carboxylic acid **7** (2.24 g, 0.0129 mol) was dissolved in 35 mL of 85% hydrazine hydrate. The solution was heated at 70 °C for 15 h and concentrated in vacuo, and the resultant residue was dried in vacuo over concentrated H_2SO_4 to give a white solid. Trituration of the solid with ethanol gave 1.15 g (68%) of a substance which was 80% D-2-amino-4-methoxy-*trans*-but-3-enoic acid (**8**) and 20% racemate: mp 220 °C dec; $[\alpha]^{25}_D$ −98° (*c* 0.8370, H_2O); NMR (D_2O) δ 7.33 (d, 1 H, *J* = 13 Hz, -OC**H**=CH-), 5.45 (dd, 1 H, *J* = 10 and 13 Hz, -OCH-=C**H**-), 4.67 (d, 1 H, *J* = 10 Hz, -OCH=CHC**H**<), 4.11 (s, 3 H, CH_3O-); mass spectrum, *m/e* 86.

Anal. Calcd for $C_5H_9NO_3$: C, 45.80; H, 6.92; N, 10.68. Found: C, 45.90; H, 6.81; N, 10.88.

The specific rotation, $[\alpha]^{25}_D$ −98°, indicates that the D isomer is present in 80% enantiomeric excess.

Acknowledgment. We thank the staff of the Physical Chemistry Department of Hoffmann-La Roche Inc. for the determination of spectral and analytical data.

Registry No.—**1a,** 35891-72-6; **2,** 14110-03-3; **3a,** 66966-87-8; **3b,** 66966-88-9; (*E*)-**4,** 66966-89-0; (*Z*)-**4,** 66966-90-3; **5,** 66966-91-4; **6,** 66966-92-5; **7,** 66966-93-6; **8,** 67010-40-6.

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(13) Some acetic acid and acetic anhydride invariably codistill with the enol ethers. Thus, a greater amount of sodium methoxide may be necessary to achieve this pH.
(14) We thank Dr. J. Scannell of the Microbiology Department at Hoffmann-La Roche Inc. for a sample of the natural amino acid **1a.**

Synthesis of DL-2-Amino-4-(2-aminoethoxy)-*trans*-but-3-enoic Acid

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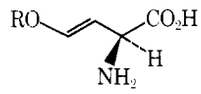
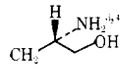
The racemic modification of the naturally occurring amino acid, L-2-amino-4-(2-aminoethoxy)-*trans*-but-3-enoic acid (**1b**), was synthesized starting from bis(2-chloroethyl) ether (**6**) and diethyl acetamidomalonate (**7**). The route included formation of the dehydroamino acid derivative **12,** followed by base-mediated isomerization of the double bond to form the critical enol ether linkage in **13.** Removal of the protecting groups from **13** then gave rise to the racemic amino acid **15** in an overall yield of 11%.

Recently, a new type of α-amino acid has been found in nature.[1-3] The members, **1,** of this class of compounds are

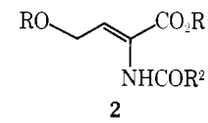


1a, R = CH_3[1]
b, R = $CH_2CH_2NH_2$[2]
c, R = 

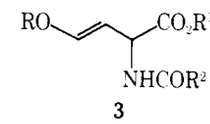
distinguished both by having a centrally located enol ether function in the molecule and by their ability to inhibit the production of ethylene in plant tissue.[2,5] Since ethylene plays a vital role in controlling certain plant life processes, this activity is both intriguing and potentially economically important.[6]

We became interested in developing synthetic methods which would make these compounds and analogues of these compounds more readily available. One such sequence, described in the preceding paper, was used to make L-2-amino-4-methoxy-*trans*-but-3-enoic acid (**1a**).[7] The important steps of that synthesis are the generation of a hemiacetal ester followed by its pyrolysis to yield an enol ether. In this paper, we wish to describe a second route to these compounds and illustrate it with a synthesis of racemic 2-amino-4-(2-aminoethoxy)-*trans*-but-3-enoic acid (**1b**).

