α-Amino Acids as Chiral Educts for Asymmetric Products. Aminoacylation of Metallo Alkyls and Alkenyls

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α-Amino acids have been developed as educts for the preparation of optically pure α-amino aliphatic ketones. The amino group of the L-amino acid was first blocked as a suitable acyl derivative, namely, acetyl, benzoyl, ethoxycarbonyl, or benzenesulfonyl. Then the lithium carboxylate was formed and treated with alkyl- and alkenyllithium or Grignard reagents. Thus butyl, allyl, and vinyl organometallics were added to the lithium carboxylates of L-α-N-substituted alanine, valine, *O*-benzyltyrosine, methionine, serine, and ε-(ethoxycarbonyl)lysine to yield the corresponding optically pure ketones, protected as amides, sulfonamides, or carbamates.

α-Amino acids are generally inexpensive compounds, readily available in many structural types and in enantiomerically pure form. We have been exploring the possibility of using a variety of them as chiral educts for the preparation of optically and regiochemically pure α-amino ketones. Previously, we have shown that aryl organometallic reagents may be added to L-*N*-(ethoxycarbonyl)- or *N*-(phenylsulfonyl)alanine to yield the optically pure N-substituted α-aminoalkyl aryl ketones.[1] Using instead butyl, allyl and vinyl organometallics, we now demonstrate the preparation of optically pure α-amino ketones from alanine as well as from valine, methionine, *O*-benzyltyrosine, ε-(ethoxycarbonyl)lysine, and serine. The N-blocking group has been expanded from ethoxycarbonyl and phenylsulfonyl to include acetyl and benzoyl groups. With this extension to a large variety of functionalized ketones, this method offers attractive alternatives to asymmetric syntheses based on carbohydrate and hydroxy acid educts,[2] especially for nitrogen-containing compounds.

General Methodology. Each amino acid is distinct in regard to the details of converting it to the N-blocked acid and ultimately to the N-protected amino ketone, but gross mechanistic considerations are common to all and have been summarized generally and in Table I.

The addition of organolithium[3] and, to a lesser extent, Grignard reagents[4] to carboxylic acids to give ketones has been used extensively. These organometallic reagents are nucleophilic but also extremely basic, so examples in the literature, though numerous, are limited in scope. One would expect, for instance, that a compound with an existent or incipient carbonyl group α to an optically active trisubstituted carbon atom, when used in an organometallic reaction, would lose its optical integrity. Nevertheless, we have carried out just such transformations with complete retention of asymmetry. Blocking of the amino acid α-nitrogen as the amide, carbamate, or sulfonamide was done as described.[5] The addition of lithium reagents to these N-blocked acids occurred largely in a manner conventional with that of simple acids with one important difference. Addition of 100 mol % of the lithium reagent to the protected amino acid **1** generated the lithium carboxylate **2**. The second 100 mol % of lithium reagent did not add to the acid as it does with simple carboxylic acids but instead most likely abstracted the hydrogen from the acylated nitrogen, resulting in a dianion **3**. The third 100 mol % of lithium reagent then added to the carboxylate to give a trianion **4** as a probable intermediate, stable in the reaction medium, which upon quenching with acid yielded the corresponding ketone. Abstraction of the nitrogen-bound hydrogen may be essential in preserving optical purity since formation of the amide or carbamate anion insulates the α-hydrogen and prevents its removal, thus averting racemization (Table I). Despite the considerable difference between the pK_a's associated with each of the N-protecting groups, each is effective in preserving optical purity.

Lithium reagents are effective in this reaction, and we found them to be useful except for adding a vinyl group. Although the preparation of vinyl ketones by addition of vinyllithium to acids has been reported,[6] the reaction conditions are harsh compared to those needed for butyl- and allyllithium reagents. Also, lithium reagents are often less convenient to prepare than the equivalent alkyl Grignard. We found that vinyllithium would not add to our N-substituted amino acids; therefore, we investigated the possibility of using organomagnesium reagents instead.

The literature precedent regarding use of Grignard reagents in the ketone-forming reaction is considerably less than that for lithium reagents, and the reaction is limited by a serious side reaction. When a Grignard reagent is added to an acid, the corresponding ketone may be isolated, but in addition an equivalent or greater amount of tertiary alcohol or other products derived from the ketonic intermediate are formed.[4] The latter products result from the instability of the magnesium salt of the dioxy anion of **4** which collapses in the reaction medium to generate ketone directly. This ketone may then react further with remaining Grignard reagent.

When we attempted the Grignard reaction with an N-acylated amino acid, our results were consistent with these observations.[4] However, by simply first forming the lithium carboxylate and then adding the Grignard reagent, we obtained good yields of ketone, and in only one example was any of the tertiary alcohol observed. Even in this worst case, *N*-(ethoxycarbonyl)alanine, only 10% of the undesired tertiary alcohol was formed (path 1). These results

(1) Buckley, T. F., III; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157.
(2) Enders, D.; Lotter, H. *Tetrahedron Lett.* **1982**, *23*, 639. Colvin, E. W.; Beck, A. K.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 2264. Reden, J.; Durckheimer, W. *Top. Curr. Chem.* **1979**, *83*, 105.
(3) Jorgenson, M. J. *Org. React.* **1970**, *18*, 1.
(4) Watanabe, S.; Suga, K.; Fujita, T.; Saito, N. *Aust. J. Chem.* **1977**, *30*, 427. Nunomoto, S.; Yamashita, Y. *Nippon Kagaku Kaishi* **1975**, 2138. Suga, K.; Watanabe, S.; Yamaguchi, Y.; Toyama, M. *Synthesis* **1970**, 189.
(5) Greenstein, J. P.; Winitz, M. "Chemistry of the Amino Acids"; Wiley; New York, 1961; Vol. II. Milne, H. B.; Peng, C.-H. *J. Am. Chem. Soc.* **1957**, *79*, 639.
(6) Floyd, J. C. *Tetrahedron Lett.* **1974**, 2877. Levine, R.; Karten, M. J. *J. Org. Chem.* **1976**, *41*, 1176. Levine, R.; Karten, M. J.; Kadunce, W. M. *Ibid.* **1975**, *40*, 1770.

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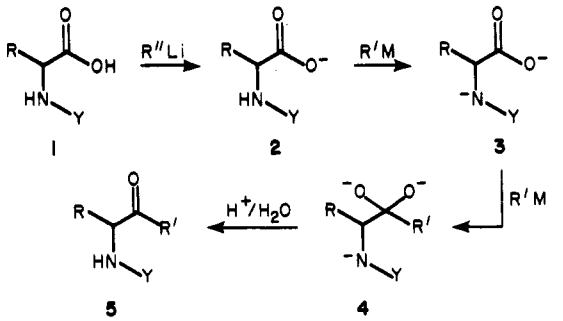
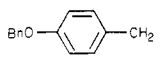
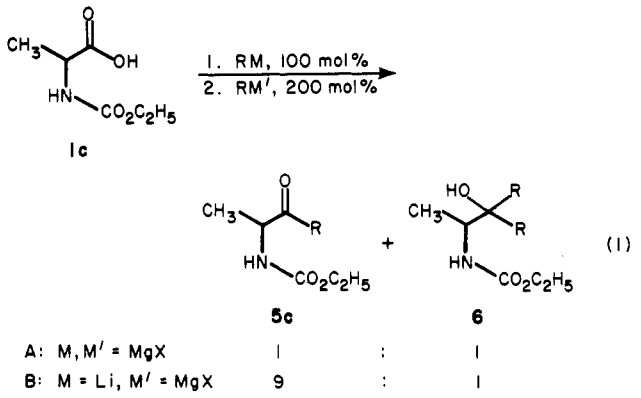
Table I. Formation of α-Amino Ketones from Various α-N-Acylated Amino Acids and Organometallic Reagents



