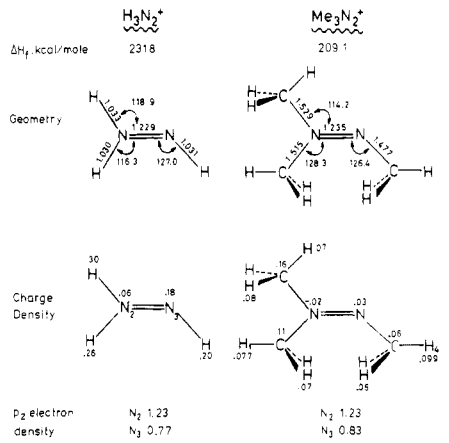

Figure 1. Summary of MNDO results for $H_3N_2^+$ and $Me_3N_2^+$.

of **6** are also in the order we had expected, i.e., more positive charge on the atoms attached to the formally positive N_2 than on those attached to N_3. Nevertheless, MNDO predicts H_1 of **6** to have a smaller positive charge than H_4. This agrees with the NMR result of H_1 appearing upfield of H_4 in **3**. Electron density is generally accepted as being an important factor in determining ^1H NMR chemical shifts, although it is not the only factor. In an attempt to see if the rather small charge difference calculated for the hydrogens of **6** could lead to the observed shift differences for **2** and **3**, we calculated the in-plane hydrogen charge densities for 1,2-*cis*-dimethyldiazene (as a model for **1**), obtaining 0.034 and for 1-protio-1,2-*cis*-dimethyldiazene (as a model for **4**) and obtaining 0.086 and 0.104 for H_1 and H_4, respectively (average 0.096). We note that the MNDO hydrogen charge densities are in the same order as the proton chemical shifts, although a plot of one against the other is not linear. Obviously the models are not perfect, and even if MNDO charge densities were perfect, and charge density were the only factor influencing chemical shift, a straight line would not be expected. The MNDO calculations emphasize the importance of N=N π-bond polarization in determining charge distribution and do predict a downfield shift for H_4 compared to H_1 of **3**, as is observed experimentally. We presume that the presence of the coplanar, formally sp^2 lone pair at N_3 is important in determining the charge distribution in diazenium salts.[4]

Experimental Section

1 and **2** were prepared as previously described.[5]

2-Methyl-2,3-diazabicyclo[2.2.2]oct-2-enylium fluorosulfonate (3) was generated by treating the azo compound with 1 equiv of methyl fluorosulfonate in CD_3CN: ^1H NMR (CD_3CN) δ 5.72 (bs, 1 H), 5.27 (bt, 1 H), 4.49 (s, 3 H), 2.0–2.2 (m, 4 H), 1.6–1.8 (m, 2 H), 1.4–1.6 (m, 2 H).

2-Protio-2,3-diazabicyclo[2.2.2]oct-2-enylium fluoroborate (4) was generated by addition of 1 equiv of an ether solution of HBF_4 to the azo compound in CD_3CN: ^1H NMR (CD_3CN) δ 5.58 (bs, 2 H), 2.12 (bd, 4 H), 1.54 (bd, 4 H).

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Registry No. **1**, 3310-62-1; **2**, 43008-10-2; **3**, 88868-48-8; **4**, 88868-49-9; $H_3N_2^+$, 51943-19-2; $Me_3N_2^+$, 88868-50-2; methyl fluorosulfonate, 421-20-5.

(4) One could presumably construct a "shielding cone" model as a framework for rationalizing the chemical shifts.

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Novel Synthesis of L-Phenylalanine

Jacob S. Tou* and Billy D. Vineyard

Nutrition Chemicals Division, Monsanto Company, St. Louis, Missouri 63167

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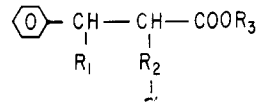
There has been considerable interest in the synthesis of phenylalanine (**1a**) since the discovery of the artificial sweetner aspartame.[1] Several synthetic routes to L-



	R_1	R_2	R_3
a.	H	NH_2	H
b.	OH	NH_2	H
c.	Cl	$NHCOCH_3$	C_2H_5
d.	$OCOCH_3$	$NH_2 \cdot HCl$	H
e.	H	$NHCOCH_3$	H
f.	$OCOCH_3$	$NHCOCH_3$	C_2H_5
g.	H	$NHCOCH_3$	C_2H_5
h.	OH	$NHCOCH_3$	H

phenylalanine have been reported in the past.[2] Among these, Vogler's procedure, to our knowledge, is the only known example demonstrating the transformation from *threo*-β-phenyl-L-serine (**1b**). This multistep procedure involved a hydrogenolysis of *N*-acetyl-β-chloro-L-phenylalanine ethyl ester (**1c**) in the presence of perchloric acid.

