Synthesis of Dehydro Amino Acids and Peptides by Dehydrosulfenylation. Rate Enhancement Using Sulfenic Acid Trapping Agents[1a]

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Received April 4, 1977

Oxidation of 3-*S*-benzylthioamino acids to the sulfoxide, using sodium metaperiodate, followed by thermolysis forms α,β-unsaturated ("dehydro") amino acid and peptide derivatives. Temperatures for the elimination are 114–140 °C for primary amino acid residues, but only 80 °C for N-methylated amino acid residues. A hydrogen bond between the sulfoxide oxygen and the amide NH group and the readdition of the sulfenic acid to the product olefin to form starting material account for the higher temperatures for primary amino acids. Substitution on the β position lowers the reaction temperature by destabilizing the hydrogen bond. Trapping agents lower the reaction temperatures by preventing readdition of sulfenic acid to the olefin. Syntheses of linear and cyclic dehydropeptides are illustrated.

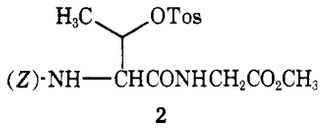
Dehydroamino acids[1c] are constituents of an increasing number of antibiotic and phytotoxic natural products ranging in structural complexity from albonoursin, *cyclo*(dehydrophenylalanyl-dehydroleucyl)[2] to nisin, a 3500 molecular weight polypeptide containing dehydroalanyl- and dehydroaminobutyric acid residues.[3] At least ten dehydroamino acids have been found in nature while these and others may serve as precursors for other unusual, naturally occurring amino acids.[4]

In connection with our studies to synthesize tentoxin **1**, a phytotoxic cyclic tetrapeptide isolated from *Alternaria tenuis*,[5] we required a method for preparing dehydroamino acid units under mild, nonbasic conditions.

cyclo(L-MeAla-L-Leu-MePhe(Δ^2)-Gly)

1

Several approaches to the synthesis of the α,β-dehydro unit have been developed,[6] but the most widely used method is based on β elimination of *O*-tosylserine (or other β-hydroxylamino acids) residues using alkali or amines.[7] However, this method does not always produce the dehydropeptide. Treatment of certain β-alkyl-substituted *O*-tosyl-β-hydroxylamino acids, e.g., **2**, with base can give aziridine carboxylic acid derivatives **3** in high yield[8,9] as shown in eq 1. This consideration plus the knowledge that peptides often rearrange in base[10] and that tentoxin is base labile[11] led us to develop a new method for synthesizing the dehydroamino acid unit under neutral conditions.



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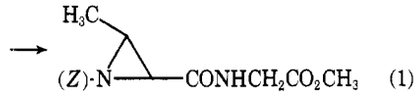
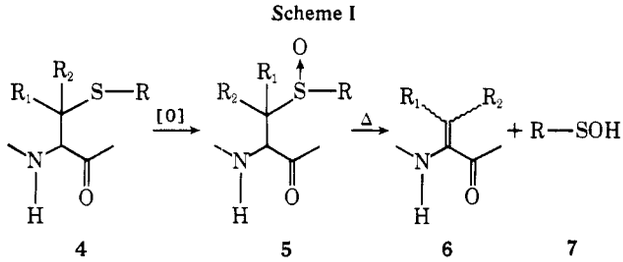


(1)

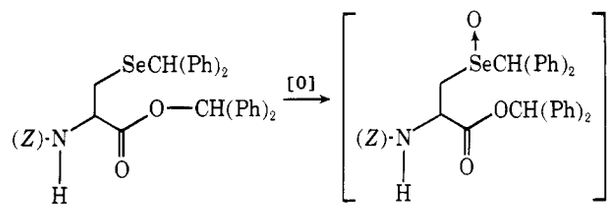
3

Thermolytic elimination of β-alkylsulfinyl derivatives of protected amino acids and peptides appeared to offer a feasible practical route to dehydropeptides (Scheme I). First, β-sulfoxides could abstract an acidic proton from the carbon α to the carbonyl group which suggested that elimination should occur at moderate temperatures. In addition, the corresponding β-S-substituted amino acid precursor sulfides **4** are readily prepared by addition of thiols to unsaturated azlactones[12] and could be incorporated easily into peptides using standard synthetic methods. Indeed, the report that selenocysteine derivative **8**, after oxidation to the expected selenoxide **9**, decomposed at room temperature to the dehydroalanine derivative **10**[13] suggested that the sulfoxide procedure also would work.

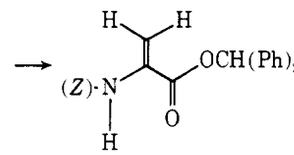
Scheme I



4 **5** **6** **7**



8 **9**



10

Our preliminary studies showed that thermolytic elimination of β-alkylsulfinyl derivatives of protected amino acids and peptides **5** gave the corresponding dehydro derivatives **6** in good yield.[14] The reaction was applied successfully to prepare tetrapeptide **11**, an intermediate in the first synthesis of tentoxin.[15]

Boc-L-MeAla-L-Leu-Phe[(*Z*)Δ^2]-Gly-OMe

11

However, the temperature required to effect elimination of β-alkylsulfinyl derivatives was found to vary over a wide range (25–140 °C) (Table I, method A). The latter conditions, which are substantially higher than normally needed to eliminate sulfoxides β to a carbonyl group,[16] appeared too severe to be applied routinely to the synthesis of larger peptides, since these might be expected to denature at these temperatures. Other dehydro units (e.g., dehydroalanine) can readily polymerize at elevated temperatures. We report herein the results of our studies to determine those factors affecting the rates of elimination and describe a new procedure for effecting this elimination at lower temperatures.

