyl-*tert*-butyl ether (MTBE), respectively. The organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness yielding 14.92 g (99%) of a colorless solid. Double recrystallization from toluene afforded 8.36 g (55%) 2d as colorless crystals: mp 91–92 °C (lit.<sup>11</sup> 92–94 °C).

**Lithium Borohydride Procedure.** This procedure is identical to the NaBH<sub>4</sub>-I<sub>2</sub> procedure with the exception of the substitution of LiBH<sub>4</sub> for NaBH<sub>4</sub> on a molar basis. Phenylalaninol was obtained in 70% yield as colorless crystals: mp 92–94 °C (lit.<sup>11</sup> 92–94 °C).

**L-Prolinol (2e)** was prepared from L-proline (1e) by the NaBH<sub>4</sub>-I<sub>2</sub> procedure and obtained in 58% yield as colorless liquid: bp 80 °C/1 mm (lit.<sup>11</sup> 74–76 °C/2 mm).

**L-Isoleucinol (2f)** was prepared from L-isoleucine (1f) by the NaBH<sub>4</sub>-I<sub>2</sub> procedure to afford, after double distillation, 75% of 2f as a colorless solid: bp 100–101 °C/5 mm (lit.<sup>11</sup> 97 °C/14mm); mp 38–40 °C (lit.<sup>11</sup> 30 °C).

**L-Methioninol (2g)** was prepared from L-methionine (1g) by the NaBH<sub>4</sub>-I<sub>2</sub> procedure to afford 65% of 2g as a colorless oil: bp 140 °C/1 mm. The oil obtained from a second experiment spontaneously solidified to give colorless crystals: mp 34–35 °C.

**L-Tyrosinol Hydriodide (2h).** A 1-L three-neck round-bottom flask equipped with a magnetic stirbar, reflux condenser, thermometer, and addition funnel was flushed with argon and charged with 500 mL of THF, 9.10 g (240 mmol) NaBH<sub>4</sub>, and 18.10 g (100 mmol) L-tyrosine (1h). A solution of 25.40 g (100 mmol) I<sub>2</sub> in 75 mL of THF was added dropwise over a period of 1 h at a temperature of 8–10 °C. After the addition was complete, the flask was heated to reflux overnight. The reaction mixture was cooled down to room temperature, and 50 mL of MeOH was added dropwise. The solvent was evaporated and the residue dissolved in 100 mL of 2 M HCl. After removal of the solvent in vacuo, the residue was twice suspended in 300 mL of EtOH which was again distilled in vacuo to remove traces of water and HCl. The residue was then

suspended in 300 mL of EtOH at 40 °C and the suspension filtered. The filtrate was concentrated until crystallization began<sup>18</sup> and was kept at 5 °C overnight. The crystals were filtered, washed with EtOH, dried, and taken up in 43 mL of EtOH. After hot filtration to remove some insoluble material, 20 mL of EtOH was distilled away and the solution left at 5 °C overnight. The resulting crystals were isolated by filtration, washed with EtOH, and dried in vacuo to yield 45% of 2h as colorless crystals: mp 214–216 °C, <sup>1</sup>H NMR (*d*<sub>6</sub>-DMSO) δ 9.3 (br, s, 1H), 7.8 (br s, 3H), 7.1 (d, 2H), 6.7 (d, 2H), 5.2 (br s, 1H), 3.5 (m, 1H), 3.3 (m, 1H), 3.2 (m, 1H), 2.7 (ABX-system, 2H); IR (KBr), 3480, 3270, 3100, 1610, 1575, 1513, 1475, 1433, 1255, 1200, 1050, 818 cm<sup>-1</sup>. Anal. Calcd for C<sub>9</sub>H<sub>14</sub>INO<sub>2</sub>: C, 36.63; H, 4.78; N, 4.57; I, 43.00. Found: C, 36.79; H, 4.82; N, 4.69; I, 42.40.

**L-N-Methylphenylalaninol (4a).** a 500-mL three-neck round-bottom flask equipped with a magnetic stirbar, reflux condenser, thermometer, and addition funnel was flushed with argon and charged with 250 mL of THF, 19.32 g (100 mmol) of *N*-formyl-L-phenylalanine (3a), and 9.10 g (240 mmol) of NaBH<sub>4</sub> whereupon a vigorous gas evolution was observed. Then, a solution of 25.40 g (100 mmol) of I<sub>2</sub> in 100 mL of THF was added slowly and dropwise at a temperature of 25–40 °C. After the addition was complete, the flask was heated to reflux overnight. Excess reducing agent was cautiously destroyed by dropwise addition of 30 mL of MeOH at room temperature. The solvents were then removed in vacuo, and the residue was taken up in 100 mL of 20% aqueous KOH and the product extracted three times with 150 mL of MTBE. After drying (Na<sub>2</sub>SO<sub>4</sub>), the extract was evaporated to a pale-yellow oil which was crystallized by the addition of 200 mL of hot *n*-hexane. Filtration and drying gave 84% colorless crystals which were recrystallized from 20 mL of toluene. Evaporation of both mother liquors and recrystallization of the residue from 5 mL of ethyl acetate yielded a second crop of crystals which was added to the first one to give a total yield of 73% of 4a as colorless crystals: mp 71–74 °C (lit.<sup>19</sup> 68 °C); [α]<sub>D</sub> = +21.8° (1, EtOH) (lit.<sup>19</sup> +17.1° (2, CHCl<sub>3</sub>)).