In our projected synthesis of **1b,** we intended to make the central enol ether function by isomerization of the double



2



3

bond in a dehydroamino acid derivative **2** to form the enol ether **3.** The suggestion that this might be a fruitful approach comes from the studies of S. J. Rhoads and co-workers[8] and J. Hine and co-workers.[9] By studying the equilibration of methyl 4-methoxybutenoates **4,** both groups demonstrated that the double bond is stabilized more effectively by the methoxy group than by the ester. Thus, at equilibrium Hine found the mixture of olefins to be 99% **4b,** while Rhoads, under two different sets of equilibrating conditions, found the mixtures to be 92.5 and 96.9% **4b,** respectively.

$CH_3OCH_2CH{=}CHCO_2CH_3$
4a

$\rightleftarrows CH_3OCH{=}CHCH_2CO_2CH_3$
4b

In order to make the enol ether by this method, we required an appropriately substituted dehydroamino acid derivative. A recent publication by Shin and co-workers describes the synthesis of such compounds by the elimination of acetic acid from an *N,O*-diacetylhydroxyamino acid derivative.[10] This result suggested to us that dehydroamino acids could also be obtained by the elimination of HCl from a suitably disposed

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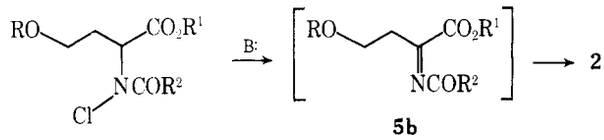


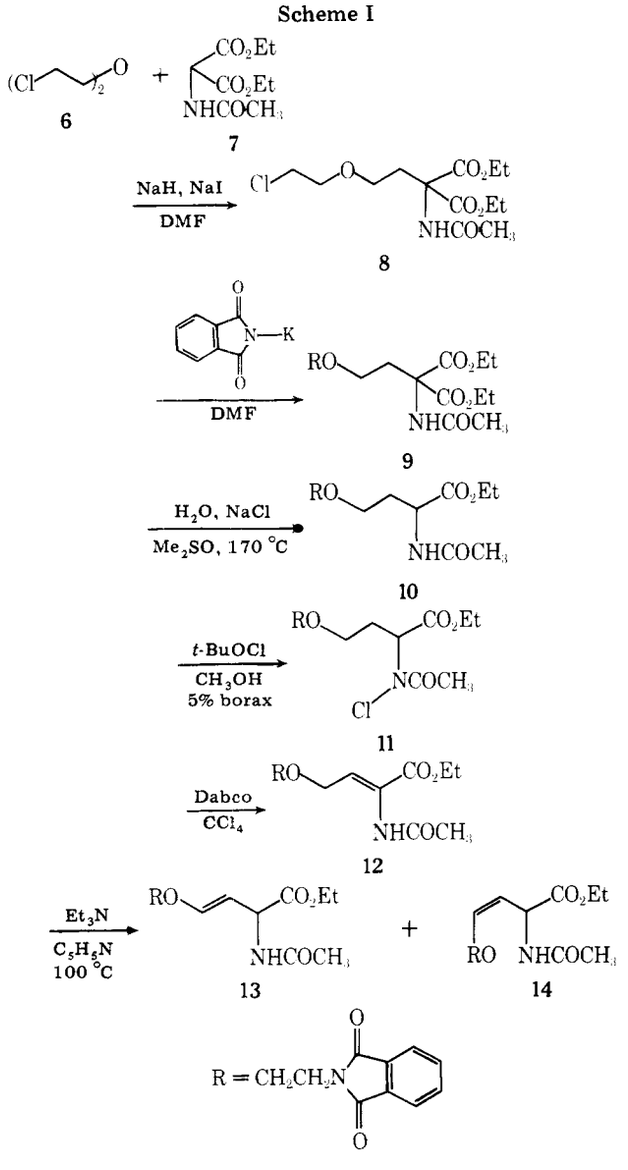
5a 5b

N-chloroamide. Thus, we hoped to convert **5a** to **2** via the acyl imine intermediate **5b.** Sometime after the completion of our work demonstrating the utility of this method, Poisel and Schmidt published essentially the same route to dehydroamino acids.[11] Following is a description of our use of this sequence to make the dehydroamino acid derivative **12.**