compd	R	R′	Y	R″	M	% yield of 5
a	CH_3	$CH_2CH{=}CH_2$	$COCH_3$	*n*-Bu	MgBr	40
b	CH_3	$CH_2CH{=}CH_2$	COPh	*n*-Bu	MgBr	87
c	CH_3	$CH_2CH{=}CH_2$	CO_2Et	$CH_2{=}CHCH_2$	Li	74
d	$(CH_3)_2CH$	$CH_2CH{=}CH_2$	SO_2Ph	*n*-Bu	MgBr	62 (91)[a]
e	$CH_3SCH_2CH_2$	$CH_2(CH_2)_2CH_3$	SO_2Ph	*n*-Bu	Li	54 (74)[a]
f	$CH_3SCH_2CH_2$	$CH{=}CH_2$	SO_2Ph	*n*-Bu	MgBr	35
g		$CH_2CH{=}CH_2$	CO_2Et	*n*-Bu	MgBr	71
h	$EtO_2CNH(CH_2)_3CH_2$	$CH_2CH{=}CH_2$	SO_2Ph	*n*-Bu	MgBr	52
i	$HOCH_2$	$CH_2CH{=}CH_2$	SO_2Ph	*n*-Bu	MgBr	53
j	$HOCH_2$	$CH{=}CH_2$	SO_2Ph	*n*-Bu	MgBr	48

[a] Yield in parentheses is based on recovered acylamino acid.

imply that the mixed lithium–magnesium salt of the dioxy anion of 4 is stable in the reaction medium.

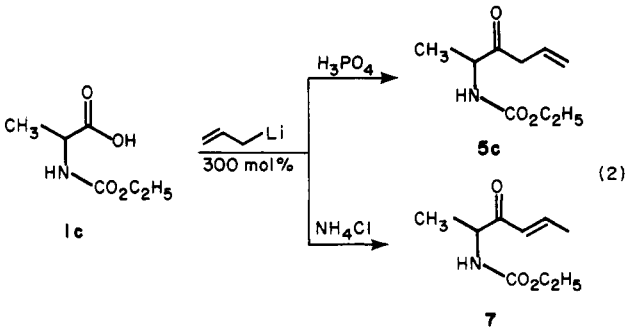


	5c		6
A: M, M′ = MgX	1	:	1
B: M = Li, M′ = MgX	9	:	1

The N-blocking groups ethoxycarbonyl, acetyl, benzoyl, and phenylsulfonyl may be used interchangeably. They are not amino acid specific, and each has its own virtues. The phenylsulfonyl group imparts considerable crystallinity to its derivatives and therefore ease of handling. In addition we were able to use the acidity of the sulfonamide and the nucleophilicity of the resulting anion to advantage in determining the optical purity of product ketones as described below. The ethoxycarbonyl group may be removed hydrolytically or may be reduced to a methyl group if desired. The acetyl may also be removed hydrolytically and serves as an incipient ethyl group. The benzoyl group has the added flexibility that it may be reduced with lithium aluminum hydride to benzyl and then removed hydrogenolytically. The common blocking groups benzyloxycarbonyl and *tert*-butyloxycarbonyl also were used but were found inferior; the former was unstable to the reaction conditions, and the latter gave lower yields.

The choice of organometallic reagent is also not amino acid specific nor limited. We chose butyl, allyl, and vinyl as representative of the variety of nucleophiles consistent with this method and our objectives. The allyl group was the most reactive, gave the best yields, and offered the option of preparing either the β,γ- or the *trans*-α,β-unsaturated ketone. The butyl group gave results similar to allyl with respect to yields and rates but is of less subsequent utility and so was not investigated extensively. Vinyl addition gave products in slightly lower yields generally and required considerably longer reaction times, but the latter was only a minor inconvenience.

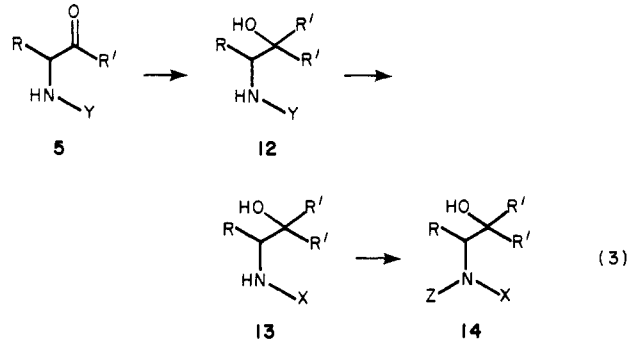
Specific Examples. Alanine. Ketone formation with L-alanine, the simplest naturally occurring chiral α-amino acid, was investigated by using allyllithium[7] as the nucleophile and ethoxycarbonyl, acetyl, and benzoyl as the N-blocking groups, as well as with vinylmagnesium bromide on the *N*-carbamate. The ethyl carbamate **1c**, synthesized by using standard Schotten–Baumann procedures,[5] was converted to the allyl ketone **5c** by using a procedure which was typical for the synthesis of all the allylic ketones. Acid **1c** was dissolved in THF and cooled to −78 °C, and 300 mol % of allyllithium was added, after which the solution was allowed to warm to room temperature. Either the initially formed β,γ-unsaturated ketone **5c** or the *trans*-α,β-unsaturated enone **7c** could be obtained by simple variation of the isolation procedure. The former was produced when the reaction mixture was poured into 40% H_3PO_4, while the α,β-unsaturated isomer was easily obtained by quenching with NH_4Cl solution (path 2).



The optical purity of the α,β-unsaturated isomer was determined by adding propyllithium to the ketone to form

(7) Eisch, J. J.; Jacobs, A. M. *J. Org. Chem.* **1963**, *28*, 2145. Claisen, L. *Justus Liebigs Ann. Chem.* **1919**, *418*, 69.

a tertiary alcohol and then hydrogenating the olefin to erase asymmetry at the hydroxyl-bearing carbon. After the carbamate was reduced with $LiAlH_4$, the resulting amine was treated with α-methoxy-α-(trifluormethyl)-phenylacetyl chloride (Mosher's acid chloride),[8] either (−) or (±), to give in the former case a single diastereomer and in the latter two diastereomers separable by HPLC. Analysis of the final tertiary alcohol product **14c** when (−) Mosher's acid was used showed it to be >99% optically pure. The β,γ-unsaturated isomer was not subjected to similar analysis because it was assumed that, as the precursor of the α,β-isomer, it must have at least an equivalent optical purity. The general method is illustrated in path 3 [**14c**; R = X = CH_3, R′ = n-C_3H_7, Z = $C_6H_5C(OCH_3)(CF_3)CO$].

