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Supplementary Material Available: A list of atomic parameters, bond distances, bond angles, and torsion angles (18 pages). Ordering information is given on any current masthead page.

Absolute Configuration of 2-Amino-4-phenylbutyric Acid (Homophenylalanine)

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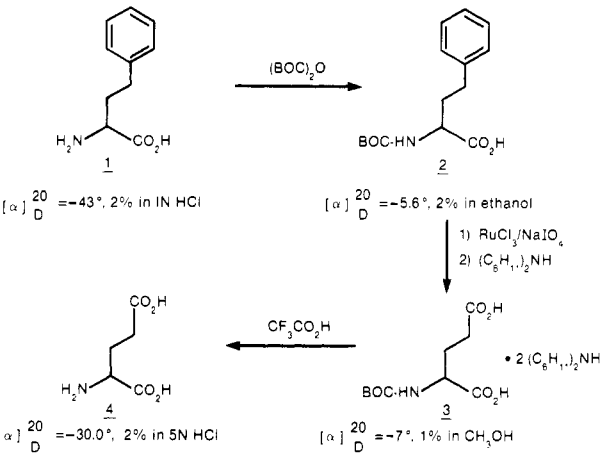
In the design of novel inhibitors of peptidase enzymes our efforts are often guided by results obtained with model peptides, some of which may contain uncommon or non-naturally occurring amino acids. Recently, our attention has been directed toward 2-amino-4-phenylbutyric acid (1). This compound, which may be viewed as a homologue of the naturally occurring amino acid phenylalanine ("homophenylalanine"),[1] is a component of new agents of pharmacological interest.[2] We thus became aware that a considerable amount of confusion has existed in the literature for some time with respect to assignment of absolute configuration to the enantiomers of this unusual amino acid.

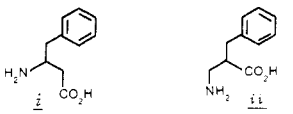
Resolution of 2-amino-4-phenylbutyric acid, by crystallization of the *N*-formyl derivative as its brucine salt, was first reported by du Vigneaud and Irish in 1938.[3] These workers assigned the natural L-configuration to the dextrorotatory isomer ($[\alpha]^{30}_D$ +48.8°, 1% in 1 N HCl) on the basis of comparison of the pH dependence of its specific rotation with that of naturally occurring amino acids. Additionally, in a series of feeding experiments initiated by Knoop[4] and verified by du Vigneaud,[3] it was concluded that the *N*-acetyl derivative of the levorotatory isomer is "less readily handled by the body" and thus corresponds to the unnatural D isomer. In 1964, Dirkx and Sixma[5] correlated the positive Cotton effect observed for the dextrotatory isomer ($[\alpha]^{25}_{600}$ +47°, 0.1% in 0.1 N HCl) with that observed for naturally occurring isomers of a number of other amino acids, including phenylalanine. Also in 1964, preparation of isotopically labeled L-homophenylalanine by submitting racemic material to D-amino acid oxidase and recovering unchanged amino acid was reported but without physical data.[6] In 1970, Sakota and co-workers[7] subjected *N*-acetyl-*dl*-α-amino-β-benzalpropionic acid to hydrolysis with "Biodiastase". Hydrogenation of the resulting free amino acid gave levorotatory 2-amino-4-phenylbutyric acid ($[\alpha]^{20}_D$ −18°, 1% in HCl), which was claimed as the naturally occurring L isomer; a literature citation used to support this claim refers only to a synthesis of the racemic material.[8] In 1976, Arold and co-workers[9] reported resolution of 1 by a procedure virtually identical with that reported earlier by du Vigneaud;[3] the levorotatory isomer ($[\alpha]^{20}_D$ −45.6°, 1% in 1 N HCl), however, was assigned the natural L configuration without comment. This material was subsequently incorporated into a nonapeptide bradykinin analogue. Indeed, the levorotatory isomer ($[\alpha]^{30}_D$ −47°, 1% in HCl) was offered commercially as "L-α-amino-4-phenylbutyric acid" as late as 1981.[10]

Confusion concerning the absolute configuration of 2-amino-4-phenylbutyric acid is related to the fact that this substance has not been chemically converted to a compound of known absolute configuration. Such a transformation has now been accomplished, thus unambiguously establishing the absolute configuration of this important amino acid.