Now we report an efficient three-step synthesis of L-phenylalanine from *threo*-β-phenyl-L-serine[3] (Scheme I), which can be prepared by the enzymatic reaction of benzaldehyde and glycine.[3a] The key step is the hydrogenolysis of the hydrochloride salt of *threo*-*O*-acetyl-β-phenyl-L-serine (**1d**) to *N*-acetyl-L-phenylalanine (**1e**). We believe that this reaction sequence offers a synthetically useful alternative for the preparation of L-phenylalanine.

Results

This study was begun with the readily available DL materials. The ideal transformation of β-phenylserine (**1b**) to phenylalanine (**1a**) would be the direct removal of the OH group in **1b**. Cleavage of a benzylic C–O bond has been widely studied in the past.[4] The most versatile procedure for this manipulation is hydrogenolysis. However, our attempts at direct hydrogenolysis of β-phenylserine under various conditions ($HClO_4$,[5] HOAc, HCl, etc.; catalyst Pd/C, $Pd/BaSO_4$; pressure 1 atm–150 psi; temperature 25–80 °C) were unsuccessful. Efforts were then made to activate the C–O bond in β-phenylserine. *threo*-*O*-Acetyl-*N*-acetyl-β-phenylserine ethyl ester (**1f**),

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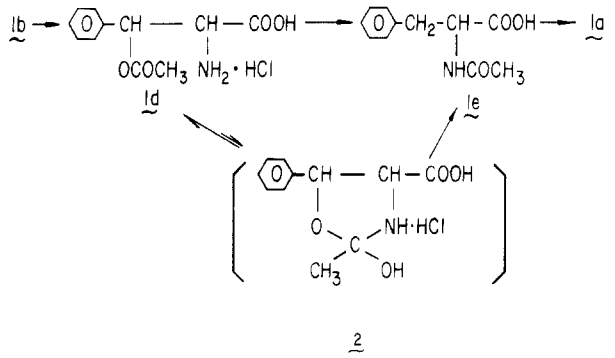
Scheme I



an *O*-acetyl derivative of β-phenylserine, was prepared in three steps according to the procedure described by Carrara.[6] The hydrogenolysis went smoothly in the presence of palladium catalyst to give *N*-acetylphenylalanine ethyl ester (**1g**) in 86% yield. The investigation was extended to *threo*-*O*-acetyl-β-phenylserine hydrochloride (**1d**), which was prepared directly from *threo*-β-phenylserine[7] in 96% yield. Hydrogenolysis of **1d** was carried out in acetic acid–water in the presence of $Pd/BaSO_4$. Surprisingly, this reaction gave mainly *N*-acetylphenylalanine (**1e**), an O → N acyl shift hydrogenolysis product, accompanied by a small amount (<10%) of phenylalanine and β-phenylserine. The major product **1e** was isolated by crystallization from water in about 82% yield.

As expected, when optically pure *threo*-*O*-acetyl-β-phenyl-L-serine hydrochloride (**1d**)[3b] was subjected to the above-mentioned hydrogenolysis condition, we obtained *N*-acetyl-L-phenylalanine (**1e**). Since the conversion of **1e** to **1a** by acidic hydrolysis is well-known, the hydrogenolysis route reported here completed a three-step sequence from *threo*-β-phenyl-L-serine to L-phenylalanine.

Mechanism

A probable mechanism for the unexpected formation of *N*-acetylphenylalanine in the hydrogenolysis reaction is shown in Scheme I. The key to this mechanism is the formation of the oxazolidine **2**—a generally accepted common intermediate for the O ⇄ N acyl migration in the acylated amino alcohol system.[8] The reduction of this cyclic intermediate **2** leads to the observed acyl shift hydrogenolysis product **1e**.[9] The two minor components, phenylalanine and β-phenylserine, found in this reaction are believed to be the hydrolysis products[10] of **1e** and **1d**, respectively.

We believe that the facile cleavage of the benzylic C–O bond of **2** drives the equilibrium from **1d** to **2** even in the acidic medium, which should favor **1d**. Furthermore, the fact that only a small amount of phenylalanine was detected indicates that direct acetoxy bond cleavage of **1d**, if it occurs at all, is much slower than the benzylic C–O bond cleavage of **2**, which gives the acyl shift product **1e**.