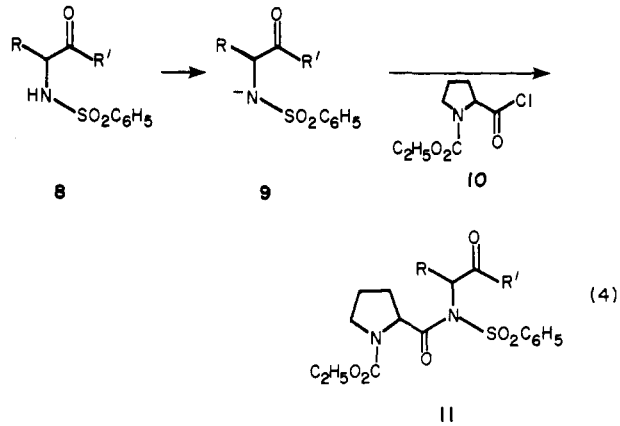


The ketone which would result from the addition of vinyllithium was of great interest as a pro-amino sugar. However, reports of the conditions required for addition of vinyllithium to simple acids were discouraging.[6] With our standard, mild conditions and vinyllithium at −78 °C, no enone was observed. When the more reactive vinylmagnesium bromide (300 mol %) was added to *N*-(ethoxycarbonyl)alanine (**1c**) we found the expected 1/1 mixture of ketone and alcohol. However, by first forming the lithium carboxylate of *N*-(ethoxycarbonyl)alanine (**2c**) with 100 mol % of n-butyllithium and then adding 200 mol % vinylmagnesium bromide,[9] we formed the enone in a 9/1 preference over the divinyl alcohol from which it was easily separated.

A similar procedure was used to prepare the allyl ketone from L-*N*-acetylalanine, i.e., 100 mol % n-butyllithium followed by 200 mol % allylmagnesium bromide. The optical purity was established by adding allyl ketone **5a** to allylmagnesium bromide. The tertiary alcohol formed was reduced with $LiAlH_4$ and the resulting ethylamine reacted with the acid chloride of L- or DL-*N*-(phenylsulfonyl)proline to give in the former case a single diastereomer and in the latter two, which were easily separated by HPLC. Thus we demonstrated via path 3 that the retention of optical purity through formation of ketone **5a** as well as subsequent reactions to **14a** (R = CH_3, R′ = $CH_2CH{=}CH_2$, X = C_2H_5, Z = N-$C_6H_5SO_2$pro) was >99%.

N-Benzoylalanine was converted to the allyl ketone **5b** by using the same method as above. Optical purity was proved by converting ketone **5b** to the tertiary alcohol [path 3; **14b**, R = CH_3, R′ = n-C_3H_7, X = H, Z = $C_6H_5C(OCH_3)(CF_3)CO$] by addition of allyl Grignard, reduction of the benzamide to the benzylamine with $LiAlH_4$, hydrogenolysis and hydrogenation with H_2/Pd/C, and finally reaction with either (−) or (±) Mosher's acid chloride to form one or two diastereomers, respectively. Purity was assayed by using ^{19}F NMR; 2% of the L-(+) diastereomer was clearly visible when added to the pure single diastereomer, demonstrating the starting ketone **5b** to have been >98% optically pure.

Valine. Valine was chosen as an example of an α-amino acid with a β branch, and *N*-(phenylsulfonyl)valine was prepared by using standard conditions.[5] The allyl ketone **5d** was made by the process described above (100 mol % of n-butyllithium followed by 200 mol % of allylmagnesium bromide). Establishing optical purity proved to be a simple task. The anion of the benzenesulfonamide was formed by addition of butyllithium at −78 °C, and this anion was then acylated with the acid chloride of either L- or DL-N-(ethoxycarbonyl)proline to afford in the former case a single diastereomer and in the latter two (path 4).



Analysis of the single diastereomer **11a** (R = i-C_3H_7, R′ = $CH_2CH{=}CH_2$, R″ = $CO_2C_2H_5$) by HPLC demonstrated that it and the precursor ketosulfonamide **5d** were >99% optically pure. All subsequent sulfonamides were assayed for optical purity by using the route of path 4.

Tyrosine. Tyrosine was blocked at its phenolic function as the benzyl ether[10] and then converted to the *N*-ethoxycarbonyl derivative[5] **1g** which was used in the standard ketone-forming reaction. The allylic ketone **5g** was examined for optical purity as was done for ketone **5c** by addition of allylmagnesium bromide, reaction with lithium aluminum hydride, and acylation with either (±) or (−) Mosher's acid chloride to give two or one diastereomer(s), respectively (path 3). Analysis of tertiary alcohol **14d** [R = p-$C_6H_7OC_6H_7$, R′ = $CH_2CH{=}CH_2$, X = CH_3, Z = $C_6H_5C(OCH_3)(CF_3)CO$] by HPLC showed that the original ketone **5g** must have been >99% optically pure and that all subsequent reactions were nonracemizing.

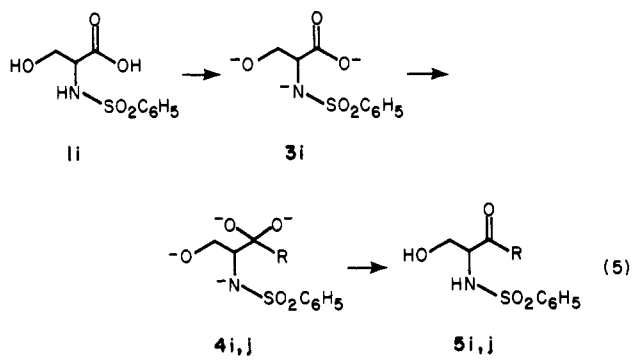
Methionine. Again, phenylsulfonyl was used to block the amine function, and the butyl ketone **5e** was prepared simply by adding 300 mol % of n-butyllithium to *N*-(phenylsulfonyl)methionine (**1e**) in THF followed by an acid quench. The yield based on easily recovered educt was 67%. An optical purity of >99% was established via the method of path 4. The vinyl ketone **5f** was also prepared, by first forming the lithium carboxylate of *N*-(phenylsulfonyl)methionine with 100 mol % of n-butyllithium and then adding 200 mol % of vinylmagnesium bromide. An optical purity of >99% was determined for **5f** by using the method described for the butyl ketone **5e**.

Lysine. Lysine has two amine sites that require blocking. The α-amino group must be blocked to impart solubility in organic solvents and, in its protected anionic form, to provide a barrier to abstraction of the α-hydrogen under the basic ketone-forming reaction conditions, thus

(8) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(9) Rosenberg, S. D.; Gibbons, A. J., Jr.; Ramsden, H. E. *J. Am. Chem. Soc.* **1957**, *79*, 2137.
(10) Wunsch, E.; Fries, G.; Zwick, A. *Chem. Ber.* **1958**, *91*, 542.

preventing racemization. The ε-amino group must be blocked too, for solubility reasons and to prevent subsequent reaction with the product ketone. Different blocking groups on the α- and ε-amines would be desirable so that they could be manipulated independently of each other. The choice to block the ε-amino as the ethoxycarbonyl[11] and the α-amino as the phenylsulfonyl derivatives was based on the principle that this would allow for simple determination of optical purity by using the general method developed for sulfonamides. We synthesized the allylic ketone **5h** as described above except that provision had to be made for the additional acidic hydrogen by addition of 200 mol % of *n*-butyllithium to the protected lysine. This was followed by 200 mol % of allylmagnesium bromide to yield the allyl ketone **5h**. Optical purity was assayed by using the sulfonamide method (path 4), and the ketone was shown to be >99% optically pure.

Serine. Encouraged by our success with lysine and its reactivity toward nucleophiles even as the trianion, we next investigated the reactivity of serine without protecting the alcohol function. We had used tyrosine, as described above, but the phenolic hydroxyl was blocked as a benzyl ether. In contrast, *N*-(phenylsulfonyl)serine was used directly. When *n*-butyllithium (200 mol %) was added to a THF suspension of *N*-(phenylsulfonyl)serine at −78 °C, the mixture became homogeneous. Then 200 mol % of either vinyl or allyl Grignard reagent was added, and the vinyl and allylic ketones, **5j** and **5i**, respectively, were isolated. Apparently trianion **3i** which results upon consumption of 300 mol % of organometallic reagents is still receptive to nucleophilic attack. The tetraanionic intermediates **4i,j** which are presumably the ultimate reaction intermediates are stable as well, since no tertiary alcohols were observed (path 5).