Reaction of the sodium salt of (−)-2-amino-4-phenylbutryic acid[11] with di-*tert*-butyl dicarbonate in aqueous *tert*-butyl alcohol afforded *t*-BOC derivative 2, which was characterized as its dicyclohexylammonium salt. Ruthenium tetraoxide oxidation of 2 (free acid) using the modification recently reported by Sharpless and co-



(1) Note that other *types* of homologues of phenylalanine can also exist (i, ii). For example, i has been reported and referred to as "β-homophenylalanine". See Ondetti, M. A.; Engle, S. L. *J. Med. Chem.* **1975**, *18*, 761.



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(11) Chemical Dynamics Corp. Stock No. 05-4525-00, see ref 10.

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workers[12] led to *N*-(*tert*-butyloxycarbonyl)glutamic acid, which was purified and characterized via its bis(dicylohexylammonium) salt.[13] Deprotection with trifluoroacetic acid afforded free glutamic acid, which was isolated by ion-exchange chromatography and recrystallized from aqueous ethanol: $[\alpha]^{20}_D$ −30.0°, 2% in 5 N HCl, [reported[14,15] for natural L-glutamic acid: $[\alpha]^{25}_D$ +31.8°, 2% in 5 N HCl].

As summarized above, levorotatory 2-amino-4-phenylbutyric acid was converted in three steps to levorotatory glutamic acid, which corresponds to unnatural D-glutamic acid.[14,15] This result is consistent with the assignment originally made by du Vigneaud[3] and later supported by Dirkx and Sixma.[5] It is thus clearly established that the absolute configuration of levorotatory 2-amino-4-phenylbutyric acid corresponds to that of the unnatural D-amino acids and the dextrotatory isomer to the natural L series.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian XL-100A or JEOL FX-60Q spectrometer and are reported in δ units, using tetramethylsilane as standard. IR spectra were recorded on a Perkin-Elmer 621 spectrometer. Mass spectra were recorded on an AEI MS-9 mass spectrometer. Melting points were recorded on a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter using a 1-dm path length. Except acetonitrile, which was distilled from calcium hydride before use, all solvents and reagents were of reagent grade and were used without further purification.

Preparation of (−)-*N*-(*tert*-Butyloxycarbonyl)-2-amino-4-phenylbutyric Acid (2). To a solution of (−)-2-amino-4-phenylbutyric acid[11] (7.9 g, 44 mmol; $[\alpha]^{20}_D$ −43°, 2% in 1 N HCl) in *tert*-butyl alcohol (40 mL) containing 5.5 M aqueous sodium hydroxide solution (8 mL) at 25 °C was added a solution of di-*tert*-butyl dicarbonate (9.6 g, 44 mmol) in *tert*-butyl alcohol (10 mL) over a period of 10 min. The resulting mixture was stirred at 25 °C for 24 h, after which water and pentane were added, and the mixture was filtered. The aqueous layer was separated, washed with pentane, and acidified with 5% aqueous potassium hydrogen sulfate. The solution was extracted four times with ethyl acetate. The combined extract was washed with water, dried over magnesium sulfate, and concentrated to give **2** as a viscous oil (6.4 g, 52%): ^{13}C NMR ($CDCl_3$) δ 176.6, 157, 140.6, 128.3, 126.0, 80, 55, 33.9, 31.5, 28.1; ^{1}H NMR ($CDCl_3$) δ 7.1–7.3 (5 H, m, aromatic H), 5.1 (1 H, NH), 4.3 (1 H, m, CH), 2.7 (2 H, t, $PhCH_2$), 2.1 (2 H, m, $CHCH_2CH_2$), 1.45 (9 H, s, $C(CH_3)_3$); IR ($CHCl_3$) 1715 cm^{-1}; mass spectrum, *m/e* 279; $[\alpha]^{20}_D$ −5.6° (*c* 2, ethanol). A salt was prepared from **2** (490 mg) and dicyclohexylamine (350 μL) in ether: mp 153.5–154.5 °C after recrystallization from acetonitrile. Anal. Calcd for $C_{27}H_{44}N_2O_4 \cdot 0.25H_2O$: C, 69.71; H, 9.64; N, 6.02. Found: C, 69.63; H, 9.44; N, 5.99.

