dimethyl-1-((p-nitrophenyl)seleno)propyl)cyclopropane (8) was shown by NMR of the reaction mixture, which was purified by recrystallization, giving a yellow crystalline solid 8: mp 176-177 °C; NMR ($CDCl_3$) δ 1.10 (s, 9 H), 1.18 (s, 9 H), 2.03 (d, J = 8.7 Hz, 1 H), 2.18 (dd, J = 8.7, 10.2 Hz, 1 H), 3.00 (d, J = 10.2 Hz, 1 H), 7.78 and 8.08 (AB q, J = 9.0 Hz, 4 H); IR (KBr) 2241, 1597, 1571, 1511, 1348 cm^{-1}.

Anal. Calcd for $C_{20}H_{25}O_2N_3Se$: C, 57.41; H, 6.02; N, 10.04. Found: C, 57.41; H, 5.99; N, 9.82.

Reaction of 2c with 2-Diazopropane. To 1 mmol of **2c** in CH_2Cl_2 at -20 °C was added an ethereal solution containing 1 mmol of 2-diazopropane. Quantitative formation of 3,3-dicyano-1,1-dimethylallyl p-nitrophenyl selenide (**4o**) was shown by the NMR of the reaction mixture, which was purified by recrystallization, giving a yellow crystalline solid **4o**: mp 149-150 °C; NMR ($CDCl_3$) δ 1.80 (s, 6 H), 7.08 (s, 1 H), 7.73 and 8.25 (AB q, J = 9.0 Hz, 4 H); IR (KBr) 2232, 1595, 1579, 1516, 1350 cm^{-1}.

Anal. Calcd for $C_{13}H_{11}O_2N_3Se$: C, 48.76; H, 3.46; N, 13.12. Found: C, 48.86; H, 3.47; N, 12.94.

Compound **2c** was treated with a large excess of 2-diazopropane. After the solvent was removed, NMR analysis of the reaction mixture showed formation of 4,4-dicyano-3,3-dimethyl-5-(2-((p-nitrophenyl)seleno)-2-methylpropyl)-Δ^1-pyrazoline (**9**): NMR ($CDCl_3$) δ 1.50 (s, 3 H), 1.83 (s, 3 H), 1.87 (s, 3 H), 2.00 (s, 3 H), 4.97 (s, 1 H), 7.29 and 8.15 (AB q, J = 9.0 Hz, 4 H). The reaction mixture was chromatographed over silica gel using benzene as an eluent, giving bis(p-nitrophenyl) diselenide and 4,4-dicyano-5,5-dimethyl-3-isopropylidene-Δ^1-pyrazoline (**10**): mp 61.5-62.0 °C; NMR ($CDCl_3$) δ 1.67 (s, 6 H), 2.30 (s, 3 H), 2.48 (s, 3 H); IR (KBr) 2246, 1663, 1501 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}N_4$: C, 63.81; H, 6.43; N, 29.77. Found: C, 63.79; H, 6.39; N, 29.52.

Resolution and Determination of the Absolute Stereochemistry of α- and β-Aryl-Substituted γ-Methylenevalerolactones, Alternate Substrate Inhibitors for Serine Proteases

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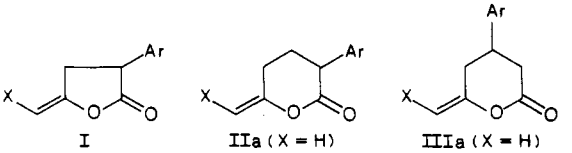
To study the enantioselectivity of alternate substrate inhibition of chymotrypsin by chiral α- and β-aryl-substituted enol lactones, we have prepared four of these lactones in homochiral form: 3-phenyl-6-methylenetetrahydro-2-pyranone (αPh6H, IIa), 3-(1-naphthyl)-6-methylenetetrahydro-2-pyranone (αNp6H, IIb), 4-phenyl-6-methylenetetrahydro-2-pyranone (βPh6H, IIIa), and 4-(1-naphthyl)-6-methylenetetrahydro-2-pyranone (βNp6H, IIIb). Their resolution was carried out on the acetylenic acid precursors α- and β-aryl-5-hexynoic acids (**2ab** and **7ab**, respectively) by silica gel chromatographic separation of the corresponding (R)-phenylglycinol amide derivatives. The homochiral acids, obtained by acid hydrolysis of the amides, have enantiomeric excesses of 94-100% and are readily converted to the enol lactones by mercury-catalyzed lactonization. The absolute configuration of the β-aryl-substituted lactones was established by X-ray crystallographic analysis of one of the phenylglycinol amide diastereomers, cocrystallized with triphenylphosphine oxide; the configuration of the α-aryl-substituted lactones is based on a stereochemical correlation. In all cases, the assigned stereochemistry of the amides is consistent with their chromatographic elution order and the chemical shift of diagnostic resonances in the ^1H NMR spectra. Both enantiomers of the IIIa hydrolysis product β-phenyl-substituted 5-oxohexanoic acid **10a** were prepared by an asymmetric synthesis using the RAMP and SAMP hydrazones; their stereochemistry was correlated with that of the corresponding acetylenic acids.

Introduction

Serine proteases play a major role in the regulation of many normal physiological and pathological processes,[1] and recently, major efforts have been directed toward the development of effective and selective serine protease inhibitors as agents of therapeutic promise.[2]

We have investigated the activity of halo enol lactones as enzyme-activated irreversible inhibitors of serine proteases and found that the α-aryl-substituted (halomethylene)butyrolactone and -valerolactone systems I and II are effective mechanism-based inhibitors of α-chymotrypsin.[3,4] Reaction proceeds by acylation of the active site serine-195, with concomitant unmasking of a latent alkylating agent, a halomethyl ketone; inactivation then results from subsequent alkylation of an active site residue (presumed to be histidine-57), a process that competes with deacylation. In further studies on the β-phenyl-substituted systems (III, X = Br, I), only transient inhibition, characteristic of a stable acyl enzyme, but not alkylation, was observed.[5] Such stable acyl enzymes were also noted with the corresponding protio enol lactones (IIIa, X = H), which do not have the latent alkylating function. In some cases, extremely stable acyl enzymes, having half-lives of several hours at pH 7.2, 25 °C, were obtained.[5]



I IIa (X = H) IIb (X = H) IIIa (X = H) IIIb (X = H)

