ture for 4 hr. To the solution cooled at 0° was added 6.1 g (0.306 mol) of D_2O followed by an additional 100 ml of water. After extraction with 2 × 100 ml of diethyl ether, the organic layer was washed with a saturated sodium chloride solution and dried over sodium sulfate. After evaporation of the ether the aldimine was distilled, yielding 13.65 g (0.0695 mol, 67.75%), bp 52-54° (1.5 mm).

Steam distillation of the aldimine from 17.2 g (0.14 mol) of aqueous oxalic acid gave 5.85 g (0.069 mol, 67%) yield of *l-d*-2-methylbutyraldehyde. The per cent deuterium incorporation was determined by nmr at δ 9.54 to be 96%.

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Registry No.—*sec*-BuBr, 78-76-2; *t*-BuBr, 507-19-7; $CH_3(CH_2)_5Br$, 111-25-1; BuBr, 109-65-9; $PhCH_2CH_2Br$, 103-63-9; cyclopentyl bromide, 137-43-9; *l-d*-2,2-dimethylpropanal, 41162-98-5; 3-heptanone, 106-35-4; 1-hydroxy-1-phenylbutanone, 16183-45-2; 2-hydroxy-4-octanone, 49707-56-4; 2-hydroxy-4-octanone *N*-phenylcarbanilate, 49707-57-5; 2-(*N*-1-trimethylsilylpropylideneamino)-2,4,4-trimethylpentane, 49707-58-6; ethyl 2-[*N*-(2-phenyl-2-butyl)]imino-3-methylpentanoate, 49707-59-7; 2-phenyl-2-butyl isocyanide, 49707-54-2.

References and Notes

(1) This support of this work by a Public Health Service Grant No. 04065 from the National Cancer Institute and, in part, by the National Science Foundation is gratefully acknowledged.
(2) For a preliminary report see H. M. Walborsky, W. H. Morrison, III, and G. E. Niznik, *J. Amer. Chem. Soc.*, **92**, 6675 (1970).
(3) F. Sachs and H. Loevy, *Chem. Ber.*, **37**, 874 (1904).
(4) H. Gilman and L. C. Heckert, *Bull. Soc. Chim. Fr.*, **43**, 224 (1928).
(5) I. Ugi and U. Fetzer, *Chem. Ber.*, **94**, 2239 (1961).
(6) H. M. Walborsky and G. E. Niznik, *J. Amer. Chem. Soc.*, **91**, 7778 (1969).
(7) This result also argues against the formation of a dimetallo aldimine RN=C(Li) CH(Li)R, since this would yield greater than 100% incorporation. However, it should be pointed out that under certain conditions lithium aldimine **1** can undergo a cleavage reaction. See M. P. Periasamy and H. M. Walborsky, *J. Org. Chem.*, **39**, 611 (1974).
(8) H. M. Walborsky and G. E. Niznik, *J. Org. Chem.*, **37**, 187 (1972).
(9) U. Schöllkopf and R. Jentsch, *Angew. Chem.*, **85**, 355 (1973), and earlier references cited therein.
(10) H. M. Walborsky, G. E. Niznik, and M. P. Periasamy, *Tetrahedron Lett.*, 4965 (1971).
(11) For a convenient synthesis see G. E. Niznik, W. H. Morrison, III, and H. M. Walborsky, *Org. Syn.*, **51**, 31 (1971).
(12) D. C. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 19.
(13) N. Koga, G. Koga, and J. P. Anselme, *Tetrahedron Lett.*, 3309 (1970).
(14) A. I. Meyers and H. W. Adickes, *Tetrahedron Lett.*, 5151 (1969).
(15) F. Gerhart and U. Schöllkopf, *Tetrahedron Lett.*, 6231 (1968).
(16) For interesting reviews see D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **8**, 639 (1969); *Synthesis*, **1**, 17 (1969); E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075 (1965).
(17) G. Stork and S. R. Dowd, *J. Amer. Chem. Soc.*, **85**, 2178 (1963); T. Cuvigny and H. Normant, *Bull. Soc. Chim. Fr.*, 3976 (1970).
(18) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portney, *J. Org. Chem.*, **38**, 36 (1973), and earlier references cited therein.
(19) Mass spectral analyses were conducted under the supervision of Professor R. C. Dougherty, The Florida State University. Elemental analyses were performed by Beller Laboratories, Gottingen, Germany.
(20) Beilstein, "Handbuch der organische Chemie," Vol. 3, Friedrich Richter, Springer-Verlag, Berlin, 1959.
(21) H. O. House, D. D. Traficante, and R. A. Evans, *J. Org. Chem.*, **28**, 353 (1963).
(22) R. Luft, *Ann. Chim. (Paris)*, **4**, 745 (1959).