Table I. Dehydrosulfenylation

Compd	Sulfoxide	Registry no.	Method[a]	Temp, °C	Time, h	Product	Registry no.	% Yield
12	Boc-Cys[(O)Bzl]-OMe[b]	55477-78-6	A	144	16	Boc-Ala(Δ^2)-OMe (**29**)	55477-80-0	80
			B	80	6			60
			B	80	10			90
			C	80	12			85
13	(*Z*)-Cys[(O)Bzl]-OMe	63658-05-9	A	144	16	(*Z*)-Ala(Δ^2)-OMe (**30**)	21149-17-7	75
			B	80	16			86
			C	80	16			88
14	(*Z*)-Cys[(O)Bzl]-Gly-OEt	55478-03-0	A	144	16	(*Z*)-Ala(Δ^2)-Gly-OEt) (**31**)	55477-82-2	75
			B	80	8			81
15	(*Z*)-Gly-Cys[(O)Bzl]-OMe	55478-05-2	A	144	16	(*Z*)-Gly-Ala(Δ^2)-OMe (**32**)	55477-84-4	60
			B	80	8			78
16	Boc-MeAla-Leu-Cys-[(O)Me]-Gly-OMe	63658-06-0	A	144	16	Boc-MeAla-Leu-Ala-(Δ^2)-Gly-OMe (**33**)	55647-60-4	75
17	Boc-MeCys[(O)Me]-OMe	63658-07-1	A	80	4	Boc-MeAla(Δ^2)-OMe (**34**)	55776-34-2	81
			B	80	12			81
18	Boc-MeCys[(O)Bzl]-OMe	63658-08-2	A	80	4			75
			B	80	4			79
19	Boc-MePhe[3-S(O)-Bzl]-OMe[c,d,g]	63658-09-3	A	80	4	Boc-MePhe(Δ^2)-OMe (**35**)	63658-14-0	81
20	Boc-MeAla-Leu-MeCys[(O)Me]-Gly-OMe[g]	63658-10-6	A	80	7	Boc-MeAla-Leu-MeAla(Δ^2)-GlyOMe (**36**)	56776-39-7	81
21	*Cyclo*(MeAla-Leu MeCys-[(O)Me]-Gly)[g]	63658-11-7	A	80	4	*Cyclo*(MeAla-Leu-MeAla(Δ^2)-Gly) (**37**)	63658-15-1	80
			C	80	4			80
22	Boc-Abu[3-S(O)Bzl]-OMe (threo)[e]	63701-03-1	A	114	6	Boc-Abu[(*E*)Δ^2]-OMe (**38**)	56776-41-1	84
			B	80	4			76
23	Boc-Abu[3-S(O)Bzl]-OMe(erythro)[e]	63701-04-2	A	80	4	Boc-Abu[(*Z*)Δ^2]-OMe (**39**)	63658-16-2	82
			B	80	3			80
24	Boc-Val[3-S(O)Bzl]-OMe	63701-05-3	A	80	4	Boc-Val(Δ^2)-OMe (**40**)	55478-14-3	89
			B	80	3			85
			C	80	3			86
25	Boc-Phe[3-S(O)Bzl]-OMe[d]	63658-12-8	A	114	8	Boc-Phe(Δ^2)-OMe[f] (**41**)		76
			B	80	6			82
26	Boc-Ala-Abu[3-S(O)-Me]-OMe[d]	63658-13-9	A	114	8	Boc-Ala-Abu(Δ^2)-OMe[f] (**42**)		75
27	Boc-Ala-Val[3-S(O)]-OMe	63658-24-2	A	80	4	Boc-Ala-Val(Δ^2)-OMe (**43**)	55647-59-1	81
28	Boc-Ala-Phe[3-S(O)-Bzl]-OMe	55478-02-9	A	114	6	Boc-Ala-Phe(Δ^2)-OMe (**44**)	55478-15-4	76
			C	80	5			84

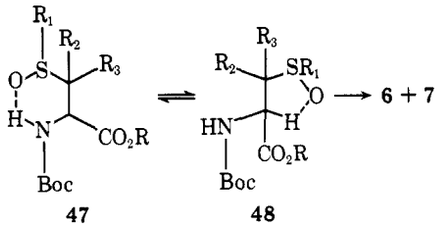
[a] Method A, refluxing xylene, toluene or benzene; Method B, triphenylphosphine added to conditions of method A; Method C, triphenyl phosphite added to conditions of method A. [b] Cys[(O)Bzl] indicates the sulfoxide of *S*-benzylcysteine. Cf., *Biochemistry*, **11**, 1726 (1972); *ibid.*, **14**, 449 (1975). [c] MePhe[3-S(O)Bzl] indicates the sulfoxide of 3-*S*-benzyl-*N*-methylphenylalanine. [d] The sulfide amino acid used to prepare the sulfoxides was a mixture of both threo and erythro diastereomers. [e] Abu = aminobutyric acid. [f] The product obtained was a mixture of *E* and *Z* isomers. [g] Compound eliminates sulfenic acid slowly at room temperature.

Results

Sulfoxides **12–28** were prepared by oxidation of the corresponding sulfides with either *m*-chloroperbenzoic acid[17] or sodium periodate in aqueous methanol.[18] All sulfoxides reported here were prepared by the periodate procedure, since this reaction produces the thermodynamically more stable sulfoxide and eliminates ambiguities caused by sulfoxide chirality. Heating sulfoxides **12–28** in refluxing xylene under nitrogen for 6–16 h gave the corresponding dehydro products **29–44** which were isolated in good yield after chromatography (Table I, method A).

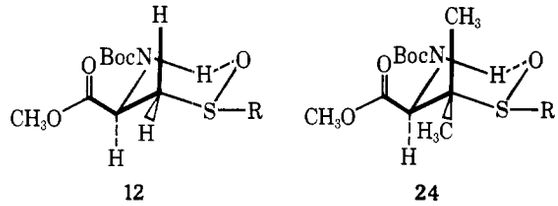
A comparison between diastereomers **22** and **23** showed that elimination is stereospecific. Threo isomer **22**[19,20] gave exclusively (*E*)-dehydroaminobutyric acid **38**,[21] while erythro isomer **23**[19,20] gave exclusively (*Z*)-dehydroaminobutyric acid **39**.[21] These results established that elimination proceeded by the expected cis mechanism (**48**). No evidence for β,γ elimination was detected in compounds with γ protons. The β,γ-dehydroaminobutyric acid **46**, prepared by pyrolysis (200 °C) of *tert*-butyloxycarbonylmethionine sulfoxide methyl ester **45** was not detected during thermolysis of **22** or **23**. Also, **46** was found to isomerize exclusively to the *Z*-isomer **39** and therefore could not be an intermediate in the formation of **38**. Exclusive abstraction of α protons is consistent with the report[16] that the rate acceleration of abstraction of an activated proton α to a carbonyl is about 15 000. In the present case, the more acidic α proton promotes regioselectivity to form the α,β-unsaturated moiety.

Replacement of the amide hydrogen in the β-alkylsulfinylamino acids with a methyl group facilitated elimination of sulfenic acid (Table I). Thus, N-methylated sulfoxides **17–21** eliminated readily at 80 °C in 3–7 h. No products were formed at the same temperature from the corresponding non-N-methylated sulfoxides **12–16**. Thus, the NH group appeared to retard elimination. Because sulfoxides can form



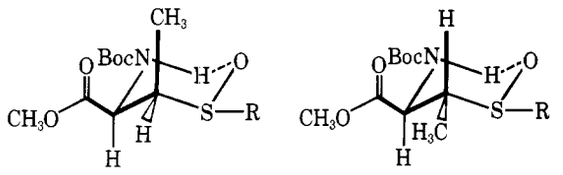
47 48

Scheme II



12 24

Scheme III



23 24

strong hydrogen bonds with amide hydrogens in peptide-derived systems, e.g., penicillin sulfoxide,[22] a study was undertaken to determine if hydrogen-bonded intermediates, such as **47**, were present.