1i **3i** **4i,j** **5i,j**

Vinyl ketone **5j** was acetylated at the alcohol function under acid-catalyzed conditions, and then, by use of the sulfonamide acylating procedure (path 4), the ketone was shown to have been >99% optically pure.

Conclusions. We have shown that α-amino acids may serve as educts for the synthesis of optically and regio pure aliphatic α-amino ketones through the addition of organolithium or organomagnesium reagents to the N-blocked lithium carboxylates **2**. Protection may be as the *N*-acetyl, benzoyl, phenylsulfonyl, or ethoxycarbonyl derivatives. A variety of amino acids, including alanine, valine, tyrosine, methionine, lysine, and serine were examined, and all gave satisfactory results. The organometallic nucleophiles butyl, allyl, and vinyl all were effective either as lithium or Grignard reagents. A key aspect of these reactions is that they proceed with no detectable racemization. The product ketones were demonstrated to be >99% optically pure, as determined primarily by HPLC analysis of diastereomer composition. On consideration of the variety of optically active amino acids available, the compatibility of this reaction with other functional groups, and the scope of potential alkyl and alkenyl organometallic reagents, this process offers considerable promise for asymmetric syntheses.

Experimental Section

Melting points were determined by using a Mel-Temp apparatus and are uncorrected. Final organic solvent solutions were dried over $MgSO_4$ and rotoevaporated in vacuo. Infrared spectra were recorded in $CHCl_3$ unless otherwise noted on a Perkin-Elmer 137 spectrophotometer; NMR spectra were recorded by using a Varian EM-390 spectrometer in $CDCl_3$ with Me_4Si as an internal standard unless otherwise indicated. The coupling constants are given in hertz. Optical rotations were measured by using a Perkin-Elmer 241 polarimeter with a 10-cm cell. HPLC analyses were performed by using an Altex Model 110A dual pump system with a Hitachi Model 100-30 spectrophotometer as the detector. Normal phase separations were made by using a Lichrosorb Si-60 5-μm column (3.2 × 250 nm); reverse-phase separations were made with an Ultrasphere C-18-5-μm column (3.2 × 250 mm).

Allyllithium was prepared as described,[7] and the lithium reagents were assayed against diphenylacetic acid. Allylmagnesium bromide was made in ether,[12] and vinylmagnesium bromide was made in THF[6] as reported. The Grignard reagents were assayed by measuring gas evolution when added to water and by titrating a water-quenched aliquot with standard acid to the phenophthalein end point. THF and ether were distilled from sodium–benzophenone.

***N*-(Ethoxycarbonyl)alanine (1c)** was made as described[5] and isolated as an oil in 90% yield: NMR δ 1.28 (t, J = 8, 3 H), 1.50 (d, *J* = 7, 3 H), 2.82 (m, 1 H), 2.9 (s, 3 H), 4.17 (q, *J* = 8, 2 H), 10.15 (s, 1 H); $[\alpha]^{22}_D$ −15.3° (*c* 2, CH_2Cl_2); IR (neat) 3350, 1750, 1700 cm^{-1}.

5-[(Ethoxycarbonyl)amino]-4-hexenone (5c). *n*-Butyllithium (8.4 mL, 1.6 M, 13.4 mmol) was added dropwise to a stirred solution of *N*-(ethoxycarbonyl)alanine (**1c**; 2.15 g, 13.4 mmol) in 40 mL dry THF at −10 °C, and the resulting white suspension cooled to −78 °C. Allyllithium (71 mL, 0.38 M, 26.9 mmol) was added slowly, and the red solution formed was stirred 30 min at −78 °C followed by warming and stirring at room temperature for an additional 30 min. The reaction mixture was poured into cold 40% H_3PO_4 and extracted with ether, and the ether was washed with cold 1 N NaOH (2×) and brine, dried, and evaporated. Kugelrohr distillation (60 °C/0.03 mm) gave a colorless oil: 1.8 g (74% yield); $[\alpha]^{23}_D$ +56.5° (*c* 2, CH_2Cl_2); IR (neat) 3450, 1725, 1700 cm^{-1}; NMR δ 1.32 (t, *J* = 7.5, 3 H), 1.33 (d, *J* = 7.5, 3 H), 3.02 (d, *J* = 6.0, 2 H), 4.02 (q, *J* = 7.5, 3 H), 4.30 (dq, *J* = 6.7, 1 H), 5.01 (dq, *J* = 7.5, 1.5, 1 H), 5.13 (d, *J* = 6.7, 1 H), 5.8 (m, 2 H). Anal. Calcd for $C_9H_{15}O_3N$: C, 58.4; H, 8.2; N, 7.6. Found: C, 58.4; H, 8.2; N, 7.4.

(*S*,*E*)-5-[(Ethoxycarbonyl)amino]-2-hexen-4-one (7c). A reaction mixture identical with the one above was poured into 100 mL of saturated NH_4Cl solution instead of 40% H_3PO_4. Isolation in the same manner yielded 1.76 g (73%) of a Kugelrohr-distilled oil (70 °C/0.3 mm): $[\alpha]^{23}_D$ +47.0° (*c* 2, CH_2Cl_2); NMR δ 1.23 (t, *J* = 6.7, 3 H), 1.35 (d, *J* = 6.7, 3 H), 1.87 (dd, *J* = 1.5, 6.7, 3 H), 4.02 (q, *J* = 6, 2 H), 4.46 (dq, *J* = 6.7, 6.7, 1 H), 5.8 (d, *J* = 6.7, 1 H), 6.16 (dq, *J* = 1.5, 16.5, 1 H), 6.90 (dq, *J* = 6.7, 16.5, 1 H). Anal. Calcd for $C_9H_{15}O_3N$: C, 58.4; H, 8.2; N, 7.6. Found: C, 58.4; H, 8.2; N, 7.4.

L-*N*-(Phenylsulfonyl)valine (1d) was prepared in 80% yield in a manner analogous to that reported for L-*N*-tosylalanine:[1] mp 149–150 °C; IR 1725, 1330, 1160 cm^{-1}; NMR δ 0.80 (d, *J* = 7, 3 H), 0.85 (d, *J* = 7, 3 H), 1.94 (dq, *J* = 7, 7, 1 H), 3.49 (d, *J* = 7, 1 H), 7.46 (m, 3 H), 7.78 (m, 2 H); $[\alpha]^{23}_D$ +7.6° (*c* 5, $CHCl_3$). Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 51.4; H, 5.9; N, 5.4. Found: C, 51.4; H, 5.9; N, 5.4.

(*S*)-5-[(Phenylsulfonyl)amino]-6-methyl-4-heptenone (5d). L-*N*-(Phenylsulfonyl)valine (**1d**; 2.57 g, 10 mmol) was dissolved

(11) Scott, J. W.; Parker, D.; Parrish, D. R. *Synth. Commun.* **1981**, *11*, 303.