Ar = phenyl (a); 1-naphthyl (b); X = H, Br, I

Questions arose concerning enantioselectivity in the three steps of enzymatic lactone hydrolysis—substrate

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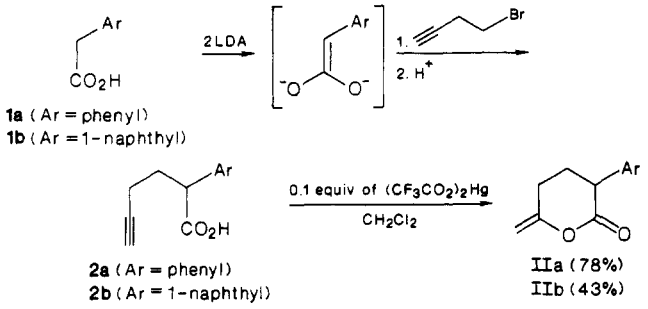
Scheme I



binding, acylation, and deacylation. Therefore, as described in this paper, we have prepared and resolved four enantiomeric sets of aryl-substituted δ-methylenevalerolactones, bearing phenyl or 1-naphthyl substituents α or β to the lactone carbonyl IIa, IIb, IIIa, IIIb. We have also established the absolute configuration of the α-substituted lactones by stereochemical correlation and analogy and of the β-substituted by X-ray crystallography and analogy. These assignments are consistent with the order of chromatographic elution and the NMR spectra of diastereomeric (*R*)-phenylglycinol amide derivatives of a precursor acetylenic acid; further correlation is also made to a related keto acid prepared by an enantioselective synthesis. The kinetics of chymotrypsin inhibition by these resolved enol lactones and derivatives of the keto acids is described elsewhere.[6]

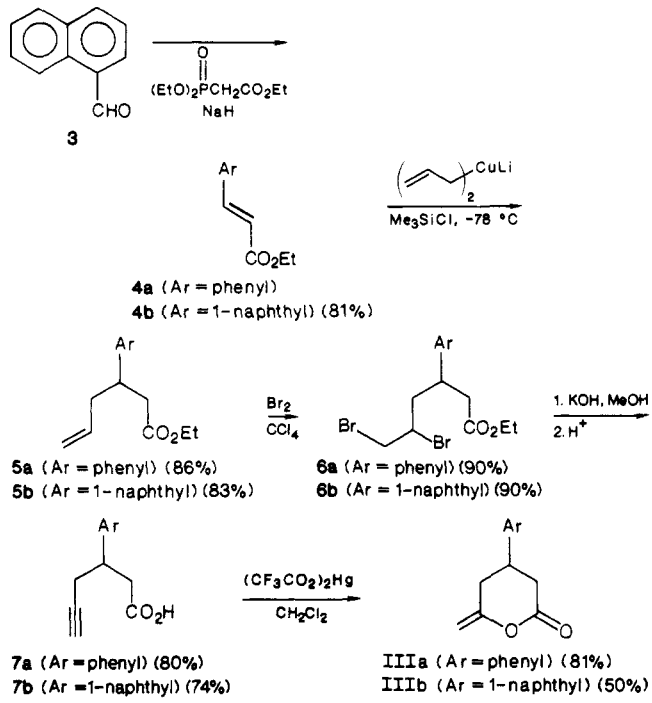
Results and Discussion

Synthesis of Protio Enol Lactones. The following lactones were prepared and resolved into their two enantiomers: 3-Phenyl-6-methylenetetrahydro-2-pyranone (IIa), 3-(1-naphthyl)-6-methylenetetrahydro-2-pyranone (IIb), 4-phenyl-6-methylenetetrahydro-2-pyranone (IIIa), and 4-(1-naphthyl)-6-methylenetetrahydro-2-pyranone (IIIb). For their synthesis, we followed the general approach developed by us previously:[3,4] preparation of an α- or β-aryl-substituted 5-hexynoic acid, followed by mercury-catalyzed cyclization to the δ-methylenevalerolactone.

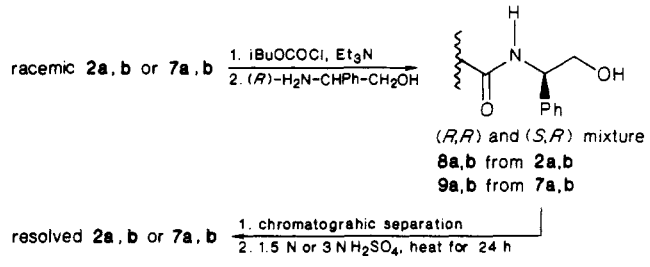
The precursors for the α-aryl-substituted protio enol lactones were prepared by direct alkylation of the dilithium salt of a 2-arylacetic acid.[4] The preparation of α-phenyl- and α-(1-naphthyl)-5-hexynoic acids (**2a** and **2b**) by alkylation of the dilithium salts of the corresponding α-arylacetic acids (**1a** and **1b**) with 3-butynyl bromide has been described, as has the cyclization of these acetylenic acids to the protio enol lactones (IIa and IIb) (Scheme I).[4]

The precursors required for the preparation of β-aryl-substituted enol lactones are the corresponding acetylenic acids, 3-phenyl-5-hexynoic acid (**7a**) or 3-(1-naphthyl)-5-hexynoic acid (**7b**). The first of these was prepared by us previously by an inefficient malonic ester enolate alkylation;[5] a more efficient sequence involving a copper-mediated conjugated addition is described here (Scheme II). To prepare the phenyl-substituted system, 1.2 equiv of diallylcuprate[7] was allowed by react with ethyl cinnamate **4a**,[7] in the presence of trimethylchlorosilane (5 equiv),[8] to give the 1,4-adduct **5a** in 86% purified yield. The acetylenic acid precursor **7a** was then generated from the

Scheme II



Scheme III



alkene **5a** by a bromination–dehydrobromination sequence. The intermediate dibromo ester **6a** was too unstable to be characterized spectroscopically and was directly dehydrobrominated with methanolic KOH. The vinyl bromide intermediate is very unreactive and required additional KOH and more vigorous conditions (60 h at reflux) to give the acetylenic acid **7a**. This acid was cyclized with mercuric trifluoroacetate to form enol lactone IIIa in 81% yield by our previously described procedure.[3a,5]

The sequence for the preparation of the corresponding β-(1-naphthyl) enol lactone IIIb (Scheme II) began with the α,β-unsaturated ester **4b**, prepared by an Emmons-modified Wittig reaction between the phosphonate anion derived from triethyl phosphonoacetate and 1-naphthaldehyde (**3**) to produce mostly trans isomer **4b** in 81% purified yield. Conjugate addition, bromination, and dehydrobromination were done in an analogous fashion to yield the acetylenic acid **7b**. The acid was cyclized with mercuric trifluoroacetate to form enol lactone IIIb.