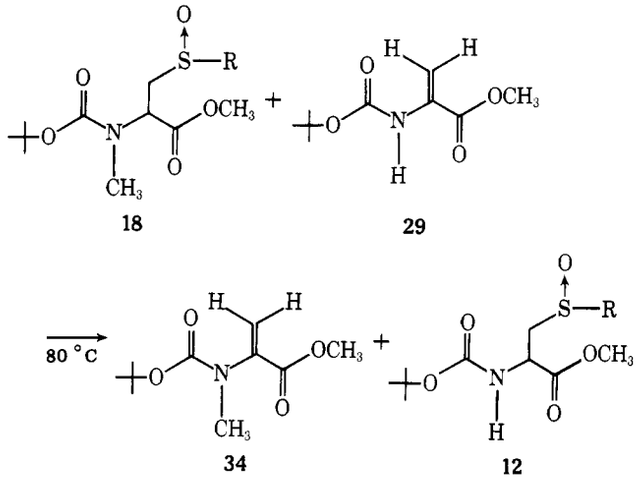
Intramolecular hydrogen bonds can be detected by observing the concentration dependence of the chemical shift of amide protons in chloroform.[22,23] Concentration-dependent chemical shifts indicate intermolecular hydrogen bonding, while concentration-independent chemical shifts are consistent with intramolecularly hydrogen-bonded protons. In sulfoxides **12–13** the amide NH resonance was independent of concentration (<0.1 ppm shift), whereas the amide proton resonances in the corresponding precursor sulfides were concentration dependent (1.5–2.0 ppm shifts). Similar results were obtained with dipeptides **14** and **15.** The cysteinyl NH was concentration independent (0.1 ppm) and the glycyl NH resonance concentration dependent (1.8-ppm shift). These results are consistent with the presence of an intramolecular hydrogen bond between the amide hydrogen and the sulfoxide oxygen.

Interestingly it was found that increasing substitution on the β position of the cysteinyl residues also lowered the minimum temperature necessary for elimination. Thus, cysteinyl compounds **12–16** eliminated only at 140 °C, whereas the β-monosubstituted derivatives **22, 23, 25, 26,** and **28** eliminated at 114 °C and the β,β-disubstituted derivatives **24** and **27** eliminated readily at 80 °C (Table I).

One explanation for the lower reaction temperatures of β-substituted derivatives could be that nonbonded interactions between the β substituents and the carbomethoxyl group destabilize the intramolecular hydrogen bond (Scheme II). Examination of molecular models indicates that the carbomethoxyl group will prefer a conformation perpendicular to the hydrogen-bonded ring system due to unfavorable interactions with the carbonyl group of the butyloxycarbonyl group. In this conformation an unfavorable steric interaction develops between the carbonyl oxygen and an axial-like substituent such as the methyl group in **24.** This interaction does not develop in **12.**

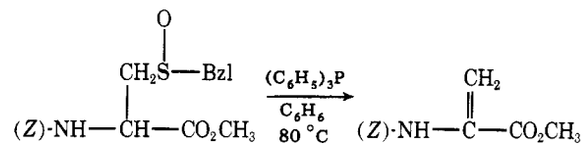
If the argument presented above was correct, it would be predicted that the erythro isomer of β-*S*-benzylaminobutyric acid **23** would eliminate at a lower temperature than the *threo*-β-*S*-benzylaminobutyric acid **22** (Scheme III) because the carbomethoxyl and methyl groups interact in the hydrogen-bonded conformation of the erythro isomer but not the threo isomer. In fact, the sulfoxide of erythro isomer **23** eliminated slowly at room temperature (10–20% in 24–48 h) and completely in 2–3 h at 80 °C, while the threo-isomer **24** required 5–6 h at 114 °C for complete elimination.

Scheme IV



18 29 34 12

Scheme V



13 30

Sulfenic acids are known to add to olefinic and acetylenic bonds,[24] but addition to α,β-unsaturated amino acids has not been reported. The following experiment established that sulfenic acids add to dehydroamino acids (Scheme IV). A solution containing *tert*-butyloxycarbonyl-*N*-methyl-3-*S*-benzylsulfinylalanine methyl ester **18** and *tert*-butyloxycarbonyldehydroalanine methyl ester **29** was heated at 80 °C. This temperature was chosen because the secondary sulfoxide **18** readily eliminates at 80 °C but the primary sulfoxide **12** does not appear to eliminate at this temperature. The reaction produced *tert*-butyloxycarbonyldehydromethylalanine **34** together with *tert*-butyloxycarbonyl-3-*S*-benzylsulfinylalanine methyl ester **12,** formed by the addition of benzylsulfenic acid to **29.** No *N*-methyl-β-*S*-benzylsulfinyl derivative **18** remained, which showed that addition of sulfenic acid to the primary dehydroamino acid **29** was preferred over addition to the secondary dehydroamino acid **34.**

The crossover experiment established that sulfenic acids add readily to dehydroamino acids. This fact suggested that primary β-alkylsulfinylamino acid derivatives (e.g., **12–16**) could be undergoing dehydrosulfenylation at 80 °C, but, because of the efficient readdition of sulfenic acid, no dehydro products accumulate. If sulfenic acids were removed from solution by reaction with thiophiles such as triphenylphosphine or trialkyl phosphites,[25] dehydrosulfenylation would be driven to completion. When 0.75–2 equiv of triphenylphosphine was added to the thermolysis of **13,** dehydrosulfenylation was completed within 3 h (Scheme V). The solution remained colorless and contained only benzyl mercaptan, triphenylphosphine, triphenylphosphine oxide, and the dehydro product **30** which was isolated in 90% yield. Similarly, sulfoxide **12** was converted to the dehydro product **29** in 25% yield when thermolyzed for only 1 h at 65 °C, whereas, in the absence of triphenylphosphine, no product could be detected at temperatures below 115 °C. Thus, addition of triphenylphosphine to the reaction mixture establishes that dehydrosulfenylation of primary β-alkylsulfinylamino acid derivatives is a reversible reaction that occurs at 65 °C. The results obtained using triphenylphosphine and trimethyl phosphite in the dehydrosulfenylation reaction are summarized in Table I under methods B and C.

Discussion

The results reported here establish that thermolysis of β-alkylsulfinylamino acids in refluxing benzene is a reversible reaction. The equilibrium is analogous to the reversible addition of sulfenic acids to ethyl acrylate at 80 °C[16] where the equilibrium favors formation of product.

$$(CH_3)_3CS(O)CH_2CH_2CO_2Et \rightleftharpoons (CH_3)_3CSOH + CH_2{=}CHCO_2Et$$

With β-alkylsulfinylamino acid derivatives, the equilibrium favors starting sulfoxides when these can be stabilized by a hydrogen bond to the amide proton. Thus, no measurable amount of product is formed when primary β-alkylsulfinyl derivatives, e.g., **13**, are heated at 80 °C for 18 h. Only when the sulfenic acids are decomposed at higher temperatures is the reaction completed. Stabilization of secondary β-alkylsulfinylamino acid derivatives by a hydrogen bond is not possible, since the NH group is absent, and these derivatives readily eliminate sulfenic acid at 80 °C and, in some cases, at even lower temperatures.