(12) Hwa, C. H.; Sims, H. In "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 608.

in 50 mL of THF and cooled to −78 °C. *n*-Butyllithium (6.25 mL, 10 mmol, 1.6 M) was added dropwise followed by allylmagnesium bromide (30 mL, 27 mmol, 0.9 M in ether). The solution was allowed to warm to room temperature, stirred for 2.5 h, poured into 1 N HCl, and extracted with $CHCl_3$. The organic phase was washed with aqueous $NaHCO_3$ and brine, dried, and evaporated to give 1.74 g (62%) of an oil. Acidification of the $NaHCO_3$ wash, extraction with $CHCl_3$, drying with $MgSO_4$, and evaporation gave 1.0 g of **1d**. Chromatography (gravity column, $CHCl_3$, silica) of the oil gave 1.56 g (56%, 91% based on recovered **1d**) of **5d**: mp 67–69 °C; IR 3300, 1725, 1635, 1160 cm^{-1}; NMR δ 0.76 (d, 3 H), 1.06 (d, 3 H, J = 7.5), 2.03 (m, 1 H), 2.96 (t, J = 7, 1 H), 3.83 (dd, J = 4.5, 9, 1 H), 3.02 (m, 2 H), 5.50 (m, 2 H), 7.46 (m, 3 H), 7.72 (m, 2 H); $[\alpha]^{22}_D$ +115° (*c* 2, $CHCl_3$). Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.8; H, 6.8; N, 5.0. Found: C, 60.0; H, 6.9; N, 4.9.

***N*-(Benzyloxycarbonyl)proline** (L and DL) was prepared according to a literature procedure.[13] The product was isolated as a viscous colorless oil which could not be crystallized.

L-*N*-(Phenylsulfonyl)methionine (1e). Methionine (14.9 g, 0.1 mmol) was dissolved in 200 mL of 1 N sodium hydroxide, and benzenesulfonyl chloride (17.6 g, 0.1 mol) was added. After being stirred 1.5 h at room temperature, the mixture was acidified with 5 N HCl to pH 2 and then extracted with ether. The organic layer was dried and evaporated, and the residue was crystallized from ethyl acetate/benzene to yield 18 g (70%) of **1e**: mp 131 °C; IR 1750, 1220 cm^{-1}; NMR (CD_3OD) δ 2.0 (s, 3 H), 2.27 (t, J = 7, 2 H), 4.02 (t, J = 7, 1 H), 7.57 (m, 3 H), 7.85 (m, 2 H); $[\alpha]^{23}_D$ +0.6° (*c* 5, CH_3OH). Anal. Calcd for $C_{11}H_{15}NO_4S_2$: C, 45.3; H, 5.3; N, 4.8. Found: C, 45.4; H, 5.2; N, 4.8.

(*S*)-1-(Methylthio)-3-[(phenylsulfonyl)amino]-4-octanone (5e). (Phenylsulfonyl)methionine (**1e**; 2.57 g, 10 mmol) was dissolved in 80 mL of dry THF and cooled to −78 °C, *n*-butyllithium (18.7 mL, 30 mmol, 1.6 M in hexane) was added via syringe (1 mL/min), and the suspension was warmed to room temperature and stirred an additional 30 min. It was then poured into 1 N HCl, the acidified aqueous layer was extracted with chloroform, and the organic layer was washed with aqueous $NaHCO_3$ and brine. Drying and evaporating the solvent left a residue (2.30 g) which was recrystallized from ether to yield 1.6 g of pure ketone **5e** in 54% yield. The starting material was recovered by acidifying the bicarbonate extract, extracting with $CHCl_3$, drying, and evaporating the solvent; the yield based on this recovery (0.7 g) was 74%: mp 115 °C; IR 3200, 1710, 1160 cm^{-1}; NMR δ 0.80 (t, J = 7, 3 H), 1.2 (m, 4 H), 1.7 (m, 2 H), 2.03 (s, 3 H), 2.25 (t, J = 6, 2 H), 2.53 (t, J = 6, 2 H), 4.03 (dt, J = 7.5, 5, 1 H), 5.68 (d, J = 7.5, 1 H), 7.55 (m, 3 H), 7.85 (m, 2 H); $[\alpha]^{23}_D$ +95.3° (*c* 5, $CHCl_3$). Anal. Calcd for $C_{15}H_{23}NO_3S_2$: C, 54.7; H, 7.0; N, 4.2. Found: C, 54.8; H, 7.2; N, 4.1.

(*S*)-6-(Methylthio)-4-[(phenylsulfonyl)amino]-3-hexenone (5f). *N*-(Phenylsulfonyl)methionine (**1e**; 515 mg, 2 mmol) was dissolved in 20 mL dry THF and cooled to −78 °C. *n*-Butyllithium (1.25 mL, 1.6 M, 2 mmol) was added dropwise followed by vinylmagnesium bromide (1.9 mL, 2.1 M, 4 mmol), and the solution was then allowed to warm to room temperature and stir for 21 h. The reaction was quenched by addition of 1 N HCl. Extraction with ether, washing with saturated $NaHCO_3$ and brine, drying, and evaporating the solvent yielded a yellow solid, which upon recrystallization from ethyl acetate/isooctane gave 210 mg (35%) of **5f**: mp 114–115 °C; NMR δ 1.86 (m, 2 H), 1.99 (s, 3 H), 2.49 (t, J = 7.5, 2 H), 4.35 (dt, J = 7.5, 3, 1 H), 5.67 (d, J = 7.5, 1 H), 5.73 (dd, J = 7.5, 4, 1 H), 6.18 (d, J = 4, 1 H), 6.20 (d, J = 7.5 1 H), 7.35 (m, 3 H), 7.82 (m, 2 H); $[\alpha]^{22}_D$ +7.3° (*c* 0.6, $CHCl_3$). Anal. Calcd for $C_{13}H_{17}NO_3S_2$: C, 52.2; H, 5.7; N, 4.7. Found: C, 51.9; H, 5.6; N, 4.4.

***O*-Benzyltyrosine** was prepared by following the literature procedure[10] to yield on crystallization a white powder: 51%; mp 246–250 °C (lit.[10] mp 223 °C); $[\alpha]^{23}_D$ −10.2° (*c* 2, 80% CH_3CO_2H) [lit.[10] $[\alpha]^{20}_D$ −9.9° (*c* 2, 80% CH_3CO_2H)].

***O*-Benzyl-*N*-(ethoxycarbonyl)tyrosine (1g).** To *O*-benzyltyrosine (2.8 g, 10.3 mmol) dissolved in 3.5 mL of 3 N NaOH at 0 °C was added ethyl chloroformate (1.15 g, 10.6 mmol) along with 3.5 mL of 3 N NaOH. The resulting mixture was stirred for 2 h, acidified with 2 N HCl, and extracted with $CHCl_3$. The organic phase was washed with brine, dried, and evaporated to a residue which was recrystallized from ether to yield 1.8 g (53%) of **1g**: mp 122–123 °C; IR 3400, 1700, 1600 cm^{-1}; NMR (CD_3OD) δ 1.16 (t, J = 7, 3 H), 2.93 (d, J = 8, 1 H), 3.03 (d, J = 5, 1 H), 4.00 (q, J = 7, 2 H), 4.30 (d, J = 5, 1 H), 4.40 (d, J = 8, 1 H), 5.00 (s, 2 H), 6.88 (d, J = 9, 2 H), 7.14 (d, J = 9, 2 H), 7.36 (s, 3 H); $[\alpha]^{23}_D$ +19.0° (*c* 5, CH_3OH). Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.5; H, 6.2; N, 4.1. Found: C, 66.2; H, 6.1; N, 4.0.