Attempts to effect direct conjugate addition of a propargyl unit to the cinnamyl system, utilizing silyl-protected propargyllithium reagents[9] and sterically hindered cinnamyl esters,[10] were not successful.

Resolution of Enol Lactones IIab and IIIab. The lactones IIab and IIIab were resolved most conveniently at the stage of the acetylenic acids (**2ab** and **7ab**) by chromatographic separation of diastereomeric amide de-

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Table I. Adjusted Retention Times and Separation Factors of (*R*)-Phenylglycinol Amide Derivatives of the α- and β-Aryl-5-hexynoic Acids[a]

(*R*)-phenylglycinol amides	t'_{R1}, min	t'_{R2}, min	α
8a (αPh)[b]	5.5	9.0	1.64
8b (αNp)[b]	5.6	9.1	1.62
9a (βPh)[c]	18.5	36.5	1.97[d]
9b (βNp)[c]	18.2	31.8	1.75

[a] Column: IBM Silica 5 μm, 25 cm × 4.5 mm. Mobile phase: 65% hexane, 35% (5:95 2-propanol/methylene chloride). Detector: UV 265 nm. Sample size: 5 μL of approx 1 mg/mL sample. [b] Flow rate is 1.0 mL/min. [c] Flow rate is 1.5 mL/min. Retention times shown are multiplied by 1.5 to compare with those of the α-aryl-substituted amides **8ab**. [d] Similar α value (1.93) was observed when the acetylenic group was replaced by hydrogen.[14]

rivatives (Scheme III). It has been reported that diastereomeric amides with a hydroxyl group located in the position γ or δ to the carbonyl group show excellent separation in liquid adsorption chromatography;[11] the diastereomeric purity and absolute configuration can be determined simultaneously by this method.[11] Thus, racemic carboxylic acid **2a** via its mixed anhydride formed with isobutyl chloroformate was allowed to react with (−)-(*R*)-phenylglycinol to give the amide derivative of acetylenic acid **8a** in quantitative yield (Scheme III).

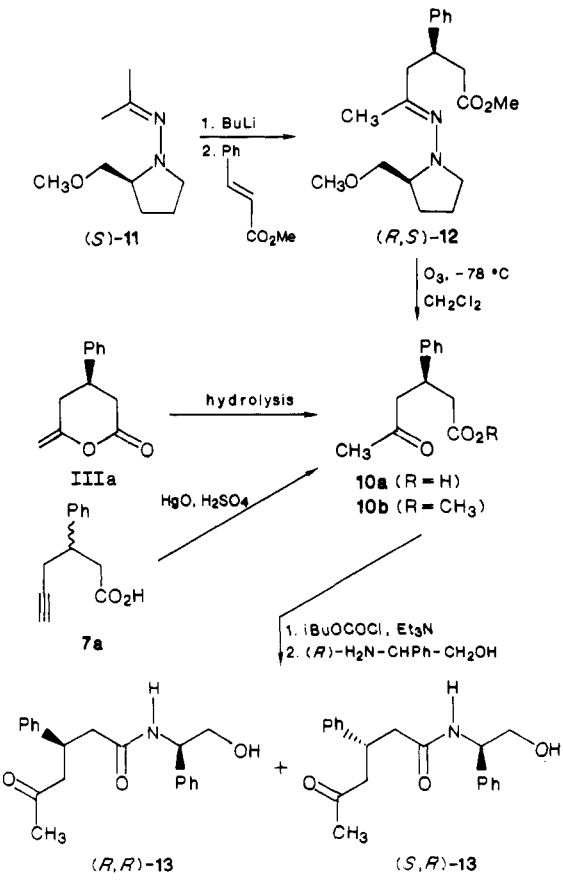
The diastereomeric amide derivatives were readily separated by HPLC using hexane/methylene chloride–2-propanol (65/33.2/1.8) (Table I). The efficiency of separation, described by a separation factor α (the ratio of the adjusted retention times),[12] is 1.64 for **8a**. Because the separation factor is high, it was possible to separate large amounts of these diastereomers by flash chromatography[13] using silica gel. Each separated diastereomer was recrystallized 2 times, and its diastereomeric purity was shown to be more than 99% by HPLC.

The separated amide diastereomers (*R*,*R*)-**8a** and (*S*,*R*)-**8a** were hydrolyzed with 1.5 N sulfuric acid in a 1:1 mixture of water and tetrahydrofuran at reflux to recover the acid. The reflux time was limited to 48 h, yielding only 70% of the acid, to minimize epimerization. The extent of epimerization at this point was about 3%, determined by HPLC reanalysis by rederivatization of the resolved acids to the amides with (*R*)-phenylglycinol. The use of higher concentrations of sulfuric acid resulted in decomposition; longer reflux times gave more epimerization. Each resolved acid was cyclized with mercuric trifluoroacetate to prepare the optically active enol lactones (*R*)- and (*S*)-IIa.

The acetylenic acid precursors to the other three enol lactones were resolved analogously. The separation factors of the other three diastereomeric amide derivatives are comparable or higher than that of **8a** and are summarized in Table I. In the case of the β-aryl amides **9a** and **9b**, a higher concentration (3 N) of sulfuric acid and a shorter reflux time (24 h) were used to hydrolyze the amide bond. Since the proton attached to the stereogenic center is not acidic, these compounds were not epimerized at all, and the hydrolysis went to completion with 75–90% purified yield.

3-Phenyl-5-oxohexanoic Acids 10a. The hydrolysis product of the lactone IIIa is the keto acid **10a**. We were

Scheme IV



interested in these keto acids, since their active esters should give the same acyl enzyme with chymotrypsin as that derived from enol lactone IIIa. Furthermore, in principle, the homochiral keto acid (see below) could be converted into the homochiral lactone or could at least be stereochemically correlated with the acetylenic acid precursor of the lactones.