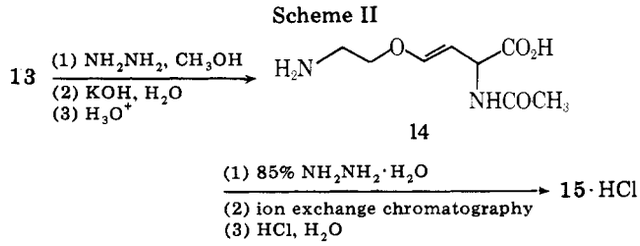
Alkylation of the sodium salt derived from diethyl acetamidomalonate (**7**) to yield the 2-chloroethyl ether **8** was accomplished in 85% yield by heating the salt at 60 °C in *N,N*-dimethylformamide solution with an excess of bis(2-chloroethyl) ether (**6**) and a catalytic amount of sodium iodide (see Scheme I). Treatment of chloroethyl ether **8** with potassium phthalimide in *N,N*-dimethylformamide solution at 100 °C gave phthalimido ether **9** (65%), which was deethoxycarbonylated by the method of Krapcho[12] to give the 2-acetamido-4-alkoxybutyrate **10** (76%). Oxidation of **10** with *tert*-butyl hypochlorite in methanol solution with borax buffer present gave an essentially quantitative yield of the *N*-chloroamide **11** as judged by TLC analysis.

The elimination of HCl from **11** followed by isomerization

Scheme I



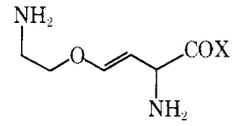
Scheme II



of the resultant acyl imine to give **12** (average yield 81%) was accomplished with 1,4-diazabicyclo[2.2.2]octane (Dabco) in carbon tetrachloride solution. In preliminary studies on a model compound, we found the choice of base to be critically important to the success of this reaction. Dabco was by far the best reagent for this conversion. The assignment of *Z* stereochemistry to **12** is based on the comparison of its NMR spectrum with a dehydroamino acid whose structure was secured by X-ray analysis.[13]

With the requisite substrate **12** in hand, we were set to attempt the deconjugation of the double bond to form the enol ether. A mixture consisting of the trans and cis enol ethers **13** and **14** and starting material **12** was obtained by heating a solution of **12** in 1:1 triethylamine/pyridine (a combination which was found empirically) at 100 °C for 37 h. The trans compound **13** was the major product from the reaction, while a moderate amount of the cis compound **14** and only a minor amount of the dehydroamino acid **12** were present in the mixture. Following the removal of solvent, the trans enol ether **13** was obtained in pure form (34%) by fractional crystallization of the reaction product. Mother liquors containing large amounts of the starting material **12** were recycled through the triethylamine/pyridine reaction conditions. Liquors containing major amounts of the cis isomer **14** were treated with iodine in glyme solution in order to effect equilibration between the trans and the cis isomers.[8] By following these procedures and then using preparative high-pressure liquid chromatography and fractional crystallization to isolate the trans isomer, yields between 50 and 65% could be realized for **13.**

Deprotection of the amino acid **13** was accomplished in the manner depicted in Scheme II. The phthalimido group was removed by treatment with anhydrous hydrazine in methanol solution. The ester was subsequently hydrolyzed by heating with 1 N potassium hydroxide solution at 90 °C for 24 h to give the *N*-acetylamino acid **14.** Lastly, the *N*-acetyl group was taken off by heating with 85% hydrazine hydrate at 80 °C for 40 h. After cation exchange chromatography, the racemic



15, X = OH
16, X = $NHNH_2$

amino acid **15** was isolated as its hydrochloride salt by crystallization from water/methanol. The synthetic material was found to have solution IR and NMR spectra which are identical with those of the natural product **1b.**[2,14] In addition, the natural and synthetic material behave identically upon analysis with an amino acid analyzer.

The mother liquors from the crystallization contained a substance shown by amino acid analysis to be more basic than the amino acid **15.** However, the NMR spectrum of this material is essentially identical with that of **15.** Most likely this new substance is the hydrazide **16,** possibly arising from hydrazinolysis of the ester during removal of the phthalimido group. In any event, treatment of the new material with 1 N KOH at 90 °C gives the amino acid **15** which can be isolated as its hydrochloride salt following cation exchange chroma-

tography. The overall yield of **15**·HCl thus obtained from **13** is 56%.