(*S*)-5-[(Ethoxycarbonyl)amino]-6-[4-(benzyloxy)-phenyl]-4-hexenone (5g). L-*O*-Benzyl-*N*-(ethoxycarbonyl)tyrosine (**1g**; 343 mg, 1 mmol) was dissolved in 10 mL of THF and cooled to −78 °C, *n*-butyllithium (0.69 mL, 1.45 M, 1 mmol) was added dropwise followed by allylmagnesium bromide (4.0 mL, 0.9 M, 3.6 mmol, in ether), and the solution was allowed to warm to room temperature and stirred for 40 min. It was poured into 1 N HCl and extracted with $CHCl_3$/EtOAc (1/1), which was washed with aqueous $NaHCO_3$ and brine and dried. Evaporation gave 300 mg of a residue which was chromatographed (MPLC, $CHCl_3$) and gave 260 mg (71%) of allyl ketone **5g**, isolated as an oil: NMR δ 1.06 (t, J = 7, 3 H), 2.76 (d, J = 7, 5, 2 H), 2.95 (d, J = 7.5, 2 H), 3.83 (q, J = 7, 2 H), 4.36 (d, J = 7, 1 H), 4.81 (s, 2 H), 4.9 (m, 4 H), 5.6 (m, 1 H), 6.8 (m, 4 H), 7.22 (s, 5 H). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.9; H, 6.9; N, 3.8. Found: C, 71.9; H, 6.8; N, 3.8.

(*S*)-4-[1-[(Ethoxycarbonyl)amino]-2-[4-(benzyloxy)-phenyl]ethyl]-1,6-heptadien-4-ol (12d). Ketone **5g** (367 mg, 1 mmol) was dissolved in 5 mL of THF, allylmagnesium bromide (4 mL, 1 M, 4 mmol) was added at room temperature, and the resulting solution was stirred for 30 min. The reaction mixture was poured into 1 N HCl and extracted with ether which was washed with brine, dried, and evaporated to yield 300 mg of an oil. This oil was chromatographed (MPLC, silica, 5% EtOAc/$CHCl_3$) to yield 160 mg (26%) of the tertiary alcohol **12d** which was carried on without further characterization.

(*S*)-4-[1-(Methylamino)-2-[4-(benzyloxy)phenyl]ethyl]-1,6-heptadien-4-ol (13d). The diallyl alcohol **12d** (150 mg, 0.4 mmol) was dissolved in 6 mL of dry ether, an excess of lithium aluminum hydride (160 mg) was added, and the resulting suspension was heated under reflux for 2 h. Cooling to room temperature and cautious addition of 10% NaOH was followed by filtering. Evaporation of the ether filtrate yielded the amino alcohol which was purified as its hydrochloride. Dissolution of the amine in benzene, shaking the benzene with 1 N HCl followed by evaporation of the benzene, redissolution of the salt in a small amount of hot ether, and cooling yielded the HCl salt (100 mg, 65%) as fine white needles. Anal. Calcd for $C_{23}H_{30}NO_2Cl$: C, 71.2; H, 7.8; N, 3.6. Found: C, 70.8; H, 7.8; N, 3.6.

L-*N*$^{\epsilon}$-(Ethoxycarbonyl)lysine. Lysine hydrochloride (20 g, 110 mmol) was dissolved in 200 mL of H_2O and heated on a steam bath while cupric carbonate (18 g) was added in portions with swirling. The resulting suspension was heated on the steam bath 20 min, filtered through Celite, diluted to 450 mL, and cooled to 20 °C. First $NaHCO_3$ (18.3 g, 220 mmol) was added in two portions, and then ethyl chloroformate (15.4 g, 142 mmol) was dissolved in 260 mL of dioxane and added with rapid stirring over 1 h, with stirring being continued overnight. The blue precipitate was collected, washed with water, and then stirred in 300 mL of MeOH overnight. Water (400 mL) was added followed by 600 mL of Chelex-100 resin which had been washed with 1.2 L of 1 N HOAc followed by 2 L of H_2O. After being stirred 3 h, the mixture was filtered and the solvent removed under reduced pressure to yield N^{ϵ}-(ethoxycarbonyl)lysine as a white powder: 13.4 g (55%); mp 198–202 °C; ^1H NMR (D_2O) δ 1.22 (t, J = 7, 3 H), 1.45 (m, 4 H), 1.85 (m, 2 H), 3.13 (t, J = 6, 2 H), 3.72 (m, 1 H), 4.13 (q, J = 7, 2 H); $[\alpha]^{22}_D$ +3.5° (*c* 2, H_2O). Anal. Calcd for $C_9H_{18}N_2O_4$: C, 49.5; H, 8.3; N, 12.8. Found: C, 49.3; H, 8.2; N, 12.7.

L-*N*$^{\epsilon}$-(Phenylsulfonyl)-*N*$^{\epsilon}$-(ethoxycarbonyl)lysine (1h). N^{ϵ}-(Ethoxycarbonyl)lysine (2.18 g, 10 mmol) was dissolved in 30 mL of 1 M NaOH solution at 0 °C, and benzenesulfonyl chloride (2.64 g, 15 mmol) was added. The cloudy solution was stirred for 4 h at room temperature, the pH was adjusted to 2 with 1 N HCl, and the white precipitate was extracted into ethyl acetate, which was dried and evaporated to yield 3.2 g (90%) of **1h**: mp 235–246 °C; NMR (CD_3COCD_3) δ 1.18 (t, J = 7, 3 H), 1.4 (m, 4 H), 1.7 (m, 2 H); $[\alpha]^{22}_D$ +12.35° (*c* 1.7, CH_3OH). Anal. Calcd

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for $C_{15}H_{22}N_2O_6S$: C, 50.3; H, 6.2; N, 7.8. Found: C, 50.5; H, 6.3; N, 7.8.

(*S*)-5-[(Phenylsulfonyl)amino]-9-[(ethoxycarbonyl)-amino]-4-nonenone (5h). To L-N^{α}-(phenylsulfonyl)-N^{ϵ}-(ethoxycarbonyl)lysine (**1h**; 2.5 g, 7.0 mmol) dissolved in 100 mL of THF and cooled to −78 °C was added dropwise *n*-butyllithium (8.75 mL, 1.6 M, 14.0 mmol) followed by allylmagnesium bromide (23.4 mL, 0.90 M, 21 mmol). The resulting suspension was stirred rapidly, warmed to room temperature, stirred for 4 h, poured into 1 N HCl, and extracted with ethyl acetate. The organic phase was washed with saturated $NaHCO_3$ and brine and dried, and the solvent was evaporated to give a solid which was recrystallized from ether/petroleum ether to yield 1.42 g (52%) of ketone **5h**: mp 103–105 °C; $[\alpha]^{25}_D$ +12.2° (*c* 4, CH_3OH); IR 3350, 1700, 1340, 1160 cm^{-1}; NMR (CD_3COCD_3) δ 1.16 (t, *J* = 7, 3 H), 1.25 (m, 4 H), 1.55 (m, 2 H), 3.03 (t, *J* = 6, 2 H), 3.26 (d, *J* = 6, 2 H), 3.90 (m, 1 H), 4.00 (q, *J* = 7, 2 H), 4.95 (d, *J* = 5, 1 H), 5.10 (s, 1 H), 5.7 (m, 1 H), 7.55 (m, 3 H), 7.80 (m, 2 H). Anal. Calcd for $C_{18}H_{26}N_2O_5S$: C, 56.5; H, 6.9; N, 7.3. Found: C, 56.5; H, 6.9; N, 7.3.