Enders has prepared the *R* enantiomer of the keto ester **10b** by use of the chiral auxiliary (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP).[15] On the basis of chiral shift reagent NMR analysis, this material is reported to be ≥99% ee. We used Enders' approach with SAMP and RAMP (the *R* antipode of SAMP) hydrazones to prepare the keto esters (*R*)- and (*S*)-**10b**, as illustrated in Scheme IV for (*R*)-**10b**. The acetone-derived hydrazone **11**[15d] was deprotonated with *n*-butyllithium[15b] and reacted with methyl cinnamate to furnish the hydrazone adduct **12**, which was converted to the keto ester **10b** by ozonolysis. SAMP removal from the adduct **12** by ozonolysis gave superior yields of (*R*)-**10b** than an alternate method employing methyl iodide in pentane/HCl (aq).

Diastereomeric amide derivatives of each enantiomer were prepared (Scheme IV) in order to determine the enantiomeric purity of *R* and *S* keto acids **10a**. The methyl ester **10b** was hydrolyzed to the acid **10a** in 89% yield, with aqueous methanolic KOH. The acid was then reacted via a mixed anhydride with (*R*)-phenylglycinol to form the amide **13**. Helmchen has shown that diastereomeric

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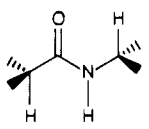
(*R*)-phenylglycinol amides prepared from acids similar in structure to **13** show high separation factors in liquid chromatography.[14] HLPC analysis of (*R,R*)-**13** and (*S,R*)-**13** shows diastereomeric excesses of >99% and >93%, respectively (α = 2.76). Further discussion of the absolute stereochemistry of the keto acids is presented in the following section.

A number of attempts were made to convert the asymmetrically prepared keto acids (*R*)- and (*S*)-**10a** into the acetylenic acid (*R*)- and (*S*)-**7a**, via their enol phosphate derivatives.[16] However, these enol phosphates proved difficult to prepare.

Determination of Absolute Configuration. Order of Chromatographic Elution of Diastereomeric Phenylglycinol Amides. According to Helmchen,[11,17] the relative elution order of a pair of diastereomeric amides on the liquid adsorption chromatography is thought to be governed by the following postulates: (1) In solution, the amide is planar and the structural element—the amide plane **14**—includes the amide bond and two approximately antiplanar arrangements of the fragments HCC=O and HNCH. (2) Binding to silica gel takes place by hydrogen bonding as shown in **15**, where a parallel alignment of the planar amide group and the surface of the silica gel is preferred. (3) Disturbance of this preferred arrangement is caused by large apolar substituents such as aryl groups, located outside the common plane and projecting toward the silica surface. (4) The diastereomer in which both faces of the common plane have apolar substituents is eluted first, due to the weak affinity of both faces of the amide plane to the silica gel.



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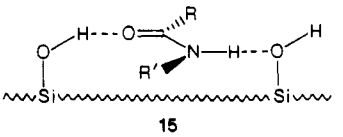
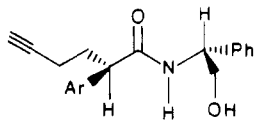
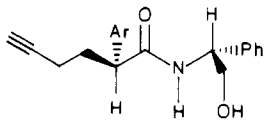


15

According to these postulates, a pair of α-aryl-substituted (*R*)-phenylglycinol amides (*R,R*)- and (*S,R*)-**8ab** will have different mobilities on liquid chromatography, with the (*R,R*)-amides eluting earlier than the *S,R* isomers, since the aryl group of the acyl portion and the phenyl group of the amine portion of the *R,R* diastereomer occupy both faces of the common plane.

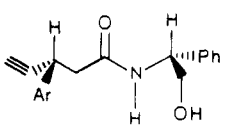


(*R,R*)-**8a,b**
(elutes first)

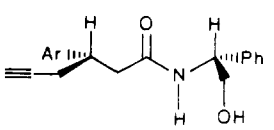


(*S,R*)-**8a,b**
(elutes last)

Similar approaches have been advanced for the amides of β-substituted carboxylic acids[14] (*R,R*)- and (*S,R*)-**9ab**, and it is believed that the first eluted diastereomer is that with the *R,R* configuration, while diastereomer with the *S,R* configuration is eluted second. However, since the rigid structure of the common plane ($CHCH_2C(=O)NH$-CH) in this second series is not so clear, the stereochemistry needs to be determined definitively by crystallographic analysis of one diastereomer (see below).



(*R,R*)-**9a,b**



(*S,R*)-**9a,b**

The assignment of absolute stereochemistry of the SAMP- and RAMP-derived keto ester (*R*)- and (*S*)-**10b** was based on analogy to other products derived from lithiated SAMP hydrazone conjugate additions.[15a] In addition, the amides (*R,R*)- and (*S,R*)-**13**, prepared from (*R*)- and (*S*)-**10a**, respectively, elute according to Helmchen's model, lending support to the stereochemical assignments of (*R*)- and (*S*)-**10a** based on their asymmetric synthesis.

For confirmation that the enol lactone inhibitor (*R*)-IIIa and the acyclic keto acid (*R*)-**10a** have an equivalent stereochemical configuration at the β-carbon, the acetylenic acid precursors (*R/S*)-**7a** and (*R*)-**7a** were converted to the amide derivatives (*R/S*)-**13** and (*R*)-**13** by hydration of the acetylenic acid **7a** to the keto acid **10a** with mercuric oxide followed by derivatization (Scheme IV). The (*R*)-phenylglycinol amide derived from the (*R*)-**7a** diastereomer co-eluted with (*R,R*)-**13** obtained from the SAMP-derived (*R*)-**10a**. The *S* enantiomer of **10a** was correlated to the alternate amide epimer obtained from (*R/S*)-**7a**.

NMR Chemical Shifts of Diastereomeric Phenylglycinol Amides. The planar conformation of these α- and β-substituted amide diastereomers and their absolute configurational assignments are supported further by the comparison of their NMR spectra. It is known that the signal of the group located on the same side of the common amide plane as the aryl group is shifted upfield relative to the other diastereomer.[18] The most distinguishable difference should occur on the methylene proton peaks at the carbon adjacent to hydroxyl group in **8ab** and **9ab**, where the methylene group is on the same side as the aryl group of the acyl portion in the *R,R* diastereomers but is on the other side in *S,R* diastereomers. Thus, in all four amides the methylene signal of the first eluted diastereomer is upfield relative to that of the second eluted diastereomer, *R,R* and *S,R*, respectively: **8a** δ 3.73 vs 3.85; **8b** δ 3.69 vs 3.76; **9a** 3.61 vs 3.72; **9b** δ 3.50 vs 3.70, again consistent with Helmchen's conformational–chromatographic models.