Partial Asymmetric Syntheses of Amino Acids Using Lithium Aldimine Precursors[1]

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Carboxylation or carbethoxylation of the lithium aldimines formed by the α addition of ethyllithium, *sec*-butyllithium, and isopropyllithium to (±)- or (*R*)-(+)-2-phenyl-2-butylisonitrile produced the corresponding α-imino acid or ester. Optically active α-amino acids were synthesized by the reduction, under a variety of conditions, of the α-imino acids and esters.

The use of lithium aldimines as useful synthetic intermediates for the preparation of aldehydes, α-keto acids, ketones, acyloins, α-diketones, and silyl ketones has previously been reported.[2,3] The use of lithium aldimines as precursors for the syntheses of optically active α-amino acids is the subject of this paper.

Results and Discussion

Chart I outlines the procedure used for the preparation of α-amino acids.

The α addition of *sec*-butyllithium, isopropyllithium, and ethyllithium to 2-phenyl-2-butylisonitrile (**1**) proceeds quite readily to yield the corresponding lithium aldimines (**2**). Treatment of **2** with carbon dioxide or ethyl chloroformate produced lithium imino carboxylate salt **3** and ethyl α-imino carboxylate (**5**), respectively. In contrast to the case of imines produced from α-keto acids and α-alkylbenzylamine,[4] attempted concomitant hydrogenation and hydrogenolysis of **3** by the use of palladium hydroxide[5] did not give good results. However, the direct reduction of the corresponding ester **5** did proceed, although in poor yields, to give α-amino acids. Most of the reductions in our studies were carried out in a stepwise fashion using **3** or **3*** as substrate. The double bond was first reduced with either lithium or sodium borohydride, diborane, diisopinocampheylborane, or triisopinocampheylborane and the resulting amine hydrochlorides were debenzylated by catalytic hydrogenolysis to produce the α-amino acids. These results are summarized in Table I.

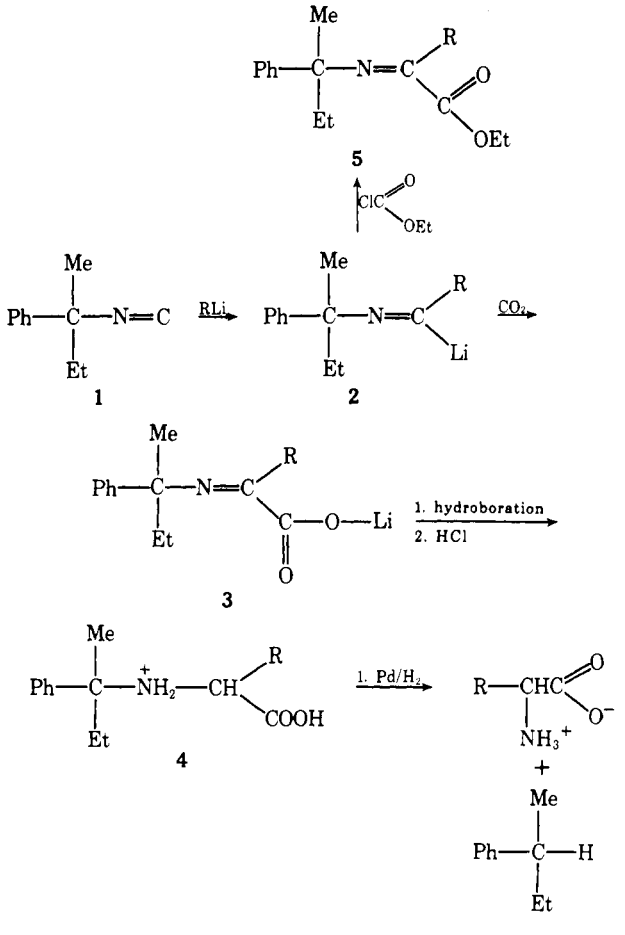
The α-amino acids isolated using standard procedures[6] contained slight impurities[7] which were difficult to remove. Therefore, all optically active α-amino acids were converted into their 2,4-dinitrophenyl derivatives[8] and purified, without attempted resolution, by use of a Celite column.[9] The diastereomeric ratio of racemic isoleucine to alloisoleucine (R = *sec*-butyl) was determined by nmr based upon the α-methine proton absorptions.[10] Catalytic reduction of **5** gave a mixture (ratio 1.3) in which isoleucine predominated, whereas stepwise reduction gave a mixture (ratio 0.7) richer in alloisoleucine. As can also be seen (Table I) the direct hydrogenation and hydrogenolysis of the imino ester **5** or **5*** is not a very satisfactory method, since one obtains a low overall yield and a very small optical induction. The stepwise reduction of **3** or **3*** is the preferred method since the optical yields are reasonably good. It should be recognized that since lithium borohydride and diborane exhibit similar stereoselectivities in the reduction of **3***, the former is obviously the re-