**D-N-Ethylphenylalaninol (4b)** was prepared from D-*N*-acetylphenylalanine (3b) by the same procedure as 4a. 4b was obtained, after recrystallization from 200 mL of *n*-hexane, in 83% yield as colorless crystals: mp 82–84 °C; <sup>1</sup>H NMR (*d*<sub>6</sub>-DMSO) δ 7.3–7.1 (m, 5H), 4.4 (br s, 1H), 3.2 (ABX-system, 2H), 2.7 (m, 1H), 2.6 (m, 2H), 2.5 (q, 2H), 1.4 (br s, 1H), 1.0 (t, 3H); <sup>13</sup>C NMR (*d*<sub>6</sub>-DMSO) δ 139.8, 129.2, 128.0, 125.7, 62.3, 60.8, 37.6, 15.5; IR (KBr), 3280, 3025, 2970, 2880, 1600, 1490, 1478, 1450, 1380, 1350, 1110, 1028, 940, 863, 790, 745, 700 cm<sup>-1</sup>; [α]<sub>D</sub> = -11.6° (1, EtOH). Anal. Calcd for C<sub>11</sub>H<sub>17</sub>NO: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.54; H, 9.69; N, 7.91.

**L-N-Ethylprolinol (4c)** was prepared by the same procedure as 4a from *N*-acetyl-L-proline (3c) with the modification that the residue from the organic extract was dissolved in 50 mL of water, the resulting solution stirred for 30 min and, after the addition of 50 mL of 5% hydrochloric acid, stirred for another 90 min in order to destroy stable boron complexes. The solution was then made alkaline with 50 mL of 20% aqueous KOH and

(17) Procedure from Houben-Weyl: *Methoden der Organischen Chemie*; Müller, E., Ed.; Georg Thieme Verlag: Stuttgart, 1962; Vol. V/3, p 517.

(18) The hydriodide was formed exclusively due to the presence of iodide formed during the borane generation. Presumably, the HI salt is less soluble than the HCl salt and crystallizes preferentially.

(19) Karim, A.; Mortreux, A.; Petit, F.; Buono, G.; Peiffer, G.; Siv, C. *J. Organomet. Chem.* 1986, 317, 93.

extracted with  $\text{CH}_2\text{Cl}_2$  ( $4 \times 150$  mL). After the solution was dried ( $\text{Na}_2\text{SO}_4$ ), the solvent was evaporated and the residue bulb-to-bulb distilled to give 57% of **4c** as colorless liquid: bp 80–85 °C/0.4 mm;  $[\alpha]_{\text{D}} = -84.8^\circ$  (1, EtOH) (lit.<sup>20</sup>  $-110.4^\circ$  (1.9, MeOH)).

**N-Benzyl-2-aminoethanol (4d)** was prepared by the same procedure as **4a** from hippuric acid (**3d**) with the modification that the residue of the reaction mixture which had been quenched with MeOH was taken up in diluted hydrochloric acid, stirred for 30 min, and made alkaline by addition of aqueous KOH. Extraction with methyl *tert*-butyl ether, drying, and evaporation of the extract and two bulb-to-bulb distillations of the residue afforded **4d** in 64% yield as colorless oil: bp 86–88 °C/0.4 mm (lit.<sup>11</sup> 153–156 °C/12 mm);  $n_{\text{D}} = 1.544$  (lit.<sup>11</sup> 1.5435).

**(S)-1-(tert-Butoxycarbonyl)-2-tert-butyl-3-methyl-1,3-imidazolidine (6)**. A 500-mL three-neck round-bottom flask equipped with a magnetic stirbar, reflux condenser, thermometer, and addition funnel was flushed with argon and charged with 150 mL of THF, 25.6 g (100 mmol) of **(S)-1-(tert-butoxycarbonyl)-2-tert-butyl-3-methyl-1,3-imidazolidin-4-one (5)**, and 7.56 g (200 mmol) of  $\text{NaBH}_4$ . After 15 min a solution of 12.70 g (50 mmol)  $\text{I}_2$  in 50 mL of THF was added over 1 h at a temperature at

5 °C. The flask was then heated to reflux for 44 h. After the reaction mixture had been cooled down to 5 °C, 250 mL of a saturated aqueous ammonium chloride solution were added cautiously and the mixture was stirred at 50 °C until hydrogen evolution had ceased. The precipitate was dissolved by addition of sufficient aqueous NaOH, the organic layer separated, and the water phase extracted four times with 150 mL of methyl-*tert*-butyl ether. The extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to a colorless oil which slowly crystallized. This was taken up in 150 mL of *n*-hexane, insoluble components were filtered off, and the solution was concentrated to 42 g and placed into a refrigerator. Large, colorless crystals were obtained this way and by further concentrations of the mother liquors, which were filtered, washed with *n*-hexane and dried in vacuo at 30–40 °C to give **6** in 61% yield: mp 50–52 °C (lit.<sup>13</sup> 47–48 °C for the (*R*)-enantiomer);  $[\alpha]_{\text{D}}^{13} = +22.5^\circ$  (1,  $\text{CHCl}_3$ ) (lit.  $-22.8^\circ$  (1.22,  $\text{CHCl}_3$ ) for the (*R*)-enantiomer).

**Acknowledgment.** The authors are indebted to the National Science Foundation and the National Institutes of Health for financial support of this research. They would also like to thank W. Jahn, M. Kraft, and D. Pfeifle for their skillful technical assistance.

(20) Hammer, C. F.; Weber, J. D. *Tetrahedron* 1981, 37, 2173.