α-Aryl-5-hexynoic Acids: Stereochemical Correlation and Analogy. Despite the consistency of the absolute stereochemical assignments of the α-aryl-5-hexynoic acids based on chromatographic elution order and relative NMR chemical shifts of the phenylglycinol amides, we sought further assurance of the validity of these configurational assignments through stereochemical correlation to a related compound of known absolute configuration.

The α-naphthylacetylenic acid **2b** was partially resolved by repeated crystallization of the cinchonidine salt from 95% ethanol until a constant negative rotation ($[\alpha]^{25}_D$ = −35.9°) was obtained.[19] The cinchonidine salt was then decomposed in acid to yield an optically enriched sample of **2b** with a positive optical rotation ($[\alpha]^{25}_D$ = +116°). The acetylenic group of this acid was reduced quantitatively by catalytic hydrogenation to yield α-butylnaphthylacetic acid (**16**) with a positive optical rotation ($[\alpha]^{25}_D$ = +70.2°) (Scheme V).

The X-ray structure of (*R*)-(+)-α-phenylethylamine (**17**) has been determined,[20] so if acid **16** can be equated to this

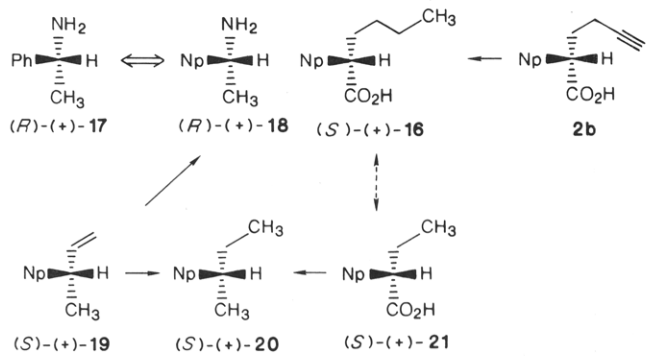
(16) Negishi, E.; King, A. O.; Klima, W. L. *J. Org. Chem.* **1980**, *45*, 2526.

(17) Helmchen, G.; Völter, H.; Schühle, W. *Tetrahedron Lett.* **1977**, *18*, 1417.

(18) Helmchen, G.; Ott, R.; Sauber, K. *Tetrahedron Lett.* **1972**, *13*, 3873.

(19) This resolution via crystallization of the diastereomeric salts was developed prior to the chromatographic separation of the (*R*)-phenylglycinol amides. It is a convenient method for preparation of *S* enantiomer of **2b**, but not the other enantiomer; the optical purity, however, is somewhat less than that obtained via the phenylglycinol amide resolutions.

Scheme V. Assignment of Absolute Configuration of α-Naphthyl-5-hexynoic Acid (2b)



structure by chemical conversion (without racemization of the chiral center) and/or physical and spectral methods, then its absolute configuration can be established. Scheme V shows the pathway of compounds used to correlate the X-ray structure of (*R*)-amine **17** with the absolute configuration of (+)-acid **16**.

The (*R*)-amine **17** has been shown to have the same absolute configuration as (*R*)-(+)-(1-naphthyl)ethylamine (**18**) by the comparison of the optical rotary dispersion spectra of some of their derivatives.[21] (*R*)-(+)-Amine **18** has been synthesized from (*S*)-(+)-3-(1-naphthyl)butene (**19**) by a route that does not affect the stereogenic center: oxidation of the double bond to form (*R*)-(−)-2-(1-naphthyl)propionic acid, followed by conversion of the carboxyl group to an amine.[22,23] (*S*)-(+)-Alkene **19** has also been converted to (*S*)-(+)-(1-naphthyl)butane (**20**) by the reduction of the double bond. (*S*)-(+)-Alkane **20** has also been formed from (*S*)-(+)-(1-naphthyl)butyric acid (**21**) by the reduction of the carboxylic acid to a methyl group.[23]

There has been no chemical conversion or spectral correlation between the (*S*)-(+)-butyric acid **21** and the (*S*)-(+)-hexanoic acid **16**, but their configurations can be equated by analogy to a series of phenyl-substituted alkanoic acids: A graded series of α-(+)-alkylphenylacetic acids, from the α-methyl to the α-pentyl, have been found to have the same *S* configuration.[24] Therefore, it appears valid to assume that a series of α-alkylnaphthylacetic acids with the same direction of optical rotation will have the same absolute configuration at their stereogenic center. This assumption is strengthened by the fact that (+)-ethyl and (+)-methyl naphthylacetic acids have the same absolute configuration as the (+)-ethyl and (+)-methyl phenylacetic acids.[25] Therefore, it is reasonable to postulate that the (+) acid **2b** has the *S* configuration at its chiral center. The acid **2b** assigned the *S* absolute configuration on the basis of chromatographic elution order and NMR chemical shifts (vide ante) also has a positive rotation (see Experimental Section).

β-Aryl-5-hexynoic Acids: Crystallographic Determination of the Absolute Configuration of Phenylglycinol Amide 9a. A number of unsuccessful attempts were made to obtain crystals suitable for X-ray crystallography from both amide diastereomers ((*R*,*R*)- and (*S*,*R*)-**9a**) and diastereomeric salts of the acids ((*R*)- and (*S*)-**7a**) with chiral amines such as (−)-cinchonidine, (+)-α-methylbenzylamine, and (*R*)-2-phenylglycinol. In all cases, however, crystals too small for satisfactory analysis were obtained.

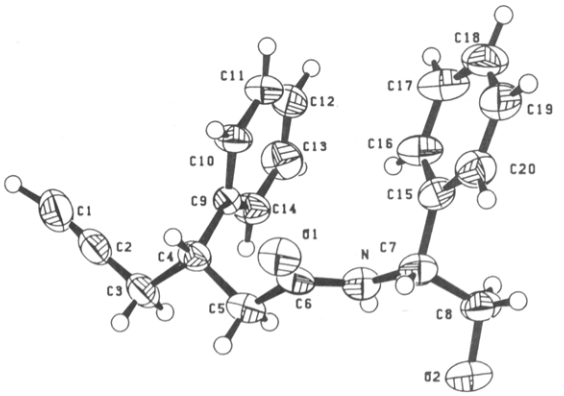


Figure 1. ORTEP view of X-ray molecular structure of the second-eluted phenylglycinol amide (*S*,*R*)-**9a**.