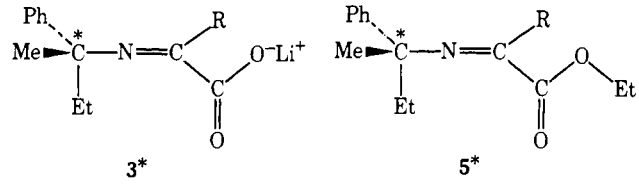
Table I
Amino Acids Obtained by Reduction of Imino Group

Registry no.	Imine reduced	R	Reducing agents[a]	Overall yield, %	Configuration	Free amino acid[b] $[\alpha]^{27}_{546}$	Free amino acid[b] Optical purity, %	DNP amino acid[c] $[\alpha]^{27}D$	DNP amino acid[c] Optical purity, %
49707-59-7	5	*sec*-Butyl	$H_2/Pd(OH)_2$	34	57/43[d]				
49690-14-4	3	*sec*-Butyl	$LiBH_4$	85	42/58[d]				
	3	*sec*-Butyl	B_2H_6	82	42/58[d]				
49690-15-5	3	Ethyl	$LiBH_4$	70					
	3	Ethyl	B_2H_6	64					
	3	Ethyl	(−)-R_2BH[e]	57	*S*[h]	+2.9	11 (12)	+15.0	16 (17)
	3	Ethyl	(+)-R_2BH[f]	58	*R*[i]	−3.5	13 (15)	−13.3	14 (16)
	3	Ethyl	(−)-$R_2BH \cdot RBH_2$[e]	45	*S*	+2.0	8 (9)	+8.1	9 (10)
49844-62-4	5*	Ethyl	$H_2/Pd(OH)_2$	23	*R*	−0.8	3	−8.4	9
49844-63-5	3*	Ethyl	$LiBH_4$[g]	77	*R*	−13.7	52	−52.1	55
	3*	Ethyl	$LiBH_4$	63	*R*	−15.0	57	−59.3	63
	3*	Ethyl	B_2H_6[g]	66	*R*	−14.5	55	−52.6	56
	3*	Ethyl	B_2H_6	57	*R*	−14.6	55	−58.3	62
49690-16-6	3	Isopropyl	$NaBH_4$	83					
	3	Isopropyl	(−)-R_2BH[e]	42	*S*[j]	+12.6	40 (43)	+41.7	42 (45)
	3	Isopropyl	(+)-R_2BH[f]	43	*R*[k]	−10.4	33 (37)	−35.2	35 (39)
	3	Isopropyl	(−)-$R_2BH \cdot RBH_2$[e]	38	*S*	+8.7	28 (30)	+34.7	35 (37)
49844-64-6	5*	Isopropyl	$H_2/Pd(OH)_2$	29	*R*	−0.2	0.6	−3.6	4
49844-65-7	3*	Isopropyl	$LiBH_4$	80	*R*	−17.6	56	−62.3	62
	3*	Isopropyl	B_2H_6	81	*R*	−16.6	53	−54.5	54

[a] All metal hydride reductions were followed by $Pd(OH)_2$ hydrogenolysis. [b] Specific rotations of all free amino acids were obtained using 5 *N* HCl as solvent; optical purities were calculated using for R = *sec*-butyl, $[\alpha]^{27}_{546}$ +26.4° (*c* 1.47, 5 *N* HCl); R = isopropyl, $[\alpha]^{27}_{546}$ +31.2° (*c* 1.57, 5 *N* HCl); values in parentheses are corrected for the optical purity of α-pinene, 93.5% [(+)-α-pinene, 89%]. [c] Based on the observed specific rotation of authentic samples: DNP-(*S*)-butyrine, $[\alpha]^{27}D$ +94.1° (*c* 0.27, 1 *N* NaOH); DNP-(*S*)-valine, $[\alpha]^{21}D$ +100.2° (*c* 0.26, 1 *N* NaOH). Values in parentheses are corrected for the optical purity of α-pinene. [d] The diastereomeric ratio of isoleucine to alloisoleucine is based upon the α-methine nmr proton absorption. [e] Prepared from (−)-α-pinene and diborane. [f] Prepared from (+)-α-pinene and diborane. [g] Worked up under alkaline conditions. [h] Registry no.: free amino acid, 1492-24-6; DNP amino acid, 4470-69-3. [i] Registry no.: free amino acid, 2623-91-8; DNP amino acid, 72-18-4. [j] Registry no.: free amino acid, 6367-34-6; DNP amino acid, 1694-97-9. [k] Registry no.: free amino acid, 640-68-6; DNP amino acid, 37696-35-8.