Dehydrosulfenylation of primary β-alkylsulfinylamino acid and peptide derivatives can be forced to products at 80 °C by using tertiary phosphines or phosphites which trap the small amount of sulfenic acid formed at this temperature. In addition to lowering the reaction temperature, which is desirable in peptide synthesis, the use of tertiary phosphines also prevents sulfenic acid catalyzed isomerization of olefins or decomposition of acid-labile protecting groups. Triphenyl phosphite and trimethyl phosphite also give the same results. The use of the latter compound is preferable as it and its oxide are water-soluble and easily removable during workup of the reaction.

Dehydrosulfenylation in the presence of tertiary phosphines has been used to prepare a variety of dehydroamino acid and peptide derivatives under mild, neutral conditions (Table I, methods B and C). An advantage of this method is that it does not require the use of base which can catalyze reactions with dehydroalanine and other dehydro residues or which can cause rearrangements of cyclic peptides and other base-labile peptide sequences. For example, the cyclic tetrapeptide **38** which decomposes in the presence of triethylamine or 0.01 N sodium hydroxide would be difficult to prepare using the Photaki[7] method.

The synthesis of dehydro peptides by dehydrosulfenylation of β-alkylsulfinyl residues is limited to peptides which are otherwise inert to the sodium periodate oxidizing conditions. Peptides containing cysteine, cystine, or tryptophan cannot be treated with sodium periodate, as these residues would be oxidized irreversibly. Methionine-containing peptides are compatible with these new conditions (80 °C) for dehydrosulfenylation because methionine sulfoxide derivatives, which will be formed by oxidation with sodium periodate, are not β to a carbonyl group and require much higher temperatures (140 °C or higher) to undergo elimination. Methionine sulfoxide can be reduced to methionine after formation of the dehydro residues.

It is clear that intramolecular hydrogen bonding retards dehydrosulfenylation in these small peptides. It is possible that larger sulfoxide-containing synthetic peptides will be found that possess unique conformations that further stabilize the intramolecular hydrogen bond and therefore prevent successful elimination. However, this kind of stabilization is likely to occur only in very large peptides with stabilized tertiary structures. In that event, it may be possible to convert the β-alkylthioamino acid residues to the corresponding methylsulfonium derivatives by methylation and then to the dehydro residue by β elimination with triethylamine.[27]

Other solvents may be needed for some peptides because most protected and probably all unprotected peptides are not very soluble in benzene. Pyridine has been shown to be a suitable solvent as have DMF and Me_2SO. Pyridine has been reported to simplify workup of dehydrosulfenylations and to minimize side reactions, presumably by converting the sulfenic acid to its anionic form. When pyridine was used as solvent in place of toluene for thermolysis of the β-alkylsulfinylamino acids, the stereospecificity of the elimination was retained and the reaction temperatures were lowered, although not as much as when triphenylphosphine is used. Water used in conjunction with water-soluble phosphites would be satisfactory for preparing some dehydroamino acids. However, it might not work well for preparing dehydroalanine residues because these can be hydrolyzed rapidly.

Some peptides may be found that are too temperature sensitive to withstand the 65–80 °C temperatures needed for dehydrosulfenylation of β-*S*-benzylsulfinyl residues. Other studies on dehydrosulfenylations have shown that aromatic sulfenic acids, e.g., benzenesulfenic acid, are better leaving groups that allow elimination to proceed at temperatures about 50 °C below that needed for the alkylsulfinic acids.[26] Thus, replacement of the *S*-benzyl or *S*-methyl groups on the amino acids used in this study with *S*-phenyl groups should lower the minimum temperature necessary for dehydrosulfenylation and permit application of this reaction to the synthesis of temperature-sensitive dehydropeptides.

Experimental Section

General. Melting points were determined on a Fisher-Johns melting-point apparatus and are uncorrected. Ultraviolet spectra were determined in methanol or ethanol solution on a Beckman Model DK-2A recording spectrophotometer. Nuclear magnetic resonance spectra were recorded on Varian Model EM-390 and Bruker Model Hx90E spectrometers. Chemical shifts are reported as δ values (ppm) relative to tetramethylsilane as an internal standard, deuteriochloroform was used as solvent unless stated otherwise. Infrared spectra were determined on a Perkin Elmer Model 257 recording spectrophotometer in chloroform solution unless otherwise noted. Low-resolution mass spectra were determined on a Finnigan Model 1015. High-resolution mass spectra and peak-matching data were obtained on AEI MS902C. Microanalyses were performed by Galbraith Laboratory, Knoxville, Tenn. Analytical and preparative thin-layer chromatography were carried out using Brinkman silica gel F-254 plates. Spots were visualized by the following methods: (a) ultraviolet light, (b) incubation in an iodine chamber, (c) ninhydrin (0.3 g in 100 mL of *n*-BuOH and 3 mL of HOAc), (d) chlorox–tolidine reagent [commercial chlorox, H_2O (1:1) for 30 min, 95% EtOH for 10 min, 1% KI, and 1% *o*-tolidine (10% HOAc)], (e) Rydon–Smith reagent (Cl_2 from $KClO_3$–concentrated HCl, 1% KI, and 1% starch solution). The following solvent systems were used: (1) methanol (1%) in chloroform, (2) methanol (2%) in chloroform, (3) methanol (10%) in benzene; (4) ethanol (11%) in ethyl acetate; (5) ethyl acetate; (6) ethyl acetate (25%) in benzene; (7) ethyl acetate (12%) in benzene. *tert*-Butyloxycarbonyl derivatives of amino acids not commercially available were prepared from the amino acid, *tert*-butyloxycarbonylazide in DMF using 1,1,3,3-tetramethylguanidine as base[28] and crystallized from ethyl acetate–hexane. S-methylated cysteine derivatives were prepared from the β-*S*-benzyl derivatives by reduction with sodium in liquid ammonia[29] followed by methylation with methyl iodide. Methyl esters of Boc-amino acids were prepared by reaction with diazomethane[30] in ether or methanol. The protected linear tetrapeptides were prepared using solid-phase techniques,[31,32] and converted to cyclic tetrapeptides by our previously reported procedures.[33] Details of these syntheses will be presented in later communications.