Some organic compounds that have a proton donor can crystallize readily as large chunky crystals by complexation with triphenylphosphine oxide.[26] Thus, the second-eluted diastereomer (*S*,*R*)-**9a** was cocrystallized with triphenylphosphine oxide from acetone by slow evaporation of the solvent, and its three-dimensional structure was determined by X-ray crystallography, as shown in Figure 1. This establishes definitively that the second-eluted diastereomer has *S*,*R* stereochemistry, as predicted by the conformational interaction model, and that, at least in the crystal structure, the β-aryl-substituted amide does have a nearly common plane. The absolute stereochemistry of the β-naphthyl-substituted lactone IIIb is based on analogy with the β-phenyl-substituted systems IIIa.

Conclusion

In previous studies, we have found that certain enol lactones form very stable acyl enzyme intermediates with chymotrypsin and therefore act as potent, though transient, alternate substrate inhibitors.[5] To study the enantioselectivity of this process, we have prepared certain of these enol lactones—those bearing phenyl and 1-naphthyl substituents at the α- and β-positions (IIab and IIIab) (and the related β-phenyl-substituted keto acids **10a**)—in homochiral form and established their absolute configuration by crystallography, stereochemical correlation, and chromatographic and NMR chemical shift models. A detailed study of the kinetics of chymotrypsin inhibition by these lactones will be presented elsewhere.[6]

Experimental Section

General. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analytical thin layer chromatography was performed using 0.25-mm Merck silica gel 60 F-254 glass-backed plates. Compounds were visualized by ultraviolet light, iodine vapor, and/or phosphomolybdic acid. Preparative thin layer chromatography was performed on 20 × 20 cm glass plates coated with Merck silia gel 60 F-254 to a thickness of 2.5 mm. All flash column chromatography was done using Woelm silica gel (32–63 μm) as described by Still.[13] High performance liquid chromatography (HPLC) was performed on a Spectra Physics Model 8700 solvent delivery system and the compounds were detected at 265 nm.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian XL-200 (200 MHz) or GE QE-300 (300 MHz) instruments; chemical shifts are reported as parts per million

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(21) Warren, M. E.; Smith, H. E. *J. Am. Chem. Soc.* **1965**, *87*, 1757.
(22) Menicagli, R.; Lardicci, L.; Botteghi, C. *Chem. Ind.* **1974**, 920.
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(25) Sjoberg, B. *Ark. Kemi* **1955**, *9*, 295.
(26) Etter, M. C.; Baures, P. W. *J. Am. Chem. Soc.* **1988**, *110*, 639.

downfield from tetramethylsilane as an internal standard (δ scale). The ^1H NMR data are presented in the form δ value of signal (peak multiplicity, integrated number of protons, coupling constant (if applicable), assignment). Infrared (IR) spectra were obtained with a IBM IR/30S FTIR spectrometer and the data are presented as cm^{-1} for important diagnostic absorptions. Low resolution electron impact mass spectra were obtained on a Varian CH-5 spectrometer at 10 or 70 eV. Data are reported in the form m/z (intensity relative to base peak = 100). High resolution electron impact mass spectra (HRMS) were performed on a Varian MAT 731 spectrometer for exact mass determination. Optical rotations were measured on a Rudolph Autopol polarimeter and Jasco DIP-360 digital polarimeter. Elemental analyses were performed by the Microanalytical Service Laboratory of the University of Illinois School of Chemical Sciences.

Solvents and reagents were purchased from the following commercial sources: Burdick and Jackson, Baker, Mallinckrodt, Aldrich, Alfa (Ventron), Eastman Kodak, Petrarch (Farchan), and Sigma. They were used as received or purified as indicated. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. Methylene chloride, triethylamine, diisopropylamine, diisopropyl sulfide, and trimethylchlorosilane were purified by distillation from calcium hydride. *n*-Butyllithium as a hexane solution was titrated to determine the organic base present with diphenylacetic acid.[27] Air- and moisture-sensitive reactions were carried out in oven-dried glassware and under an atmosphere of dry nitrogen.

Compounds **2a**, **2b**, IIb, and IIIa are known and were synthesized by the literature procedure.[4]

X-ray Crystallography. Crystals of (*S*,*R*)-**9a**–triphenylphosphine oxide complex were grown by slow evaporation at 25 °C of an acetone solution of a one-to-one molar mixture of the two components. A transparent, colorless, chunky crystal used for data collection was cut from a larger crystal. The resultant crystal uniformly extinguished plane-polarized light. There were no crystalites or other contaminating substances attached to the surface of the sample. The crystal was approximately bound by the inversion related forms: {1,–2,1} and {1,1,1} and faces: (–1,3,–1), (–1,3,3) and (0,–1,–1). Distances from the crystal center to these facial boundaries were 0.34, 0.45, 0.29, 0.38, and 0.41 mm, respectively. The crystal was mounted with use of epoxy to a thin glass fiber with the (–5,1,0) scattering planes roughly normal to the spindle axis. The crystal was larger than ideal (maximum dimension 0.3 mm), but no problems were encountered collecting the data, and there was no change in the appearance of the sample during the experiment. The third shell was collected to confirm the crystal system.

Diffraction experiments were performed at room temperature with Mo radiation ($\lambda(K_\alpha^-)$ = 0.71073 Å). Final cell dimensions were obtained by a least-squares fit to the automatically centered settings for at least 15 reflections. Three reference reflections monitored during each experiment showed no significant variation. Intensity data were corrected for Lorentz–polarization effects. Crystal data are listed in Table II. Systematic conditions unambiguously determined the space group. The structure was solved by direct methods (SHELXS-86);[28] correct positions for all non-hydrogen atoms were deduced from an *E* map. Subsequent least-squares difference Fourier calculations gave positions H, H1, and H2. Positional parameters for atoms H and H2 were independently refined and the position for atom H1 was constrained to ride on atom C1. The remaining hydrogen atoms were included as fixed contributors in "idealized" positions. In the final cycle of least squares non-hydrogen atoms were refined with anisotropic thermal coefficients, a group isotropic thermal parameter was varied for all hydrogen atoms except H1, and an empirical isotropic extinction coefficient was refined. The isotropic thermal parameter for atom H1 converged to a negative value, suggesting the possible presence of a disordered atom, heavier than hydrogen, near this position. The highest peak in the final difference map was in the vicinity of H1. Successful convergence was indicated by the maximum shift/error for the last cycle. A final analysis of variance between observed and calculated structure factors showed no apparent systematic errors.