Experimental Section

General. Melting points were taken on a Kofler hot stage melting point apparatus (Reichert) and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 621 or a Beckman IR-9. Ultraviolet spectra were recorded on a Cary Model 16 spectrophotometer. Proton NMR spectra were obtained on Varian HA-100 and XL-100 instruments and are reported in parts per million downfield from internal or external tetramethylsilane.

A Waters Associates Prep LC/System 500 with a PrePAK-500 compression chamber and PrePAK-500/silica cartridges was used for preparative high-pressure liquid chromatography.

Silica gel 60 (0.063–0.200 mm) and plates precoated with silica gel 60 F-254 (both from E. Merck) were used for column and thin-layer chromatography, respectively.

Elemental analyses and amino acid analyses were carried out under the supervision of Dr. F. Scheidl of our Microanalytical Laboratories.

Ethyl 2-Acetamido-4-(2-chloroethoxy)-2-ethoxycarbonylbutyrate (8). Sodium hydride (30.9 g of a 50% oil dispersion; 0.65 mol) was placed in a dry three-neck flask equipped with a mechanical stirrer, an addition funnel, a reflux condenser, and an argon inlet. The hydride was washed with hexane and dried under a stream of argon. Dry *N,N*-dimethylformamide (500 mL) was added, and the suspension was cooled to 5 °C in an ice bath. Diethyl acetamidomalonate (**7**; 140 g, 0.65 mol) was added in portions with stirring at a rate which maintained a vigorous effervescence. After the addition was complete and the effervescence subsided, sodium iodide (9.66 g, 0.065 mol) was added in one portion and 460 g (3.2 mol) of bis(2-chloroethyl) ether (**6**) was added rapidly through the addition funnel. The reaction mixture was then heated at 60 °C with stirring for 24 h. The mixture was transferred to a one-neck flask and concentrated in vacuo on a rotary evaporator (600–800 mL removed). The residue was subjected to steam distillation until the distillate was clear (2–2.5 L). The pot residue was taken up in 500 mL of ether, and the organic solution was washed five times with 100-mL portions of brine. The ether solution was dried over anhydrous sodium sulfate and concentrated in vacuo to yield 175.7 g (84.5%) of crude **8**. This material is suitable for use in the next step.

A portion was purified by distillation to yield **8**: bp 135–140 °C (0.1 mm); IR ($CHCl_3$) 3400, 1715, 1655, 1470 cm^{-1}; NMR ($CDCl_3$) δ 6.96 (broad, 1 H, NH), 4.22 (q, 4 H, J = 6 Hz, $2CH_3CH_2O$–), 3.5 (m, 6 H, $ClCH_2CH_2OCH_2$–), 2.65 (t, 2 H, J = 6 Hz, $-CH_2CH_2C<$), 2.03 (s, 3 H, CH_3CO–), 1.25 (t, 3 H, J = 6 Hz, CH_3CH_2O–); mass spectrum, *m/e* 324 ($M^+ + H$), 217, 93, 63.

Anal. Calcd for $C_{13}H_{22}ClNO_6$: C, 48.23; H, 6.85; N, 4.33. Found: C, 48.06; H, 6.71; N, 4.18.

Ethyl 2-Acetamido-2-ethoxycarbonyl-4-[2-(2-phthalimido)-ethoxy]butyrate (9). A three-neck flask equipped with a mechanical stirrer, a reflux condenser, and an argon inlet was charged with 128.1 g (0.396 mol) of the chloroacetamidomalonate **8**, 109.9 g (0.59 mol) of potassium phthalimide, 6.57 g (0.04 mol) of potassium iodide, and 600 mL of dry *N,N*-dimethylformamide. The mixture was heated with stirring under argon at 100 °C for 18 h. The reaction mixture was allowed to cool and was divided into two equal portions which were processed as follows. Each was diluted with 2 L of ether, causing salts to precipitate. The solids were removed by filtration through diatomaceous earth, and the filtrates were concentrated in vacuo to remove the ether and *N,N*-dimethylformamide. The residues were each diluted with 1.5 L of ether and 100 mL of ethyl acetate. The organic phases were washed six times with water (300 mL) and once with brine (300 mL). The organic solutions were combined, dried with anhydrous sodium sulfate, and concentrated in vacuo until crystallization began. At that point, the mixture was heated on a steam bath until a clear solution was obtained. The solution was diluted with hexane until the cloud point and then set aside to crystallize. Pure **9** was collected in two crops (111.6 g, 65%): mp 101–103 °C; UV (EtOH) max 220 nm (ϵ 42 000), 240 infl (4300), 293 (920); IR ($CHCl_3$) 3410, 1775, 1738, 1712, 1678, 1495 cm^{-1}; NMR ($CDCl_3$) δ 8.0 (broad, 1 H, NH), 7.88 (s, 4 H, aromatic), 4.13 (q, 4 H, J = 7 Hz, CH_3CH_2O–), 3.5 (m, 6 H, $PhthNCH_2CH_2OCH_2$–), 2.45 (t, 2 H, J = 6 Hz, $-OCH_2CH_2C<$), 2.03 (s, 3 H, CH_3CO), 1.15 (t, 3 H, J = 7 Hz, CH_3CH_2O–); mass spectrum, *m/e* 389, 361, 319, 244, 217.