L-*N*-(Phenylsulfonyl)serine (1i). Serine (10.5 g, 100 mmol) was dissolved in 200 mL of 1 N NaOH at 0 °C, and benzenesulfonyl chloride (17.6 g, 100 mmol) was added all at once. The heterogeneous mixture was stirred rapidly while warming to room temperature, stirring was continued for 5 h, and the reaction mixture was poured into 1 N HCl. After the acidic solution sat for 1 day, the crystals which formed were collected and washed with H_2O and a small amount of methanol to yield **1i**: 12.6 g (51%); mp 223–225 °C; $[\alpha]^{22}_D$ +9.25 (*c* 2, CH_3OH). Anal. Calcd for $C_9H_{11}NO_5S$: C, 44.1; H, 4.5; N, 5.7. Found: C, 44.0; H, 4.6; N, 5.6.

(*S*)-5-[(Phenylsulfonyl)amino]-6-hydroxy-4-hexenone (5i). To L-*N*-(phenylsulfonyl)serine (**1i**; 2.45 g, 10 mmol) stirred in 100 mL of THF at −78 °C was added dropwise *n*-butyllithium (12.5 mL, 1.6 M, 20 mmol) followed by allylmagnesium bromide (33 mL, 0.9 M, 30 mmol), and the resulting suspension was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was poured into 1 N HCl and extracted with ether, and the organic layer was washed with saturated $NaHCO_3$ and brine, dried, and evaporated. Recrystallization of the resulting solid from ether/ligroin yielded 1.41 g (53%) of allyl ketone **5i**: mp 108–109 °C; IR (KBr) 3550, 3300, 1725, 1175 cm^{-1}; NMR (CD_3CN, 5% D_2O) δ 3.07 (d, *J* = 7, 2 H), 3.50 (d, *J* = 5, 1 H), 3.60 (d, *J* = 5, 1 H), 3.93 (t, *J* = 5, 1 H), 4.80 (d, *J* = 10), 2.95 (s, 1 H), 5.5 (m, 1 H), 7.5 (m, 3 H), 7.7 (m, 2 H); $[\alpha]^{25}_D$ +22.5° (*c* 2, CH_3OH). Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.5; H, 5.6; N, 5.2. Found: C, 53.5; H, 5.6; N, 5.3.

(*S*)-4-[(Phenylsulfonyl)amino]-5-hydroxy-3-pentenone (5j). To *N*-(phenylsulfonyl)serine (**1i**; 4.90 g, 20 mmol) stirred in 100 mL THF at −78 °C was added dropwise *n*-butyllithium (22.0 mL, 1.6 M, 35 mmol) followed by vinylmagnesium bromide (60.0 mL, 0.9 M, 54 mmol). The suspension was allowed to warm to room temperature and stirred for 20 h, then poured into 1 N HCl and extracted with ether. The ether layer was washed with saturated $NaHCO_3$ and brine, dried and evaporated to yield 2.85 g of a white solid which, after trituration with 15 mL ether, yielded 2.45 mg (48%) of pure enone **5j**: mp 110–111 °C; NMR (CD_3CN) δ 3.72 (d, *J* = 5, 2 H), 4.22 (t, *J* = 5, 1 H), 5.76 (dd, *J* = 2, 10, 1 H), 6.25 (d, *J* = 2, 1 H), 6.39 (d, *J* = 10, 1 H), 7.57 (m, 3 H), 7.80 (m, 2 H); $[\alpha]^{25}_D$ +12.8° (*c* 2, CH_3OH). Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.8; H, 5.1; N, 5.5. Found: C, 51.7; H, 5.1; N, 5.4.

(*S*)-5-(Benzoylamino)-4-hexenone (5b). To L-*N*-benzoylalanine (**1b**; 3.86 g, 20 mmol) dissolved in 200 mL of THF at −78 °C was added dropwise *n*-butyllithium (12.5 mL 1.6 M in hexane, 20 mmol) followed by allylmagnesium bromide (50 mL, 0.9 M in ether, 45 mmol). The resulting suspension was allowed to warm to room temperature and stirred for 3 h after which the reaction mixture was poured into 1 N HCl and extracted with $CHCl_3$. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated to yield 4.19 g of an oil. Filtration through a short volume of silica ($CHCl_3$) yielded 3.8 g (87%) of **5b**: mp 50–52 °C; IR 3600, 1675, 1520, 1495 cm^{-1}; NMR δ 1.43 (d, *J* = 7, 3 H), 3.33 (d, *J* = 7, 2 H), 4.80 (d, t, *J* = 7.7, 1 H), 5.09 (d, *J* = 8, 1 H), 5.12 (s, 1 H), 6.19 (m, 1 H), 7.4 (m, 3 H), 7.8 (m, 2 H); $[\alpha]^{22}_D$ +82.8° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.9; H, 7.0; N, 6.4. Found: C, 71.8; H, 6.9; N, 6.4.

(*S*)-5-(Acetylamino)-4-hexenone (5a) To L-*N*-acetylalanine (**1a**; 1.31 g, 10 mmol) in 100 mL of THF was added dropwise *n*-butyllithium (6.3 mL, 1.6 M in hexane, 10 mmol). This suspension was cooled to −78 °C, and allylmagnesium bromide (28 mL, 0.9 M in ether, 25 mmol) was added in a slow stream. The reaction mixture was warmed to room temperature, stirred 16 h, poured into 1 N HCl, and extracted twice with ethyl acetate which was washed with saturated aqueous $NaHCO_3$ and brine. Drying of the organic phase ($MgSO_4$), treatment with decolorizing carbon, and evaporation yielded 800 mg of a pale oil. Filtration through a short column of silica (20% EtOAc/$CHCl_3$) yielded **5a** as a colorless oil: 600 mg (39% yield); $[\alpha]^{23}D$ +49.6° (*c* 1, $CHCl_3$); IR (neat) 1725, 1650 cm^{-1}; NMR δ 1.30 (d, *J* = 7, 3 H), 1.98 (s, 3 H), 3.26 (d, *J* = 7, 2 H), 4.57 (dt, *J* = 7, 7, 1 H), 5.07 (d, *J* = 9, 1 H), 5.22 (s, 1 H), 5.8 (m, 1 H). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.9; H, 8.4; N, 9.0. Found: C, 61.7; H, 8.5; N, 8.7.

Procedures for Determining Enantiomeric Purity. Preparation and Separation of Diastereomers of *N*-Methyl Amines. The *N*-methyl amine was dissolved in CH_2Cl_2 (9 mL/mmol), and triethylamine (100 mol %) was added followed by Mosher's acid chloride (200 mol %). The reaction mixture was stirred and heated if necessary until the educt was consumed. Isolation involved washing the organic phase with aqueous acid and alkali and yielded the diastereomer(s) contaminated with unreacted acid chloride, easily separated by HPLC (40% EtOAc/isooctane).

Preparation and Separation of Diastereomers of Benzenesulfonamides. The sulfonamide was dissolved in THF (10 mL/mmol) and cooled to −78 °C, and *n*-butyllithium (100 mol %) was added followed by 200 mol % of the acid chloride of *N*-(benzyloxycarbonyl)- or *N*-(ethoxycarbonyl)proline. The solution was allowed to warm to room temperature, poured into 1 N HCl, and extracted with ether, and the organic extract was washed with aqueous $NaHCO_3$ and brine and dried. Evaporation left a residue containing the resulting diastereomer(s) and unreacted acid chloride. Separation was effected on reverse-phase HPLC for the methionine and serine derivatives (42% H_2O/CH_3CN) and on normal-phase HPLC for valine (50/50 $CHCl_3$/isooctane) and lysine (25% EtOAc/$CHCl_3$). The hydroxy group of ketones **5i,j** derived from serine was first acetylated (acetic anhydride/H_2SO_4) before applying the above procedure.