Preparation of Threo and Erythro Isomers of 3-*S*-Benzylaminobutyric Acid. The preparation followed the procedure of Carter and Stevens.[34] Addition of benzyl mercaptan to the azlactone (93 g, 0.5 M), obtained from the condensation of freshly distilled acetaldehyde with hippuric acid, in acetic anhydride and NaOAc at 65 °C for 45 min followed by hydrolysis gave a mixture of two diastereomers of benzoyl-3-*S*-benzyl-2-aminobutyric acid (85 g). The benzene-soluble fraction, A isomer according to Carter and Stevens, was isolated (40 g) (mp 145–147 °C; this is the threo isomer[19,20]). The benzene-insoluble fraction, B isomer, was isolated (38 g) (mp 181–184 °C, erythro isomer). Subsequent acid hydrolysis on both threo and erythro isomers separately gave the *threo*-amino acid (28 g, mp

190–192 °C) and *erythro*-amino acid (24 g, mp 200–202 °C). These were converted by the general procedures described above into the following derivatives.

***threo-tert*-Butyloxycarbonyl-3-*S*-benzylthio-2-aminobutyric acid (49):** mp 115–116 °C (85% yield); IR 3430, 1727 cm^{-1}; NMR δ 1.29 (3 H, d, J = 2 Hz, β-CH_3), 3.75 (2 H, s, $SCH_2C_6H_5$). Anal. ($C_{18}H_{27}NO_4S$): C, H, N.

***erythro-tert*-Butyloxycarbonyl-3-*S*-benzylthio-2-aminobutyric acid (50):** 87% yield; IR 3400, 1710 cm^{-1}; NMR δ 1.23 (3 H, d, J = 7 Hz, β-CH_3), 3.81 (2 H, s, $SCH_2C_6H_5$). Anal. ($C_{16}H_{23}NO_4S$): C, H, N.

***threo*-Methyl *tert*-Butyloxycarbonyl-*N*-methyl-3-*S*-benzylthio-2-aminobutyrate (51):** 92% yield; IR 3430, 1750, 1740 cm^{-1}; NMR δ 1.28 (3 H, d, J = 7 Hz, β-CH_3), 3.62 (2 H, s). Anal. ($C_{17}H_{25}NO_4S$): C, H, N.

***erythro*-Methyl *tert*-Butyloxycarbonyl-*N*-methyl-3-*S*-benzylthio-2-aminobutyrate (52):** 95% yield; IR 3430, 1750, 1720 cm^{-1}; NMR δ 1.22 (3, d, J = 7 Hz, β-CH_3), 3.72 (2 H, s). Anal. ($C_{17}H_{25}NO_4S$): C, H, N.

Oxidation of Sulfides Using Sodium Metaperiodate.[18] The amino acid derivative (10 mmol) was placed in a 1:1 mixture of MeOH and H_2O (50 mL total volume) and powdered $NaIO_4$ (10.5 mmol) was added. The reaction mixture was stirred for 15 h at 4 °C (cold room) and then filtered through a Büchner funnel. The filter cake of sodium iodate was washed with small portions of MeOH. The filtrates were combined and the methanol was removed by evaporation at 34 °C under reduced pressure. The aqueous portions were then extracted with ethyl acetate (three 25-mL portions). The extracts were combined and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to yield the solid sulfoxide which was crystallized from ethyl acetate–hexane mixtures. In general, the sulfoxide showed a medium intensity band due to the S → O stretching vibration at 1050 cm^{-1} in chloroform.

Physical Properties of Sulfoxides. Methyl *N-tert*-Butoxycarbonyl-3-benzylsulfinylalaninate (12): 86% yield; mp 152–156 °C; IR (KBr) 1040 cm^{-1}; NMR (acetone-d_6) δ 4.13 (2 H, s), 6.06 (1 H, d, NH). Anal. ($C_{18}H_{27}NO_5S$): C, H, N.

Methyl *N*-Benzyloxycarbonyl-3-benzylsulfinylalaninate (13): 82% yield; IR (KBr) 1745, 1700, 1048 cm^{-1}; NMR (acetone-d_6) δ 3.07 (2 H, m, $-CH_2SO$), 4.08 ($OSCH_2Ph$); mass spectrum M^+ 461.4. Anal. ($C_{19}H_{21}NO_5S$): C, H, N.

Ethyl *N*-Benzyloxycarbonyl-3-benzylsulfinylalanylglycinate (14): 90% yield; IR 3700, 1742, 1726, 1675, 1020 cm^{-1}; NMR δ 3.95 (2 H, dd, Gly), 4.0 (2 H, s, $-SOCH_2$), 5.12 (2 H, s, OCH_2Ph); mass spectrum calcd. for $C_{22}H_{26}N_2O_6S$: 434.514. Found: 434.5. Anal. ($C_{22}H_{26}N_2O_6S$): C, H, N.

Methyl *N*-Benzyloxycarbonylglycyl-3-benzylsulfinylalaninate (15): 89% yield; IR 3440, 3300 (NH), 1741, 1734, 1692, 1672, 1500, 1040 cm^{-1}; NMR δ 3.85 (2 H, d, $GlyCH_2$), 3.98 (2 H, s, $SOCH_2Ph$), 5.10 (2 H, s, OCH_2Ph). Anal. ($C_{21}H_{24}N_2O_6S$): C, H, N.

Methyl *N-tert*-Butyloxycarbonyl-*N*-methyl-L-alanyl-L-leucyl-L-3-*S*-methylcysteinylglycinate: mp 102–104 °C; IR 3430, 3330, 1745, 1700, 1680, 1520, 1500 cm^{-1}; NMR δ 1.38 (3 H, d, J = 7 Hz), 1.48 (9 H, s), 2.13 (3 H, s, SCH_3), 2.95 (2 H, d, Cys-SCH_2), 2.88 (3 H, s, NCH_3), 3.72 (3 H, s), 4.03 (2 H, d, Gly), 4.3 (1 H, q, J = 7 Hz), 4.38 (1 H, m, Leu), 4.65 (1 H, m, Cys), 6.21 (NH, br d, Leu), 7.09 (NH, m, Gly).

Methyl *N-tert*-Butyloxycarbonyl-*N*-methyl-3-methylsulfinyl-2-aminobutyrate (17): 80% yield; IR 1745, 1700, 1040 cm^{-1}; NMR δ 2.99 (3 H, d, NCH_3), 4.10 (2 H, m, SCH_2Ph). Anal. ($C_{17}H_{25}NO_5S$): C, H, N.

Methyl *N-tert*-Butyloxycarbonyl-*N*-methyl-3-benzylsulfinylalaninate (18): IR 1742, 1683 cm^{-1}; NMR δ 2.82 (3 H, d), 3.60 (2 H, s), 7.27 (5 H, d). Anal. ($C_{17}H_{25}NO_4S$): C, H, N.

Methyl *N-tert*-Butyloxycarbonyl-*N*-methyl-3-benzylsulfinylphenylalaninate (19): NMR δ 1.41 (9 H, s), 3.05 (3 H, s), 3.60 (3 H, s), 3.63 (1 H, d, J = 13 Hz), 3.77 (1 H, d, J = 13 Hz), 4.57 (1 H, d, J = 5.5 Hz), 5.3 (1 H, d, J = 5.5 Hz), 7.3 (5 H, m). Anal. ($C_{23}H_{29}NO_5S$): C, H, N.