Anal. Calcd for $C_{21}H_{26}N_2O_8$: C, 58.06; H, 6.03; N, 6.45. Found: C, 58.32; H, 5.79; N, 6.40.

Ethyl 2-Acetamido-4-[2-(2-phthalimido)ethoxy]butyrate (10). A suspension consisting of 143.6 g (0.331 mol) of phthalimidoacetamidomalonate **9**, 11.9 g (0.66 mol) of water, 19.3 g (0.33 mol) of sodium chloride, and 330 mL of dimethyl sulfoxide was heated with magnetic stirring at 170 °C under argon for 8 h. The reaction mixture was allowed to cool to room temperature, diluted with 1500 mL of ethyl acetate, and washed two times with 350-mL portions of water followed by six 100-mL water washes and two 300-mL brine washes. Each aqueous layer was backwashed with a small portion of ethyl acetate which was then added to the main organic phase. The ethyl acetate solution was dried over anhydrous sodium sulfate and concentrated in vacuo to yield 91.7 g (77%) of a brown oil. This material was suitable for use in the next step.

An analytical sample was prepared by taking a portion of the oil in ether, treating the solution with charcoal, and filtering the mixture through diatomaceous earth. The filtrate was concentrated in vacuo and crystallized from ethyl acetate/petroleum ether to yield **10**: mp 90–90.5 °C; UV (EtOH) max 219 nm (ϵ 40 600), 232 infl (13 400), 240 (9400), 294 (1900), 300 infl (1800); IR ($CHCl_3$) 3300, 1775, 1730, 1720, 1640, 1555 cm^{-1}; NMR ($CDCl_3$) δ 7.8 (m, 4 H, aromatic H), 6.73 (broad, 1 H, NH), 4.64 (m, 1 H, $-CH_2CH<$), 4.08 (q, 2 H, J = 8 Hz, CH_3CH_2O–), 3.9–3.4 (m, 6 H, $PhthNCH_2CH_2OCH_2$–), 2.07 (s, 3 H, CH_3CO–), 2.02 (t, 2 H, J = 6 Hz, $-OCH_2CH_2CH<$), 1.17 (t, 3 H, J = 8 Hz, CH_3CH_2O–); mass spectrum, *m/e* 362 (M^+), 317, 289, 160.

Anal. Calcd for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.80; H, 6.32; N, 7.75.

Ethyl 2-(*N*-Chloroacetamido)-4-[2-(2-phthalimido)ethoxy]-butyrate (11). A solution consisting of 73.8 g (0.204 mol) of acetamide **10**, 8.69 g (0.023 mol) of sodium tetraborate, and 224 mL of methanol was protected from light and cooled with an ice bath to 5 °C under an atmosphere of argon. *tert*-Butyl hypochlorite (37.1 mL, 0.31 mol) was added with magnetic stirring to the solution. The ice bath was removed after addition was complete. After 45 min, an aliquot was removed and TLC analysis [silica gel plates; $CHCl_3/Et_2O$ (8:1)] showed that some starting material was still present. More *tert*-butyl hypochlorite was added in portions until TLC analysis indicated that the reaction was complete. The reaction solution was then concentrated in vacuo with protection from light to yield an oil which was taken up in carbon tetrachloride (350 mL), causing sodium salts to precipitate. The solids were removed by filtration, yielding a carbon tetrachloride solution of **11** which was used directly in the next step.