Determination of Optical Purity of (*S*)-5-(Benzoylamino)-4-hexenone (5b). The ketone **5b** was added to allylmagnesium bromide in ether at 0 °C over 40 min and stirred 2 h. Isolation through an aqueous wash gave the tertiary alcohol which was reduced in ether with excess lithium aluminum hydride at reflux for 8 h. Standard isolation with chloroform as the solvent and including a dilute phosphoric acid extraction gave the benzylamine which was converted to its HCl salt and hydrogenolyzed in ethanol with 10% Pd/C and H_2 at 55 psi for 30 min. The resulting primary amine was treated with Mosher's acid chloride as described above. The two diastereomers were easily distinguished by their ^{19}F NMR resonances at δ 26.6 and 26.8.

Determination of Optical Purity of (*S*)-5-(Acetylamino)-4-hexenone (5a). The ketone **5a** (1.1 g, 7.1 mmol) was dissolved in 30 mL ether, added to an ice cold solution of allylmagnesium bromide (16.5 mL, 15.1 mmol) in ether, and stirred for 2 h. Standard isolation yielded 670 mg of the desired diallyl alcohol which was dissolved in 5 mL ether, 500 mg of $LiAlH_4$ was added, and the reaction mixture was heated under reflux for 8 h. After the reaction was quenched with 10% NaOH and $CHCl_3$ added, the organic phase was washed with dilute H_3PO_4 and aqueous NaOH and evaporated to give 470 mg of the ethylamine, which was Kugelrohr distilled (80 °C/0.05 mm). The amine (45 mg, 0.25 mmol) was dissolved in 3 mL of THF and the acid chloride of either L- or DL-*N*-(phenylsulfonyl)proline (82 mg, 0.3 mmol) was added followed by 5 drops of triethylamine. After a few minutes, the mixture was poured into 1 N HCl, extracted twice with ethyl acetate, and washed with aqueous $NaHCO_3$. Evaporation of the solvent gave a white solid (100 mg, quantitative) which HPLC analysis (reverse phase, Ultrasphere ODS column, 50/50 H_2O/CH_3CN) showed to be the L diastereomer of >99% purity.

Registry No. **1a**, 97-69-8; **1b**, 2198-64-3; **1c**, 16639-86-4; **1d**,

85849-94-1; **1e**, 51786-15-3; **1g**, 29210-09-1; **1h**, 85828-28-0; **1i**, 85828-29-1; **5a**, 85828-30-4; **5b**, 85828-31-5; **5c**, 85828-32-6; **5d**, 85828-33-7; **5e**, 85828-34-8; **5f**, 85828-35-9; **5g**, 85828-36-0; **5h**, 85828-37-1; **5i**, 85828-38-2; **5j**, 85282-39-3; **7c**, 85828-40-6; **12d**, 85828-41-7; **13d**·HCl, 85828-42-8; allyllithium, 3052-45-7; allylmagnesium bromide, 1730-25-2; methionine, 63-68-3; benzenesulfonyl chloride, 98-09-9; *n*-butyllithium, 109-72-8; vinylmagnesium bromide, 1826-67-1; *O*-benzyltyrosine, 16652-64-5; ethyl chloroformate, 541-41-3; lysine hydrochloride, 657-27-2; L-N^{ϵ}-(ethoxycarbonyl)lysine, 5701-16-6; serine, 56-45-1.

Polyene Pheromone Components from an Arctiid Moth (*Utetheisa ornatrix*): Characterization and Synthesis[1]

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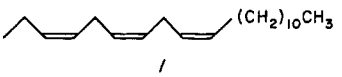
In our earlier study of the female sex attractant from an arctiid moth (*Utetheisa ornatrix*), the occurrence of an uncharacterized C-21 tetraene was noted along with (*Z,Z,Z*)-3,6,9-heneicosatriene, the major pheromone constituent. The sex attractant glands of females from other populations of this moth have now yielded this C-21 tetraene as a major component, accompanied by a new C-21 diene. Spectral and chemical studies of these two EAG-active compounds led to their characterization as (*Z,Z,Z*)-1,3,6,9-heneicosatetraene and (*Z,Z*)-6,9-heneicosadiene. These structures and configurations were confirmed by synthesis.

We previously reported the characterization and synthesis of (*Z,Z,Z*)-3,6,9-heneicosatriene (**1**), the principal



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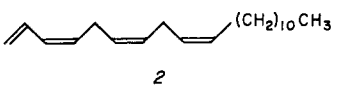

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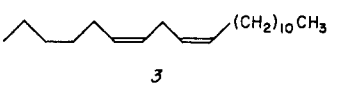

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component of the sex attractant secretion of female *Utetheisa ornatrix*. This C-21 triene was shown to be biologically active in field and electroantennogram (EAG) bioassays.[1] We also noted an accompanying minor component, an EAG-active C-21 tetraene. In order to characterize the *U. ornatrix* pheromone more fully, we have examined new samples of this glandular product. We now report the full characterization and synthesis of the rather unstable tetraene [(*Z,Z,Z*)-1,3,6,9-heneicosatetraene (**2**)], as well as of an EAG-active diene [(*Z,Z*)-6,9-heneicosadiene, (**3**)] also found in the secretion.

Moths from five locations were used in our studies (Gainesville, FL; Lake Placid, FL; Poplarville, MS; Cameron, NC; Isabela, Puerto Rico). Composition of the secretion was found to vary geographically, within populations, and even from year to year. Details of variability, involving the nature, number, and ratio of gland components, will be published elsewhere. We here deal only with the chemistry of the diene and tetraene, two compounds not previously known from an insectan source.

Secretion was obtained by hexane extraction of glands freshly extricated with forceps from 318 live females (1–14 days old). These had been laboratory reared on a semisynthetic diet[5] supplemented with either *Crotalaria mucronata* beans (one of their natural food sources) or pinto beans; they represented first and third generation descendants stemming respectively from Gainesville and Poplarville field populations. The extract was concentrated, and a small portion was analyzed on GLC (10% XF-1150 at 150 °C). This analysis showed the presence of two components, designated as A and B. Neither of these corresponded to the previously reported triene **1**. However, A, now the major component, proved to be identical with the previously noted C-21 tetraene. Component B, also EAG active, had not been detected in our original samples of secretion (Lake Placid populations). These two compounds were separated and purified by preparative GLC and characterized as described below.

The mass spectrum of A showed a molecular ion at m/z 288.2818 (CI MS 289, MH^+) corresponding to the molecular formula $C_{21}H_{36}$ (calcd 288.2817). Microhydrogenation gave a product indistinguishable (GC/MS) from *n*-heneicosane ($C_{21}H_{44}$), indicating the presence of four centers of unsaturation in an unbranched chain of 21 carbon atoms. Microozonolysis, followed by reduction of the ozonide with triphenylphosphine, gave a material indistinguishable from *n*-dodecanal (GC/MS) as the only isolable product. The ultraviolet spectrum of A showed a strong absorption at 229 nm, indicating the presence of a conjugated diene chromophore. The 300-MHz ^1H NMR spectrum of A allows only a small number of possible structures. The presence of a total of nine protons in the olefinic region, along with the observation of only one terminal methyl group, requires one of the double bonds to occupy a terminal position (C-1). The ozonolysis experiment requires

(1) For the previous paper in this series, see: Conner, W. E.; Eisner, T.; Vander Meer, R. K.; Guerrero, A.; Ghiringhelli, D.; Meinwald, J. *Behav. Ecol. Sociobiol.* **1980**, *7*, 55.

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(5) Miller, J. R.; Baker, T. C.; Cardé, R. T.; Roelofs, W. L. *Science (Washington, D.C.)* **1976**, *192*, 140.

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