Methyl *N-tert*-Butyloxycarbonyl-L-*N*-methylalanyl-L-leucyl-L-*N*-methyl-3-methylsulfinyllalanylglycinate (20): IR 3410, 3320, 1750, 1690, 1670, 1660, 1530, 1520, 1050 cm^{-1}; NMR δ 0.97 (6 H, dd), 1.32 (3 H, d, J = 7.2 Hz), 2.66 (3 H, s, $SOCH_3$), 2.80 (6 H, s, NCH_3), 3.24 (2 H, br q), 3.72 (3 H, s), 3.98 (2 H, br d), 4.75 (1 H, q, Ala), 4.86 (1 H, m, Cys), 5.40 (1 H, br t, Leu), 6.80 (NH, d, Leu), 7.32 (NH, m, Gly); mass spectrum M^+ calcd: 534.677. Found: 534.67. Anal. ($C_{23}H_{42}N_4O_8S$): C, H, N.

***cyclo*(L-Methylalanyl-L-leucyl-*N*-methyl-3-*S*-methylcysteinylglycyl):** IR (KBr) 1695, 1686, 1670, 1635, 1520, 1510, 1500 cm^{-1}; NMR (MeSO-d_6, $CDCl_3$) δ 0.91 (3 H, d, J = 4.5 Hz), 0.93 (3 H, d, J = 4.3 Hz), 1.47 (3 H, d, J = 7.2 Hz), 1.78–1.55 (3 H, m), 2.15 (3 H, s), 2.87 (1 H, d, 11.6 Hz), 3.15 (1 H, dd, J = 11.6, 3.0 Hz), 2.97 (3 H, s), 2.99 (3 H, s), 3.46 (1 H, d, J = 14.7 Hz), 4.60 (1 H, dd, J = 14.7, 9.46 Hz), 4.31 (1 H, q, J = 3.3 Hz), 4.11 (1 H, q, J = 7.2 Hz), 4.73 (1 H, br q, J = 7.03 Hz), 8.11 (NH, d, J = 9.46 Hz), 8.36 (NH, d, J = 9.46 Hz); mass spectrum M^+ calcd: 386.518. Found: 386.5. Anal. ($C_{17}H_{30}N_4O_4S$): C, H, N.

***threo*-Methyl *N-tert*-Butyloxycarbonyl-3-benzylsulfinyl-2-aminobutyrate (22):** 91% yield; mp 116–119 °C; IR 1035 cm^{-1}; NMR δ 1.38 (3 H, d, J = 7 Hz, β-CH_3), 4.02 (2 H, $SCH_2C_6H_5$), 5.58 (1 H, d, J = 9 Hz, NH, δ invariant upon dilution). Anal. ($C_{17}H_{25}NO_5S$): C, H, N.

***erythro*-Methyl *N-tert*-Butyloxycarbonyl-3-benzylsulfinyl-2-aminobutyrate (23):** 90% yield; IR 1030 cm^{-1}; NMR δ 1.10 (3 H, d, J = 7 Hz, β-CH_3), 4.12 (2 H, $SCH_2C_6H_5$), 5.50 (1 H, d, J = 8.5 Hz, NH, δ invariant upon dilution). Anal. ($C_{17}H_{25}NO_5S$): C, H, N.

Methyl *N-tert*-Butyloxycarbonyl-3-benzylsulfinylpenicillaminate (24): 85% yield; IR 1037 cm^{-1}; NMR δ 4.2 (2 H, dd, SCH_2–), 5.45 (2 H, d, NH). Anal. ($C_{18}H_{27}NO_5S$): C, H, N.

Methyl *N-tert*-Butyloxycarbonyl-3-benzylsulfinylphenylalaninate (25): NMR δ 1.40 (9 H, s), 3.56 (3 H, s), 3.59 (1 H, d, J = 14 Hz), 3.79 (1 H, d, J = 14 Hz), 4.60 (1 H, d, J = 5 Hz), 5.22 (1 H, dd, J = 5, 7 Hz), 6.9–7.3 (5 H, m), 8.2 (NH, d, J = 7 Hz). Anal. ($C_{22}H_{27}NO_5S$): C, H, N.

Methyl *N-tert*-Butyloxycarbonyl-L-alanyl-3-methylthio-2-aminobutyrate: IR 1739, 1730, 1700, 1500 cm^{-1}; NMR threo isomer δ 1.28 (3 H, d), 1.40 (3 H, d), 2.12 (3 H, s, SCH_3); erythro isomer 1.35 (3 H, d), 1.40 (3 H, d), 2.20 (3 H, s, SCH_3). Anal. ($C_{14}H_{26}N_2O_5S$): C, H, N.

Methyl *N-tert*-Butyloxycarbonyl-L-alanyl-3-methylthio-2-aminoisovalerate: IR 1740, 1725, 1689, 1496 cm^{-1}; NMR δ 1.33 (6 H, s), 1.43 (9 H, s), 1.42 (3 H, d), 2.02 (3 H, s, SCH_3). Anal. ($C_{15}H_{28}N_2O_5S$): C, H, N.

Methyl *N-tert*-Butyloxycarbonyl-L-alanyl-3-benzylsulfinylphenylalaninate (28): NMR δ 1.35 (3 H, d, J = 7 Hz), 1.413 (9 H, s), 3.61 (3 H, s), 3.65 (1 H, d, J = 13.5 Hz), 3.80 (1 H, d, J = 13.5 Hz), 4.21 (1 H, m, J = 7, 10 Hz), 4.6 (1 H, d, J = 5 Hz), 5.27 (1 H, dd, J = 8, 5 Hz), 7.26–7.33 (10 H, m), 7.62 (NH, d, J = 8 Hz). Anal. ($C_{25}H_{32}N_2O_6S$): C, H, N.

Elimination of Sulfoxides. Method A. (1) The sulfoxide (10.0 mmol) was suspended in 150 mL of the appropriate solvent (benzene, toluene, xylene; see Table I) and heated to reflux for the required period of time (Table I). The solution usually changed from a clear to pinkish and then to a light brown color. The solvent was then cooled, filtered, and evaporated under reduced pressure to obtain a brownish syrup. The dehydroamino acid derivatives were directly distilled (Kugelrohr) at 80–110 °C at 0.3–0.5 mm Hg to obtain the colorless oily liquid. Better results from distillation were obtained if a few milligrams of norite was present. The dehydropeptides and dehydrotetrapeptides were chromatographed on silica gel (100 g of silica gel/2 g of residue, C_6H_6/EtOAc, 1:1, as eluent for dipeptides and C_6H_6/EtOAc, 1:3, as eluent for tetrapeptides). Dehydroalanine amino acid derivatives and dipeptides polymerized easily, particularly if chromatography was involved; e.g., (*Z*)-GlyAla(Δ)–OCH_3 was recovered in 10% yield after chromatography. Good results were obtained if the chromatography was carried out at 4 °C in the dark. Purified products also polymerized quickly; e.g., (*Z*)-Ala(Δ)GlyOEt polymerized to a plastic film upon exposure to light at room temperature. This was avoided by storing under argon in the dark. Good results were also obtained from purifying dehydrotetrapeptides by gel filtration through LH-20 using ethyl acetate as eluent in glassware wrapped with tin foil.