Table II. Crystal Data for (*S*,*R*)-9a–Triphenylphosphine Oxide Complex

	(*S*,*R*)-**9a**–triphenylphosphine
formula	$C_{38}H_{36}NOP$
crystal system	orthorhombic
space group	$P2_12_12_1$ (D_2^4)
a, Å	10.280 (4)
b, Å	15.573 (4)
c, Å	19.865 (10)
α, deg	90
β, deg	90
γ, deg	90
V, Å^3	3180 (4)
z	4
density calcd, g/cm^3	1.223
crystal dimensions, mm	0.6 × 0.7 × 0.8
diffractometer	Enraf-Nonius CAD4
μ, cm^{-1}	1.19
transmission factor range	not applied
extinction	1.8 (3) × 10^{-7}
2θ limit, deg (octants)	54.0 (±*h*,±*k*,±l)
intensities (unique, R_i)	3923
intensities > 2.58σ(*I*)	2269
R	0.044
R_w (for $w = 1/\sigma^2(F_o) + pF_o^2$)	0.052 (p = 0.020)
max density in Δ*F* map, e/Å^3	0.26

Method A. Mercury-Catalyzed Lactonization of Acetylenic Acids. A solution of arylhexenoic acid and mercuric trifluoroacetate (0.1 equiv) in methylene chloride (usually 10–15 mL per mmol of acid) was stirred at room temperature for 3 h under nitrogen and quenched with saturated aqueous sodium bicarbonate (10 min). The reaction mixture was then diluted with water and extracted several times with methylene chloride. The methylene chloride layer was washed with water and dried ($MgSO_4$), and the solvent was evaporated in vacuo to yield the crude product.

3-Phenyl-6-methylidenetetrahydro-2-pyranone (IIa). This compound was prepared from 2-phenyl-5-hexynoic acid (**2a**)[3b] (0.2 g, 1.06 mmol) and mercuric trifluoroacetate (0.046 g, 0.108 mmol) according to method A and purified by flash column chromatography using ethyl acetate/hexane (1/3): yield 0.155 g (78%); mp 60–61 °C; NMR ($CDCl_3$) δ 2.0–2.3 (complex, 2, $-CH_2CHPhCO_2-$), 2.5–2.8 (complex, 2, $-CH_2CH_2CHPhCO_2-$), 3.81 (dd, 1, J = 10.4, 6.8 Hz, methine), 4.36 (t, 1, J = 0.8 Hz, vinylic), 4.74 (s, 1, vinylic), 7.2–7.4 (complex, 5, aromatic); mass spectrum, m/z (rel intensity) 189 (M + 1, 14), 188 (M$^+$, 57), 160 (100), 118 (30), 117 (24), 105 (13), 104 (21), 69 (6), 43 (5); IR (Nujol mull) 3020, 1750 cm^{-1}.

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.20; H, 6.78.

Lithium Diallylcuprate. Allyllithium was generated from tetraallyltin (2.74 g, 9.7 mmol) and phenyllithium (1.88 M, 20.6 mL, 38.7 mmol) following a literature procedure.[29] After filtration of the precipitated tetraphenyltin under nitrogen, 79.2 mL of the ethereal solution was obtained and was found to be 0.43 M by titration; yield 34.1 mmol (88%). Cuprate was prepared according to a literature procedure[7] from 10 mL of the diisopropyl sulfide solution of copper(I) iodide (99.999%, 3.24 g, 17.0 mmol) and allyllithium (34.1 mmol) described above. This compound was used in the conjugate addition reactions without characterization.

Ethyl 3-Phenyl-5-hexenoate (5a). To a solution of lithium diallylcuprate (17.0 mmol) in dry ether (110 mL) were added trimethylsilyl chloride (9.0 mL, 70.9 mmol) and a solution of ethyl cinnamate (**4a**) (2.5 g, 14.2 mmol) in dry ether (10 mL) successively at –78 °C. The solution was slowly warmed up to room temperature and stirred for an additional 2 h. The solution was quenched with aqueous ammonium chloride (30 mL) and stirred for 15 min. Black and white precipitates appeared during this time. The ether layer was washed with brine, dried ($MgSO_4$), and concentrated. The resulting yellow oil was purified by bulb-to-bulb distillation (170 °C/0.9 mm): yield 2.65 g (86%); NMR ($CDCl_3$) δ 1.13 (t, 3, J = 7.1 Hz, CH_2CH_3), 2.39 (t, 2, J = 7.0 Hz, CH_2CO_2Et),

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(28) Sheldrick, G. M. In *Crystallographic Computing 3*; Sheldrick, G. M., Kruger, C., Goddard, R., Eds.; Oxford University: 1985; pp 175–189.
(29) Seyferth, D.; Weiner, M. A. *J. Org. Chem.* **1961**, *26*, 4797.

2.60 (dd, 1, J = 15.2, 14.2 Hz, CH_2=CHCH_2), 2.64 (dd, 1, J = 15.2, 12.8 Hz, CH_2=CHCH_2), 3.20 (quintet, 1, J = 7.6 Hz, methine), 4.02 (quartet, 2, J = 7.1 Hz, CH_2CH$_3$), 4.97 (d, 1, J = 9.6 Hz (cis), CH_2=CHCH$_2$), 5.00 (d, 1, J = 17.0 Hz (trans), CH_2=CHCH$_2$), 5.66 (complex (ddt), 1, J = 8.9 (methylene), 10.2 (cis), 14.0, 17.2 Hz (trans), CH_2=CHCH$_2$), 7.2–7.6 (complex, 5, aromatic); mass spectrum, m/z (rel intensity) 219 (M + 1, 0.9), 218 (M^+, 5.6), 177 (11), 144 (21), 135 (100), 131 (24), 130 (33), 107 (15), 105 (54), 104 (19), 103 (15), 91 (36), 77 (16); HRMS calcd for $C_{14}H_{18}O_2$ m/e 218.1307, found m/e 218.1313.