Chart I
Asymmetric Syntheses of α-Amino Acids





agent of choice. Moreover, based on optical yields, the reduction of 3* with achiral borohydrides is superior to the reduction of 3 with chiral borohydrides. It should also be noted that reduction of (*R*)-3* and (*R*)-5* leads to the formation of *R* amino acids.

The results of the reduction of 3 with chiral borohydrides lead to the following observations. (1) Diisopinocampheylborane and triisopinocampheylborane prepared from (−)-α-pinene lead to the formation of *S* amino acids. (2) Diisopinocampheylborane exhibits slightly higher optical yields than triisopinocampheylborane.[11] (3) Higher optical yields are observed for valine (R = isopropyl) than for butyrine (R = ethyl), presumably owing to the greater steric interaction of the isopropyl group.

Interpretation of our results in terms of transition state models postulated[12] for asymmetric reduction of olefins is not possible, since our system is more complicated. The addition may not involve a four-centered transition state[12] owing to the possible complexing of the borane with the nonbonding pair of electrons on the nitrogen. Moreover, it is also difficult to assess at this time the effect of geometric isomerism of these imines on the steric course of the reduction.

Experimental Section

Melting points were determined in capillary tubes using a Mel-Temp apparatus with a calibrated thermometer. Infrared spectra were obtained with a Perkin-Elmer Model 257 infrared spectrophotometer. Solution spectra were run using either carbon tetrachloride or chloroform solutions in a 0.5-mm sodium chloride cell.

Optical rotations were measured at the 546-nm line of mercury and D line of sodium on a O. C. Rudolph and Sons Inc. Model 80 No. 714 polarimeter. Nmr spectra were obtained on a Varian Associates A-60 and a Brucker 90 spectrometer. Nmr spectra of amino acids were determined as a solution in deuterium oxide with TMS as external standard using a Brucker 90 spectrometer.

2-Amino-3-methylpentanoic Acid (Isoleucine and Alloisoleucine). A. Lithium Borohydride Reduction. To a stirred solution of 1.59 g (10 mmol) of racemic 2-phenyl-2-butyl isonitrile dissolved in 500 ml of anhydrous ether at 0° under a nitrogen atmosphere was added rapidly 11.0 ml of 0.97 *M sec*-butyllithium solution in cyclohexane. The mixture was stirred at 0° for 30 min and added dropwise to an excess of carbon dioxide in ether at −20°. The solvent was removed *in vacuo* to give the carboxylated imine [ir ($CHCl_3$) 1620 cm^{-1} (s)], which was dissolved in 50 ml of anhydrous tetrahydrofuran (THF), treated with 0.22 g (10 mmol) of lithium borohydride at −10°, and stirred at room temperature for 2 days. After the mixture was cooled to −15°, dilute hydrochloric acid was added to decompose excess lithium borohydride. The solvent was removed *in vacuo* and the remaining aqueous solution was extracted with ether and concentrated to dryness. Three 20-ml portions of water were added and evaporated to remove hydrochloric acid, and three 20-ml portions of absolute ethanol and then four 30-ml portions of benzene were added and evaporated to remove water. The residue was extracted thoroughly with anhydrous benzene to filter off the boron compound. Removal of the solvent afforded crude 2-[*N*-(2-phenyl-2-butyl)]amino-3-methylpentanoic acid hydrochloride in quantitative yield as a white powder: mp 57–119°; ir ($CHCl_3$) 3400–2400 (broad), 1710 (m), and 1570 cm^{-1} (s). An analytical sample was obtained by recrystallization from ether–ethyl acetate: mp 95–129°; ir (KBr) 3400–2360 (broad), 1730 (m), 1565 (s), 765 (s), and 700 cm^{-1} (s).

Anal. Calcd for $C_{16}H_{26}ClNO_2$: C, 64.09; H, 8.74; N, 4.67. Found: C, 64.26; H, 8.85; N, 4.54.