Preparation of (−)-*N*-(*tert*-Butyloxycarbonyl)glutamic Acid (3). To a mixture of **2** (5.2 g, 18.6 mmol), sodium metaperiodate (70 g, 0.33 mol), carbon tetrachloride (80 mL), acetonitrile (80 mL), and water (120 mL) was added ruthenium trichloride hydrate (130 mg, 0.5 mmol). The resulting mixture was stirred at 25 °C for 21 h, after which it was diluted with water (500 mL) and ethyl acetate (500 mL) and filtered. The filtrate was separated and the aqueous layer was extracted four more times with ethyl acetate. The organic layers were combined and extracted three times with 10% aqueous sodium bicarbonate solution. The aqueous extracts were then acidified with 5% potassium hydrogen sulfate solution and extracted three times with ethyl acetate. The extracts were combined, dried over magnesium sulfate, and concentrated to give a foamy solid (2.0 g), which was chromatographed on Silicar CC4 (Mallinckrodt, chloroform to ethyl acetate elution gradient) to give **3** as a clear, viscous oil (900 mg, 19%). A salt was prepared from dicyclohexylamine and recrystallized twice from ethanol/ether (900 mg, 8%): mp 172–173 °C; $[\alpha]^{20}_D$ −7° (*c* 1, CH_3OH) [lit. for the naturally occurring L isomer:[13] mp 171–172 °C; $[\alpha]_D$ + 9.1° (*c* 1, CH_3OH)]. Anal. Calcd for $C_{38}H_{63}N_3O_6 \cdot 0.5H_2O$: C, 65.98; H, 10.42; N, 6.79. Found: C, 66.10; H, 10.27; N, 6.77.

The free acid was liberated from the salt by dissolution in 5% aqueous potassium hydrogen sulfate and extraction with ethyl acetate: ^{13}C NMR (CD_3OD) δ 176.4, 175.6, 157.8, 80.6, 55, 31.1, 28.7, 28.1; $[\alpha]^{20}_D$ +13.2° (*c* 1, CH_3OH) [lit.[13] $[\alpha]_D$ −16.1° (*c* 1, CH_3OH) for the naturally occurring L isomer].

Preparation of (−)-Glutamic Acid (4). A solution of **3** (free acid, derived from 900 mg of the bis(dicyclohexylammonium) salt as described above) in trifluoroacetic acid was stirred at 25 °C for 1 h, after which it was concentrated by rotary evaporation. The residue was dissolved in water and applied to a column of excess AG50W × 2 ion-exchange resin (proton form). The column was eluted with water to remove trifluoroacetic acid and then with 5% aqueous pyridine. Fractions were monitored with ninhydrin spray reagent; those giving a positive stain were combined and concentrated. The residue was recrystallized to give (−)-glutamic acid (109 mg, 50%): $[\alpha]^{20}_D$ −30.0° (*c* 2, 5 N HCl) [lit.[14,15] $[\alpha]^{25}_D$ +31.8° (*c* 2, 5 N HCl) for the naturally occurring L isomer]. The synthetic material was identical with an authentic sample: ^{1}H NMR, IR, TLC, melting point.

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Palladium-Catalyzed Reactions of Allylic Electrophiles with Organometallic Reagents. A Regioselective 1,4-Elimination and a Regio- and Stereoselective Reduction of Allylic Derivatives[1]

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Palladium complexes have been shown to be effective catalysts in the cross-coupling reaction[3] of allylic electrophiles with alkenyl- or arylmetals containing Al,[4] B,[5] Hg,[6] Mg,[7] Si,[8] Sn,[4] and Zr,[4,9] as well as allylmetals containing Na[10] and Sn.[11] In addition, a few Pd-promoted stoi-

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