Ethyl (*Z*)-2-Acetamido-4-[2-(2-phthalimido)ethoxy]but-2-enoate (12). To the carbon tetrachloride solution of **11** obtained from the previous reaction was added 25.2 g (0.224 mol) of 1,4-diazabicyclo[2.2.2]octane (Dabco). The resultant solution was stirred magnetically for 15 h. A copious white precipitate formed after 2 h. Ethyl acetate (1 L) was added to the mixture to break up the precipitate. After allowing time for the solid to settle, the solution was decanted and the remaining precipitate washed twice with 500-mL portions of ethyl acetate. The combined organic solutions were filtered through diatomaceous earth, and the filtrate was concentrated in vacuo. The residue was taken up in chloroform and passed through a column (i.d. 47 mm) of silica gel 60 (100 g) packed in chloroform. The column was developed with 2 L of chloroform, and the chloroform solution was concentrated in vacuo to yield an oil. Crystallization from ethyl acetate/ether/hexane yielded, in two crops, 68.1 g (92.9%) of butenoate **12**, mp 113–116 °C. The average yield of **12** obtained from several large scale preparations was 81%. An analytical sample was prepared by recrystallization from the same solvent: mp 120–122.5 °C; UV (EtOH) max 220 nm (ϵ 49 200), 233 infl (21 000), 241 infl (15 700), 294 (1930), 300 (1800); IR ($CHCl_3$) 3410, 1775, 1713, 1695 infl, 1495 cm^{-1}; NMR ($CDCl_3$) δ 7.80 (m, 4 H, aromatic H), 7.53 (broad, 1 H, NH), 6.51 (t, 1 H, J = 6 Hz, $-OCH_2CH=$), 4.24 (q, 2 H, J = 8 Hz, CH_3CH_2O–), 4.18 (d, 2 H, J = 6 Hz, $-OCH_2CH=$), 3.93 and 3.74 (2 m, 2 H in each, $-NCH_2CH_2O$–), 2.13 (s, 3 H, CH_3CO–), 1.29 (t, 3 H, J = 8 Hz, CH_3CH_2O); mass spectrum, *m/e* 360 (M^+), 317, 314, 287, 174, 160.

Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 60.20; H, 5.56; N, 7.80.

Ethyl 2-Acetamido-4-[2-(2-phthalimido)ethoxy]-*trans*-but-3-enoate (13) and Ethyl 2-Acetamido-4-[2-(2-phthalimido)ethoxy]-*cis*-but-3-enoate (14). A solution consisting of 74.5 g (0.21 mol) of butenoate **12**, 487 mL of triethylamine, and 485 mL of pyridine was heated with stirring at reflux temperature under an atmosphere of argon for 37 h. The solution was allowed to cool and concentrated in vacuo. Ethyl acetate was added to the remaining oil, and the solution was concentrated again in vacuo. After repeating this process one more time, the dark brown residue was dissolved in ethyl acetate and the resultant solution was brought to the cloud point with hexane and set aside overnight to crystallize. The resultant light brown solid was collected and shown by NMR spectroscopy to consist mainly of the trans and cis enol ethers **13** and **14**. The filtrate from this crystalli-

zation was concentrated in vacuo, yielding a dark oil which was processed as described in a subsequent paragraph.

The solid was dissolved in a minimum amount of ethyl acetate, and the resultant solution was applied to a column (i.d. 47 mm) of silica gel 60 (100 g) packed in ethyl acetate. The column was developed with ethyl acetate until all UV-absorbing material was eluted. The ethyl acetate solution was concentrated in vacuo. Ether was added until the cloud point was reached, and the solution was allowed to stand undisturbed overnight while crystallization occurred (occasionally scratching or seed crystals were used to induce crystallization). The crystals which were deposited were collected by filtration (30.2 g, 41%) and shown by NMR spectroscopy to be approximately an 85:15 mixture of trans and cis enol ethers. A further crystallization from the same solvent system gave 25.5 g (34%) of **13:** mp 95–96.5 °C; UV (EtOH) max 219 nm (ϵ 49 400), 239 (11 200), 293 (2020), 300 (1860); IR ($CHCl_3$) 3435, 1778, 1717, 1678, 1504 cm^{-1}; NMR ($CDCl_3$) δ 7.8 (m, 4 H, aromatic H), 6.52 (d, 1 H, J = 12 Hz, -OC**H**=CH-), 6.25 (broad, 1 H, NH), 4.6–5.0 (m, 2 H, -OCH=C**H**C**H**), 4.16 (q, 2 H, J = 8 Hz, CH_3CH_2O-), 3.94 (broad s, 4 H, $>NCH_2CH_2O$-), 1.97 (s, 3 H, CH_3CO-), 1.24 (t, 3 H, J = 8 Hz, CH_3CH_2O-); mass spectrum, *m/e* 360 (M^+), 317, 314, 287, 174 (base), 160.

Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.96; H, 5.41; N, 7.65.

The mother liquors from the crystallizations described above contained varying amounts of the starting material **12,** trans enol ether **13,** and the cis enol ether **14.** Liquors which contained a large amount of starting material **12** were resubjected to the reaction with triethylamine and pyridine. Such material was processed as described above to yield further quantities of trans enol ether **13.**

Mixtures consisting principally of the cis enol ether were treated with iodine (20 mg of I_2/g of mixture) in dry peroxide-free glyme (10 mL/g of mixture) at 40 °C for 40 h.[8] The reaction mixture was concentrated in vacuo, leaving a residue which was dissolved in ethyl acetate. The solution was washed with 10% sodium thiosulfate solution and dried over anhydrous sodium sulfate. Concentration on a rotary evaporator yielded an oil consisting of a 3:2 mixture of trans and cis enol ethers, respectively, as determined from the NMR spectrum. This material was chromatographed in batches of 5 g each on a Waters Prep LC/System 500 with one PrePAK-500/silica cartridge using ethyl acetate/hexane/methanol (10:10:1) as the eluent. Several recycles were required for complete separation of the isomers. The α,β-unsaturated ester **12** was eluted first, followed by the trans enol ether **13** and then the cis enol ether **14.** Concentration of the appropriate fractions followed by crystallization yielded approximately 1 g of pure **13** for each 5 g of 3:2 mixture.

By diligently following these procedures, yields between 50 and 65% were realized for the trans enol ether **13.** Concentration of the fractions containing the cis isomer followed by crystallization from ethyl acetate/petroleum ether gave **14:** mp 88–90 °C; UV (EtOH) max 218 nm (ϵ 42 800), 239 infl (9800), 292 (1870), 300 infl (1750); IR ($CHCl_3$) 3435, 3410, 1775, 1735, 1715, 1670, 1513 cm^{-1}; NMR ($CDCl_3$) δ 7.8 (m, 4 H, aromatic H), 6.65 (broad, 1 H, NH), 6.07 (d, 1 H, J = 6 Hz, -OC**H**=CH-), 5.07 (t, 1 H, J = 8 Hz, -OCH=CHC**H**<), 4.61 (dd, 1 H, J = 6 and 8 Hz, -OCH=C**H**-), 4.0 (m, 6 H, CH_3CH_2O- and $>NCH_2CH_2O$-), 2.06 (s, 3 H, CH_3CO-), 1.17 (t, 3 H, J = 7 Hz, CH_3CH_2O-); mass spectrum, *m/e* 360 (M^+), 317, 314, 287, 174 (base), 160, 147, 130.

Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.86; H, 5.41; N, 7.65.

DL-2-Amino-4-(2-aminoethoxy)-*trans*-but-3-enoic Acid (15). The protecting groups were removed from **13** by the following multistep procedure. A solution consisting of 3.5 g (0.0097 mol) of enol ether **13,** 0.47 g (0.0146 mol) of anhydrous hydrazine, 10 mL of methanol, and 17 mL of ethanol was stirred magnetically under argon for 24 h. During this time, a copious white precipitate formed which stopped the stirring. The solid is most probably the salt which results from the reaction of the freed ϵ amine with the newly formed phthalhydrazide.