The crude hydrochloride (1.44 g, 4.81 mmol) dissolved in 50 ml of 95% ethanol was subjected to hydrogenolysis using 0.5 g of palladium hydroxide on carbon catalyst[5] and 2 ml of 0.01 *N* hydrochloric acid. The mixture was stirred under 3.5 atm pressure of hydrogen at room temperature for 12 hr. The catalyst was filtered and washed with 95% ethanol and the combined filtrates were evaporated *in vacuo*. The residue, dissolved in 50 ml of water, was extracted with ether and the aqueous layer was concentrated to 10 ml. The amino acids were isolated according to a published procedure[6] and there was obtained 0.54 g (85% overall yield based on the isonitrile) of the product, identified by comparison of the ir spectrum in potassium bromide and the nmr spectrum in deuterium oxide with those of an authentic sample. The diastereomeric ratio of isoleucine to alloisoleucine was 42:58 based upon the α-methine proton nmr absorptions.

B. Hydroboration. The carbonated imine (10 mmol), prepared as described above, was dissolved in 40 ml of THF and treated with 7.4 ml of a 1.44 *M* solution of diborane in THF at −15° and the mixture was stirred at 2–3° for 3 hr.[13] After cooling to −20° dilute hydrochloric acid was added and the mixture was worked up as described above to afford the hydrochloride in quantitative yield: mp 55–125°; ir ($CHCl_3$) was superimposable with that of the hydrochloride of an authentic sample.

The crude hydrochloride (1.46 g, 4.87 mmol) was hydrogenolyzed according to the procedure described above and 0.52 g (82% overall yield) of the amino acids was obtained. The diastereomeric ratio was 42:58.

C. *Via* Ester. To a stirred solution of 4.35 g (27.3 mmol) of the racemic isonitrile dissolved in 50 ml of ether at 0° under a nitrogen atmosphere was added rapidly 29.6 ml of 0.97 *M sec*-butyllithium solution in cyclohexane and the mixture was stirred for 30 min at 0°. After cooling to −20° the mixture was added dropwise to a stirred solution of 15.0 g (0.138 mol) of ethyl chloroformate in 80 ml of THF at −78° and stirred overnight at room temperature. Filtration of lithium chloride and distillation of the residue under reduced pressure gave 5.07 g (64.1%) of ethyl 2-[*N*-(2-phenyl-2-butyl)]imino-3-methylpentanoate: bp 100–102° (0.25 mm); ir (CCl_4) 1735 (s), 1665 (m, broad), 699 cm^{-1} (m); mass spectrum *m/e* (measured mass) 289.2032 (calcd for $C_{18}H_{27}NO_2$, 289.2041).

A mixture of 2.02 g (7 mmol) of the imino ester and 1.0 g of palladium hydroxide on carbon catalyst in 30 ml of anhydrous benzene was shaken under 3.5 atm pressure of hydrogen at room temperature for 3 days. The catalyst was filtered and washed with benzene. The combined filtrates were extracted with 50 ml of 3 *N* hydrochloric acid. From the organic layer there was obtained 0.97 g of a mixture which consisted of 35% of *sec*-butylbenzene and 23% of ethyl 3-methyl-2-oxopentanoate. The latter was obtained by hydrolysis of the imine ester with dilute hydrochloric acid in 66.2% yield: bp 66–67° (15 mm) [lit.[14] bp 78–79° (15 mm)]; ir (CCl_4) 1735 cm^{-1} (s, broad); nmr (CCl_4) 0.90 (t, 3, J = 7 Hz), 1.09 (d, 3, J = 7 Hz), 1.35 (t, 3, J = 7 Hz), 1.63 (m, 2), 3.03 (sextet, 1), 4.26 (q, 2, J = 7 Hz); 2,4-DNP mp 106–106.5° (needles from ethanol); ir (CCl_4) 3290 (w), 3210 (w, broad), 3100 (w), 1735 (w), 1710 (m), 1625 (s), 1510 (s), 1345 cm^{-1} (s).

Anal. (2,4-DNP) Calcd for $C_{14}H_{18}N_4O_6$: C, 49.70; H, 5.36; N, 16.56. Found: C, 49.60; H, 5.34; N, 16.55.

The aqueous layer was refluxed for 6 hr, extracted with ether, and concentrated to dryness. To the residue 30 ml of water was added and evaporated and the residue was dissolved in 10 ml of water and desalted to afford 0.48 g (52%, 34% overall yield based on the isonitrile) of the amino acid. The diastereomeric ratio was 57:43.