Method B. Elimination of Sulfoxides in the Presence of Triphenylphosphine. The sulfoxide (10.0 mmol) was suspended in benzene with triphenylphosphine (7.5–1.5 mmol) and heated at the required temperature for the specified time (Table I). The solution usually remained colorless but contained mercaptans. The solution was cooled to 10 °C, and filtered to remove triphenylphosphine oxide. After removal of solvent, the syrupy mixture was triturated with an ethyl acetate–hexane mixture to remove more insoluble phosphine oxide. For dehydroamino acids and dipeptides, the remaining phosphine oxide could be removed by passing through a short column of silica gel in 1:1 mixture of benzene–ethyl acetate. Further purification could be achieved by the procedures described under general method A.

Method C. Elimination of Sulfoxides in the Presence of Triphenyl Phosphite. The procedure described in method B was followed, except that triphenylphosphite or trimethylphosphite was used in place of triphenylphosphine. When the latter compound was used, the product trimethyl phosphate was removed by washing with

water.

Properties of Dehydroamino Acid and Peptide Derivatives. **Methyl *tert*-Butyloxycarbonyl-α-aminoacrylate (29):** $R_{f\,(2)}$ 0.72, $R_{f\,(6)}$ 0.79; IR 1640 cm^{-1}; NMR δ 6.73 (1 H, d, J = 1.6 Hz), 6.19 (1 H, s). Anal. ($C_9H_{15}NO_4$): C, H, N.

Methyl Benzyloxycarbonyl-α-aminoacrylate (30): $R_{f\,(2)}$ 0.77; IR 1635 cm^{-1}; NMR δ 5.34 (1 H, s), 5.81 (1 H, s).

Ethyl Benzyloxycarbonyl-α-aminoacrylylglycinate (31): $R_{f\,(6)}$ 0.29; IR 3430, 3385, 1737, 1665, 1621, 1500 cm^{-1}; NMR δ 1.27 (3 H, t), 4.05 (2 H, d), 4.23 (2 H, q), 5.17 (2 H, s), 5.28 (1 H, t), 6.5 (1 H, s), 7.33 (5 H, s). Anal. ($C_{15}H_{18}N_2O_5$): C, H, N.

Methyl Benzyloxycarbonylglycyl-α-aminoacrylate (32): $R_{f\,(6)}$ 0.27; IR 3430, 3390, 1725, 1718, 1692, 1635, 1510, 1500 cm^{-1}; NMR δ 3.80 (3 H, s), 3.92 (2 H, d), 5.10 (2 H, s), 5.72 (1 H, d, J = 1 Hz), 5.87 (1 H, d, J = 1 Hz), 6.54 (1 H, s), 7.28 (5 H, s), and 8.25 (NH, s). Anal. ($C_{14}H_{16}N_2O_5$): C, H, N.

Methyl *tert*-Butyloxycarbonyl-L-methylalanyl-L-leucyl-α-aminoacrylylglycinate (33): $R_{f\,(5)}$ 0.43, $R_{f\,(2)}$ 0.66; IR 3440, 3300, 1740, 1690, 1635 cm^{-1}; NMR δ 0.98 (6 H, t), 1.40 (3 H, d, J = 7.2 Hz), 1.48 (9 H, s), 2.77 (3 H, s), 3.80 (3 H, s), 4.13 (2 H, m), 4.64 (1 H, q, J = 7.2 Hz), 5.44 (1 H, d, J = 1.5 Hz), 6.51 (1 H, s), 6.84 (NH, m), 7.18 [NH(Leu), m], 8.40 [NH(Δ-Ala), d]. Anal. ($C_{21}H_{36}N_4O_7$): C, H, N.

Methyl *tert*-Butyloxycarbonyl-*N*-methyl-α-aminoacrylate (34): $R_{f\,(1)}$ 0.43, $R_{f\,(7)}$ 0.30; IR 1730, 1630 cm^{-1}; NMR δ 5.35 (1 H, s), 5.82 (1 H, s). Anal. ($C_{10}H_{17}NO_4$): C, H, N.

Methyl *tert*-Butyloxycarbonyl-*N*-methyl-α-aminocinnamate (35): $R_{f(2)}$ 0.62; IR 1665 cm^{-1}; NMR δ 1.3 (9 H, s), 3.8 (3 H, s), 3.0 (3 H, s), 7.25 (1 H, s), 7.32 (5 H, s). Anal. ($C_{16}H_{21}NO_4$): C, H, N.

Methyl *tert*-Butyloxycarbonyl-L-*N*-methylalanyl-L-leucyl-*N*-methyl-α-aminoacrylylglycinate (36): $R_{f\,(5)}$ 0.23, $R_{f\,(4)}$, 0.32; IR 3430, 3296, 1755, 1680, 1670, 1632, 1530, 1515, 1500 cm^{-1}; NMR δ 0.86 (3 H, d), 0.90 (3 H, d), 1.29 (3 H, d, J = 7.2 Hz), 1.46 (9 H, s), 2.73 (3 H, s), 3.10 (3 H, s, ΔNCH_3), 3.70 (3 H, s), 4.12 (2 H, d), 4.48 (1 H, m, Leu-αH), 4.62 (1 H, q, Ala-αH), 5.58 (1 H, s), 6.33 (1 H, s), 6.57 (NH, d, Leu), 8.10 (NH, m, Gly). Anal. ($C_{22}H_{38}N_4O_7$): C, H, N.

***cyclo*(L-*N*-Methylalanyl-L-leucyl-*N*-methyl-α-aminoacrylylglycyl) (37):** $R_{f\,(2)}$ 0.20, $R_{f\,(3)}$ 0.17, $R_{f\,(5)}$ 0.16; IR (KBr) 1690, 1660, 1630 cm^{-1}; NMR δ 0.93, 0.95 (6 H, dd), 1.49 (3 H, d, J = 7.2 Hz), 1.68 (3 H, m), 3.03 (3 H, s), 3.06 (3 H, s), 3.45 (1 H, d, J = 14.7 Hz), 4.88 (1 H, dd, J = 14.7, 9.3 Hz), 4.34 (1 H, q, J = 7.2 Hz), 4.98 (1 H, m, Leu), 5.65 (2 H, s), 7.89 (NH, d, 9.42, Leu), 8.01 (NH, d, J = 9.3 Hz, Gly); mass spectrum: M^+ 338.4 (1.5), 253, 225, 195, 170, 142, 127, 113, 87, 58 (100). Anal. ($C_{16}H_{26}N_4O_4$): C, H, N.