Experimental Section

^1H NMR spectra were taken on a Varian T-60 NMR spectrometer with Me_4Si as an internal standard. Hydrogenolysis reactions were performed in a 100-mL glass bottle on a Parr shaker apparatus. Optical rotations were recorded on a Perkin-Elmer Model 141 polarimeter, using a 10-cm microcell. Reaction progress was monitored with a liquid chromatograph (Waters Associates) equipped with a UV detector (210 nm). The column (C18) was eluted with 20% acetonitrile in 0.01 M phosphoric acid. Gas chromatographic data was obtained on a Varian 3700 instrument (FID, 3% OV-101 on Chromosorb). *threo*-β-Phenyl-DL-serine was purchased from Sigma Chemical Co., St. Louis, MO.

Hydrogenolysis Procedure. *N*-Acetyl-DL-phenylalanine Ethyl Ester (1g). Compound **1f** (0.8 g, 2.73 mM) in 10 mL of ethanol, 1 mL of triethylamine,[11] and 0.4 g of 5% $Pd/BaSO_4$ was hydrogenated at 50 psi for 6 h at 70 °C. Catalyst was removed by filtration. GC analysis indicated that the starting material **1f** was completely converted to **1g**. Solvent was removed in vacuo. The resulting solid was triturated with ether to give product **1g** (0.55 g, 86% yield): ^1H NMR ($CDCl_3$) δ 7.2 (s, 5 H), 6.6 (m, 1 H), 4.8 (q, 1 H), 4.2 (q, 2 H), 3.1 (d, 2 H), 2.0 (s, 3 H), 1.3 (t, 3 H). A similar result was obtained when this reaction was carried out with 5% $Pd/BaSO_4$ in acetic acid solution.

***N*-Acetyl-DL-phenylalanine (1e).** Compound **1d** (2 g, 7.7 mM) was dissolved in 22 mL of water–acetic acid (1:4 ratio) solution. Catalyst (98 mg of 5% $Pd/BaSO_4$) was added and then hydrogenated at 50 psi for 8 h at 60 °C. Catalyst was removed by filtration and the filtrate concentrated in vacuo. The resulting oily residue solidified on standing. *N*-Acetyl-DL-phenylalanine (**1e**) was isolated (1.3 g, 81.8% yield) after triturating the above crude solid with water. This material displayed the same physical and spectroscopic properties as an authentic sample: ^1H NMR (Me_2SO-d_6) δ 8.2 (d, 1 H), 7.3 (s, 5 H), 4.4 (m, 1 H), 3.1 (m, 2 H), 1.9 (s, 3 H).

The hydrogenolysis of optically pure **1d**, $[\alpha]^{20}_D$ −50.4° (*c* 0.4, 4:1 HOAc–H_2O), was conducted in the same manner. Solvent was removed to give a crude reaction residue whose rotation was $[\alpha]^{20}_D$ +48.5° (*c* 1.0, 4:1 HOAc–H_2O) after correction for the two minor side products (**1a** and **1b**). Pure authentic sample: $[\alpha]^{20}_D$ +52.1° (*c* 1.3, 4:1 HOAc–H_2O).

Registry No. DL-*threo*-**1d**, 88854-16-4; L-*threo*-**1d**, 88854-17-5; DL-**1e**, 2901-75-9; L-**1e**, 2018-61-3; DL-*threo*-**1f**, 88854-18-6; DL-**1g**, 4134-09-2; L-phenylalanine, 63-91-2.

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(9) We also found that the hydrogenolysis of *N*-acetyl-β-phenylserine (**1h**) gave *N*-acetylphenylalanine in the presence of 1 equiv of hydrochloric acid. This reaction may also involve the oxazolidine **2** intermediate. When this reaction was carried out without palladium catalyst, the starting material **1h** was recovered. This result rules out the possible dehydration–hydrogenation pathway that would also give **1e**.
(10) When the stirring time was extended on completion of hydrogen uptake, the relative amount of phenylalanine was clearly increased while that of β-phenylserine was essentially unchanged as evidenced by HPLC analysis. The other possible path that would also account for the formation of phenylalanine is direct reduction of the starting material **1d**.
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Synthesis of 3-Methoxycycloheptatrienones

Victoria A. Roberts, Michael E. Garst,*[1] and Norman E. Torres[2]

Department of Chemistry, D-006, University of California, San Diego, La Jolla, California 92093

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Methods have been developed to convert cycloheptatrienone into hydroazulenes,[3a] (*E*)- or (*Z*)-cyclodecenes,[3b] and bicyclo[5.4.0]undecanes.[3c] Extension of these model studies to naturally occuring substances will require efficient preparations of substituted cyclo-

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