2-Aminobutyric Acid (Butyrine). A. Hydroboration. To a stirred solution of 0.80 g (5 mmol) of 2-phenyl-2-butyl isonitrile dissolved in 30 ml of anhydrous ether at 0° under a nitrogen atmosphere was added rapidly 5.1 ml of 1.0 *M* ethyllithium solution in benzene and the mixture was stirred at 0° for 1 hr. After cooling to −78° the mixture was added to a large excess of carbon dioxide in ether at −40°. The solvent was evaporated to leave the carbonated imine [ir ($CHCl_3$) 1630 cm^{-1} (s)], which was dissolved in 50 ml of THF and treated with 4.0 ml of 1.3 *M* diborane solution in THF at −15°. The mixture was stirred at 2–3° for 3 hr and decomposed with dilute hydrochloric acid. After removal of THF, the aqueous solution was extracted with ether, concentrated to dryness, and worked up as previously described to yield 1.17 g (86.2%) of crude 2-[*N*-(2-phenyl-2-butyl)]aminobutyric acid hydrochloride as a white powder: mp 66–113°; ir ($CHCl_3$) 3400–2400 (broad), 1715 (m), and 1575 cm^{-1} (s). An analytical sample was obtained by recrystallization from ether–ethyl acetate–acetone: mp 173–175°; ir (KBr) 3530 (w, broad), 2450 (w, broad), 3090 (m, broad), 2740 (s, broad), 2510 (m), 2420 (m), 1720 (m), and 1570 cm^{-1} (s).

Anal. Calcd for $C_{14}H_{22}ClNO_2$: C, 61.87; H, 8.16; N, 5.15. Found: C, 61.63; H, 8.14; N, 5.14.

The crude hydrochloride (1.14 g, 4.2 mmol) was subjected to hydrogenolysis to give 0.32 g (64% overall yield) of the amino acid. Identity was confirmed by comparison of the infrared spectrum and nmr spectrum with those of an authentic sample.

B. Lithium Borohydride Reduction. The carbonated imine (10 mmol) prepared as described above was dissolved in 50 ml of THF and treated with 0.22 g (10 mmol) of lithium borohydride at −10°. The mixture was stirred at room temperature for 2 days. The work-up, as previously described, furnished 2.27 g (83.6%) of the crude hydrochloride: mp 85–119°; superimposable ir spectrum with that of an authentic sample.

The crude hydrochloride (1.16 g, 4.27 mmol) was hydrogenolyzed in the usual way to yield 0.37 g (70% overall yield) of the amino acid.

2-Amino-3-methylbutyric Acid (Valine). To a stirred solution of 1.11 g (7 mmol) of 2-phenyl-2-butyl isonitrile dissolved in 50 ml of ether at 0°, under a nitrogen atmosphere, was added rapidly 6.4 ml of a 1.2 *M* isopropyllithium solution in pentane. The mixture was stirred at 0° for 30 min and added dropwise to an excess of carbon dioxide in ether at −30°. The solvent was removed *in vacuo* to give the carbonated imine [ir ($CHCl_3$) 1635 cm^{-1} (s, broad)], which was dissolved in 50 ml of anhydrous methanol; 0.3 g (8 mmol) of sodium borohydride was added and the mixture was stirred at room temperature for 3 days. After removal of the solvent *in vacuo* the residue was dissolved in water and extracted with ether. The aqueous layer was made acidic with dilute hydrochloric acid, extracted with ether, concentrated to dryness, and worked up as previously described to yield 1.94 g (97%) of crude hydrochloride as a white powder: mp 103–143°; ir ($CHCl_3$) 3400–2400 (broad), 1710 (s), and 1565 cm^{-1} (s).

The 1.61 g (5.63 mmol) of the crude hydrochloride afforded 0.57 g (83% overall yield) of the amino acid. Identity was confirmed by comparison of the infrared spectrum in potassium bromide with that of an authentic sample.

Asymmetric Syntheses of Amino Acids Using Optically Active Hydroborating Agents. Diisopinocampheylborane[15] and triisopinocampheyldiborane[12] were prepared according to the published procedure utilizing (−)-α-pinene ($[\alpha]^{20}D$ −48.2°, 93.5% optical purity) and (+)-α-pinene ($[\alpha]^{20}D$ +46°, 89% optical purity).

2-Amino-3-methylbutyric Acid (Valine). A. (+)-Diisopinocampheylborane Reduction. To a solution of 3.3 g (24.3 mmol) of (−)-α-pinene in 20 ml of THF was added 11.5 ml of a 0.91 *M* solution of diborane (5.2 mmol of B_2H_6) in THF at 0° and the reaction mixture was stirred for 4 hr at 0°.