At this point, 60 mL of 1 N KOH was added directly to the reaction flask, causing the solid to dissolve. The resultant solution was heated at 90 °C under argon for 24 h. The reaction mixture was allowed to cool to ambient temperature, concentrated in vacuo to approximately half of its original volume, and acidified with 1 N HCl (3 N HCl in larger scale runs) to pH 4. This caused the precipitation of phthalhydrazide, which was removed by filtration. The pH of the filtrate, which contains the *N*-acetylamino acid **14,** was adjusted to between 6 and 7, and the filtrate was then concentrated in vacuo. The residue was dissolved in 25 mL of 85% hydrazine hydrate and the solution heated at 80 °C for 40 h. After cooling to ambient temperature, the reaction mixture was concentrated in vacuo to remove the hydrazine hydrate. The residue was dissolved in water and the pH of the solution adjusted to between 9 and 10. The solution was concentrated in vacuo, giving a yellow solid which was dried in vacuo over P_2O_5 for 4 h and then over concentrated H_2SO_4 (16 h).

The resultant yellow residue was taken up in water and applied to a cation exchange column (10-fold excess of AG 5, W-X4; 100–200 mesh; H^+ form). The column was washed with water and 10% aqueous pyridine. The amino acid **15** was eluted with 1.5 N NH_4OH. The fraction was concentrated in vacuo and the residue dried for a short time at 0.1 mm. It was then dissolved in water and the pH of the solution adjusted to 3.6 with 1 N HCl. Concentration of the solution followed by crystallization of the resultant oil from water/methanol gave 0.658 g (35%) of the monohydrochloride salt of **15.** An analytical sample was prepared by recrystallization: mp 187.5–189 °C dec; IR (KBr) 3500–2250 (broad), 1650, 1600, 1500; NMR (D_2O) δ 7.35 (d, 1 H, J = 12.4 Hz, -OC**H**=CH-), 5.53 (dd, 1 H, J = 10 and 12.4 Hz, -OCH=C**H**CH<), 4.71 (d, 1 H, J = 10 Hz, -OCH=CHC**H**<), 4.58 (m, 2 H, $-OCH_2CH_2N<$), 3.85 (m, 2 H, $-OCH_2CH_2N<$).

Anal. Calcd for $C_6H_{12}N_2O_3$·HCl: C, 36.65; H, 6.66; N, 14.25. Found: C, 36.44; H, 6.57; N, 14.08.

The synthetic amino acid was found to have solution IR and NMR spectra which are identical with those of the natural L-amino acid **1b.** Furthermore, the two materials behaved identically when they were analyzed on the Beckman Model 121M amino acid analyzer.[2,14]

The mother liquors from the crystallization of the hydrochloride salt were found by analysis on the amino acid analyzer to contain a substance which was more basic than **15.** This substance is most probably the hydrazide **16.** Upon heating the mother liquors with 15 mL of 1 N KOH at 90 °C for 40 h followed by ion exchange chromatography and crystallization, as described above, a further 0.402 g (21%) of the monohydrochloride salt **15** was obtained. Thus, the total yield of **15** from the protected amino acid was 56%.

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Registry No.—**6,** 111-44-4; **7,** 1068-90-2; **8,** 66966-94-7; **9,** 66966-95-8; **10,** 66966-96-9; **11,** 66966-97-0; **12,** 66966-98-1; **13,** 66966-99-2; **14,** 66967-00-8; **15,** 67010-41-7; **15**·HCl, 67010-42-8; potassium phthalimide, 1074-82-4.

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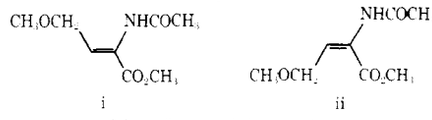
(13) During the course of our studies on these amino acids, we prepared the dehydroamino acid derivatives i and ii. The structure of i is based on an X-ray analysis carried out by Dr. J. Blount of the Physical Chemistry Department of Hoffmann-La Roche Inc. A comparison of the chemical shifts of the



i ii

methylene protons and the adjacent olefinic proton of i, ii, and **12** is shown below. Clearly, the chemical shifts of the protons in **12** are much closer to those of i than those of ii. Thus, the stereochemistry of **12** is almost certainly the same as that present in i.

	—CH_2—	—CH=
i	δ 4.10	δ 6.70
ii	δ 4.44	δ 7.30
12	δ 4.18	δ 6.51

(14) We are grateful to Dr. J. Scannell of the Microbiology Department at Hoffmann-La Roche Inc. for a sample of the natural amino acid **1b.**