Methyl *tert*-Butyloxycarbonyl-(*E*)-α-aminocrotonate (38): $R_{f\,(2)}$ 0.37, $R_{f\,(6)}$ 0.34; IR 3500, 1750, 1735, 1530, cm^{-1}; NMR δ 1.47 (9 H, s, 2.05 (3 H, d, J = 7.2 Hz), 3.82 (3 H, s), 6.53 (NH, s), 6.78 (1 H, br q). Anal. ($C_{10}H_{17}NO_4$): C, H, N.

Methyl *tert*-Butyloxycarbonyl-(*Z*)-α-aminocrotonate (39): $R_{f\,(2)}$ 0.46, $R_{f\,(6)}$ 0.44; IR 3450, 1720, 1660, 1495 cm^{-1}; NMR δ 1.48 (9 H, s), 1.81 (3 H, dd, J = 0.5, 7.3 Hz), 3.78 (3 H, s), 6.04 (1 H, br s), 6.67 (1 H, q, J = 7.32 Hz). Anal. ($C_{10}H_{17}NO_4$): C, H, N.

Methyl *tert*-Butyloxycarbonyl-Δ²-valinate (40): $R_{f\,(3)}$ 0.83; IR 1740 cm^{-1}; NMR, δ 1.89 (3 H, s), 2.12 (3 H, s). Anal. ($C_{11}H_{19}NO_4$): C, H, N.

Methyl *tert*-Butyloxycarbonyl-α-aminocinnamate (41): $R_{f\,(2)}$ 0.60; IR 1665 cm^{-1}; NMR δ 1.3 (9 H, s), 3.8 (3 H, s), 7.25 (1 H, s), 7.32 (5 H, s). Anal. ($C_{15}H_{19}NO_4$): C, H, N.

Methyl *tert*-Butyloxycarbonylalanyl-α-aminocrotonate (42): $R_{f(2)}$ 0.31; IR 3350, 1730, 1680, 1635, 1520, 1495 cm^{-1}; NMR δ 1.40 (3 H, d, J = 7.2 Hz), 1.5 (9 H, s), 1.75 (3 H, d, J = 7 Hz), 3.8 (3 H, s), 4.80 (1 H, m), 7.14 (1 H, q, J = 7 Hz); mass spectrum: M^+ 272.3 Anal. ($C_{13}H_{22}N_2O_5$): C, H, N.

Methyl *tert*-Butyloxycarbonyl-L-alanyl-Δ²-valinate (43): $R_{f\,(2)}$ 0.30; IR 3430, 1736, 1718, 1687, 1500 cm^{-1}; δ 1.20 (3 H, d), 1.36 (9 H, d), 1.82 [3 H, s, (*Z*)-CH_3], 2.14 (3 H, s, (*E*)-CH_3), 3.75 (3 H, s), 4.5 (1 H, m), 5.3 (1 H, q, J = 7 Hz). Anal. ($C_{14}H_{24}N_2O_5$): C, H, N.

Methyl *tert*-Butyloxycarbonyl-L-alanyl-(*Z*)-α-aminocinnamate (44): $R_{f\,(2)}$ 0.41; NMR 1.40 (3 H, d, J = 7.2 Hz), 1.45 (9 H, s), 3.62 (3 H, s), 4.34 (1 H, q, J = 7.2 Hz), 5.17 (NH, d, Ala), 7.21 (5 H, s), 7.46 (1 H, s, vinyl proton), 8.73 (NH, s, Phe); mass spectrum: M^+ 348.4. Anal. ($C_{18}H_{24}N_2O_5$): C, H, N.

Methyl *tert*-butyloxycarbonyl-2-amino-3-butenoate (46). Oxidation of *tert*-butyloxycarbonylmethionine methyl ester with sodium periodate gave the corresponding sulfoxide (**45**). A solution of **45** in xylene (1 mmol to 50 mL of xylene) was passed through a hot tube (200–200 °C) packed with glass helixes. The flow rate was controlled by nitrogen inflow and the products were collected in a trap maintained at −78 °C. The mixture was worked up as described under elimination, method A. Olefin **46** was obtained in 75% yield: IR 1740, 1720, 1656 cm^{-1}; NMR δ ($CDCl_3$) 1.45 (9 H, s), 3.76 (3 H, s), 4.82 (1 H, br t, α-CH), 5.28 (1 H, m), 5.43 (2 H, m), 5.90 (1 H, m); mass spectrum Calcd: 215.25. Found: 215.3. Anal. ($C_{10}H_{17}NO_4$): C, H, N.

Registry No.—*erythro*-**26** thio deriv, 63701-06-4; *threo*-**26** thio deriv, 63701-07-5; (*E*)-**41**, 63658-17-3; (*Z*)-**41**, 63658-18-4; (*E*)-**42**, 63701-60-0; (*Z*)-**42**, 63701-08-6; **45**, 63701-09-7; **46**, 63658-19-5; **49**, 63658-20-8; **50**, 63658-21-9; **51**, 63658-22-0; **52**, 63658-23-1; *threo*-3-*S*-benzylthio-2-aminobutyric acid, 63701-10-0; *erythro*-3-*S*-benzylthio-2-aminobutyric acid, 63701-11-1; BOC-methioninemethyl ester, 33900-24-2; methyl *N*-*tert*-butyloxycarbonyl-L-alanyl-3-methylthio-2-aminoisovalerate, 63701-12-2; methyl *N*-tert-butyloxycarbonyl-*N*-methyl-L-alanyl-L-leucyl-L-*S*-methylcysteinylglycinate, 63658-25-3; *cyclo*(L-methylalanyl-L-leucyl-*N*-methyl-3-*S*-methylcysteinylglycyl), 63658-26-4.

References and Notes

(1) (a) Supported by Grant GM-19311 from the National Institutes of Health. (b) Abstracted in part from the Ph.D. Thesis of J. P. Tam, University of Wisconsin, May 1976. (c) Dehydroamino acids denote amino acids that contain a double bond in their side chains. The following abbreviations are used: dehydroalanine, Ala(Δ); *N*-methyldehydroalanine, MeAla(Δ); dehydrophenylalanine, Phe(Δ²); 2-aminobutyric acid, Abu; 2-amino-2-butenoic acid, Abu(Δ²); *N*-methyl-2-amino-2-butenoic acid, MeAbu(Δ²). The abbreviations for parent amino acids are based on the rules and tentative rules for symbols for amino acid derivatives [*Biochemistry*, **11**, 1726 (1972); *ibid.*, **14**, 449 (1975)]. In this paper, the symbol, Δ, indicates a double bond and the superscript indicates its position in the molecule. The olefin geometry is indicated by *E*, entgegen, or *Z*, zusammen.

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