The carbonated imine was prepared in the usual way using 0.80 g (5 mmol) of the racemic isonitrile, 4.2 ml of 1.25 *M* isopropyllithium solution in pentane, and then carbon dioxide. To the optically active hydroborating agent in THF was added, at −10°, the solution of the carbonated imine in 30 ml of THF and the reaction mixture was stirred for 3 weeks at room temperature. After the mixture was cooled to −10°, 50 ml of dilute hydrochloric acid was added and the THF was removed under reduced pressure. Ether was added to the remaining aqueous solution and the solution was stirred overnight at room temperature. The aqueous layer was separated, concentrated to dryness, and worked up as previously described to afford 1.20 g of the crude hydrochloride, mp 78–123°.

The hydrochloride (1.17 g, 4.1 mmol) was hydrogenolyzed in the usual way to give 0.24 g (42% overall yield) of valine, identified by the infrared spectrum in potassium bromide:[16] $[\alpha]^{27}_{546}$ +12.6° (*c* 3.1, 5 *N* HCl), optical purity 40%; DNP-valine: $[\alpha]^{27}_{D}$ +41.7° (*c* 0.27, 1 *N* NaOH), optical purity 42%.

B. (−)-Diisopinocampheylborane Reduction. The reaction was carried out in the same way as described above using (+)-α-pinene instead of (−) enantiomer. Overall yield of the amino acid was 43%: $[\alpha]^{27}_{546}$ −10.4° (*c* 3.1, 5 *N* HCl); optical purity 35%.

C. Triisopinocampheyldiborane Reduction. To 12.1 ml of a 0.64 *M* solution of diborane (7.7 mmol of B_2H_6) in THF was added a solution of 3.1 g (23 mmol) of (−)-α-pinene in 10 ml of THF at 0° and the reaction mixture was stirred for 3 hr at 0°. To this mixture was added a solution of 7 mmol of the carbonated imine, and the reaction mixture was stirred at 0° for 3 days. The previously described work-up gave 1.83 g of the hydrochloride, which was subjected to hydrogenolysis to yield 0.31 g (38% overall yield) of valine: $[\alpha]^{27}_{546}$ +8.7° (*c* 3.0, 5 *N* HCl), optical purity 28%; DNP-valine $[\alpha]^{27}_{D}$ +34.7° (*c* 0.27, 1 *N* NaOH), optical purity, 35%.

2-Aminobutyric Acid (Butyrine). A. (+)-Diisopinocampheylborane Reduction. To a solution of 4.0 g (29.4 mmol) of (−)-α-pinene in 20 ml of THF was added 9.9 ml of a 1.27 *M* solution of diborane (6.3 mmol of B_2H_6) in THF at 0° and the reaction mixture was stirred for 4 hr at 9°.

To the optically active hydroborating agent in THF was added the solution of the carbonated imine (6 mmol) in 30 ml of THF at −10° and the reaction mixture was stirred for 2 weeks at room temperature. After the mixture was cooled to −10°, 50 ml of dilute hydrochloric acid was added. The THF was removed under reduced pressure, and the remaining aqueous layer was worked up as previously described to afford 1.33 g of the crude hydrochloride, mp 82–142°.

The hydrochloride (1.32 g, 4.86 mmol) was hydrogenolyzed in the usual way to give 0.35 g (57% overall yield) of butyrine, identified by the infrared spectrum in potassium bromide: $[\alpha]^{27}_{546}$ +2.9° (*c* 3.0, 5 *N* HCl), optical purity 11%; DNP-butyrine $[\alpha]^{27}_{D}$ +15.0° (*c* 0.28, 1 *N* NaOH), optical purity 16%.

B. (−)-Diisopinocampheylborane Reduction. The reaction was carried out in the same way as described above using (+)-α-pinene instead of (−)-α-pinene. Overall yield of the amino acid was 58%: $[\alpha]^{27}_{546}$ −3.5° (c 3.2, 5 *N* HCl), optical purity 13%; DNP-butyrine $[\alpha]^{27}_{D}$ −13.3 (*c* 0.25, 1 *N* NaOH), optical purity 14%.

Asymmetric Syntheses of Amino Acids Using Optically Active (*R*)-(+)-2-Phenyl-2-butyl Isonitrile. Optically pure (*R*)-(+)-2-phenyl-2-butyl isonitrile, $[\alpha]^{24}_{546}$ +2.87° (*c* 3, dioxane), was prepared according to the published procedure.[17]

The reduction procedures described previously were repeated on the optically active (*R*)-(+)-isonitrile and the identity of amino acids was confirmed by comparison of the infrared spectrum with that of an authentic sample.[16] The results are summarized in Table I.

Registry No.—(±)-**1**, 49690-21-3; (*R*)-**1**, 32528-86-2; isoleucine, 443-79-8; alloisoleucine, 3107-04-8; 2-[*N*-(2-phenyl-2-butyl)]amino-3-methylpentanoic acid hydrochloride, 49690-23-5; ethyl 3-methyl-2-oxopentanoate, 26516-27-8; ethyl 3-methyl-2-oxopentanoate 2,4-dinitrophenylhydrazone, 49690-24-6; 2-[*N*-(2-phenyl-2-butyl)]aminobutyric acid hydrochloride, 49690-25-7; butyrine, 80-60-4; valine, 516-06-3; 2-[*N*-(2-phenyl-2-butyl)]amino-3-methylbutyric acid hydrochloride, 49690-26-8; (*S*)-2-[*N*-[(*R*)-2-phenyl-2-butyl]]amino-3-methylbutyric acid hydrochloride, 49690-27-9; (*S*)-2-[*N*-[(*R*)-2-phenyl-2-butyl]]aminobutyric acid hydrochloride, 49690-28-0.

References and Notes

(1) The support of this work by Public Health Service Grant No. 04065 from the National Cancer Institute is gratefully acknowledged.
(2) H. M. Walborsky and G. E. Niznik, *J. Amer. Chem. Soc.*, **91**, 7778 (1969).
(3) H. M. Walborsky, W. H. Morrison, III, and G. E. Niznik, *J. Amer. Chem. Soc.*, **92**, 6675 (1970); G. E. Niznik, W. H. Morrison, III, and H. M. Walborsky, **39**, 600 (1974).
(4) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971, p 305.
(5) R. G. Hiskey and R. C. Northrop, *J. Amer. Chem. Soc.*, **83**, 4798 (1961).
(6) (a) E. J. Corey, R. J. McCaully, and H. S. Sachdev, *J. Amer. Chem. Soc.*, **92**, 2476 (1970); (b) E. J. Corey, H. S. Sachdev, J. Z. Gougoutas, and W. Saenger, *ibid.*, **92**, 2488 (1970).
(7) (a) K. Harada, *J. Org. Chem.*, **32**, 1790 (1967); (b) K. Harada and T. Yoshida, *Bull. Chem. Soc. Jap.*, **43**, 921 (1970).
(8) K. R. Rao and H. A. Sober, *J. Amer. Chem. Soc.*, **76**, 1328 (1954).
(9) (a) J. C. Perrone, *Nature (London)*, **167**, 513 (1951); (b) A. Courts, *Biochem. J.*, **58**, 70 (1954); (c) ref 7b and references cited therein.
(10) In the nmr spectra authentic L-isoleucine gave the α-methine proton absorption at 4.10 ppm as a doublet with a coupling constant of 3.7 Hz, whereas the authentic mixture of racemic isoleucine and alloisoleucine exhibited two doublets at 4.11 (*J* = 3.7 Hz) and 4.18 ppm (*J* = 3.6 Hz).
(11) In the asymmetric hydroboration of Δ^1-piperidines with both reagents, no difference in the optical activities was observed: D. R. Boyd, M. R. Grundon, and W. R. Jackson, *Tetrahedron Lett.*, 2101 (1967).
(12) H. C. Brown, N. R. Ayyangar, and G. Zweifel, *J. Amer. Chem. Soc.*, **86**, 1071 (1964); D. R. Brown, S. F. A. Kettle, J. McKenna, and J. M. McKenna, *Chem. Commun.*, 667 (1967); A. Streitwieser, Jr., L. Verbit, and R. Bittman, *J. Org. Chem.*, **32**, 1530 (1967).
(13) G. Zweifel, N. R. Ayyangar, T. Munekata, and H. C. Brown, *J. Amer. Chem. Soc.*, **86**, 1076 (1964).
(14) R. Locquin, *Bull. Soc. Chim. Fr.*, **35**, 964 (1966).
(15) H. C. Brown, M. R. Ayyangar, and G. Zweifel, *J. Amer. Chem. Soc.*, **86**, 397 (1964).
(16) The authentic sample was prepared by dissolving 55 mg of (*R*)-valine and 45 mg of (*RS*)-valine in water and evaporating the solution to dryness. An authentic sample of butyrine was prepared in a similar manner.
(17) H. M. Walborsky and G. E. Niznik, *J. Org. Chem.*, **37**, 187 (1972).