3-Phenyl-5-hexynoic Acid (7a). To a solution of ethyl 3-phenyl-5-hexenoate (**5a**) (2.5 g, 11.5 mmol) in carbon tetrachloride (30 mL) was added a solution of bromine (2.0 g, 12.5 mmol) in carbon tetrachloride (10 mL) during the course of 20 min at room temperature, and the solution was stirred for additional 1 h. After the solvent and excess bromine were evaporated under reduced pressure, the crude product was purified by flash column chromatography using ethyl acetate/hexane (1/4) to yield 2.65 g (61%) of the dibromide **6a**. Because of its instability, this compound was used for the next reaction without characterization.

To a solution of potassium hydroxide (1.5 g, 26.7 mmol) in 95% methanol (15 mL) was added a solution of the brominated compound **6a** (2.5 g, 6.6 mmol) in 95% methanol (2 mL), and the solution was heated to reflux for 60 h. After the solution was cooled, the mixture was acidified with 3 N aqueous hydrochloric acid. Methanol was then removed under reduced pressure, and the remaining aqueous solution was extracted with ethyl acetate. The organic layer was washed with water and brine and dried ($MgSO_4$), and the solvent was evaporated in vacuo. The resulting yellow oil was purified by flash column chromatography using ethyl acetate/hexane (1/2) and by recrystallization from ether/hexane: yield 1.0 g (80%); mp 91–93 °C (lit.[5] mp 88 °C); NMR ($CDCl_3$) δ 1.98 (t, J = 1.9 Hz, acetylenic), 2.50–2.56 (complex, 2, CH_2 α to acetylenyl group), 2.74 (dd, 1 J = 17.0, 8.5 Hz, CH_2CO$_2$H), 2.96 (dd, 1, J = 17.0, 8.5 Hz, CH_2CO$_2$H), 3.34 (quintet, 1, J = 8.5 Hz, methine), 7.21–7.37 (complex, 5, aromatic), 9.96 (br, 1, CO$_2$$H$); mass spectrum, m/z (rel intensity) 188 (M^+, 1), 149 (21), 143 (10), 129 (22), 121 (70), 107 (100), 105 (13), 103 (15), 79 (31), 77 (29), 51 (14); IR (Nujol mull) 3310, 3020, 2400, 1710 cm^{-1}.

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.46; H, 6.59.

Ethyl 3-(1-Naphthyl)-2-propenoate (4b). Sodium hydride (50% dispersion in mineral oil, 2.7 g, 56.3 mmol) was placed in a 100-mL flask under nitrogen and washed free from mineral oil with three portions of dry tetrahydrofuran (50 mL each). Tetrahydrofuran (50 mL) was added to the washed sodium hydride, and the suspension was stirred at 0 °C. Triethyl phosphonoacetate (10.85 g, 48.4 mmol) was added dropwise over a 20-min period, and hydrogen evolution ceased about 10 min after the addition was complete. The solution was stirred for an additional 2.5 h at 0 °C, and 1-naphthaldehyde (8.2 g, 52.5 mmol) was added dropwise over a 5-min period. A pasty precipitate was formed during this time. After being stirred for 15 min at room temperature, the reaction mixxture was poured onto a slurry of ice, 3.5 mL concentrated hydrochloric acid, and 40 mL of half-saturated ammonium chloride solution. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with water, dried ($MgSO_4$), and concentrated. The resulting yellow oil was purified by flash column chromatography using ethyl acetate/hexane (1/4): yield 3.85 g (81%); mp 37–38 °C; NMR ($CDCl_3$) δ 1.37 (t, 3, J = 7.1 Hz, CH_2CH_3), 4.32 (quartet, 2, J = 7.1 Hz, CH_2CH$_3$), 6.53 (d, 1, J = 16.0 Hz, NpCH=CH), 7.44–8.22 (complex, 7, aromatic), 8.53 (d, 1, J = 15.9 Hz, NpCH=CH); mass spectrum, m/z (rel intensity) 226 (M^+, 71), 197 (5), 181 (15), 153 (100), 152 (39), 127 (12), 116 (11), 99 (11), 57 (8).

Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.37; H. 6.31.

Ethyl 3-(1-Naphthyl)-5-hexenoate (5b). This compound was prepared by the same method as **5a** from a solution of lithium diallylcuprate (13.3 mmol) in dry ether (90 mL), trimethylsilyl chloride (7.0 mL, 55.3 mmol), and a solution of ethyl 3-(1-naphthyl)-2-propenoate (**4b**) (2.5 g, 11.1 mmol) in dry ether (10 mL). The resulting yellow oil was purified by bulb-to-bulb distillation (215 °C/0.3 mm): yield 2.45 g (83%); NMR ($CDCl_3$) δ 1.07 (t, 3, J = 7.2 Hz, CH_2CH_3), 2.55 (m, 2, J = 7.3 Hz, CH_2CO$_2$Et), 2.78 (dd, 2, J = 7.5, 2.4 Hz, CH_2=CHCH_2), 4.00 (quartet, 2, J = 7.0 Hz, CH_2CH$_3$), 4.18 (quintet, 1, J = 7.1 Hz, methine), 4.97 (d, 1, J = 11.5 Hz (cis), CH_2=CHCH$_2$), 5.04 (d, 1, J = 17.7 Hz (trans), CH_2=CHCH$_2$), 5.70 (m (ddt), 1, J = 8.4 (methylene), 10.3 (cis), 14.3, 17.2 Hz (trans), CH_2=CHCH$_2$), 7.3–7.6 (complex, 4, aromatic (7.3–8.19)), 7.72 (d, 1, J = 7.9 Hz), 7.85 (d, 1, J = 7.6 Hz), 8.19 (d, 1, J = 8.3 Hz); mass spectrum, m/z (rel intensity) 269 (M + 1, 1.0), 268 (M^+, 4.9), 227 (10), 185 (22), 155 (23), 154 (100), 153 (35), 152 (26), 77 (12), 76 (17); HRMS calcd for $C_{18}H_{20}O_2$ m/e 268.1464, found m/e 268.1470.

3-(1-Naphthyl)-5-hexynoic Acid (7b). This compound was prepared by the same method as **7a**. Ethyl 3-(1-naphthyl)-6-hexenoate (**5b**) (2.5 g, 9.3 mmol) was reacted with bromine (1.6 g, 10.0 mmol) to yield 2.75 g (69%) of the dibromide **6b** after flash column chromatography using ethyl acetate/hexane (15/85). This dibromide **6b** was dehydrobrominated by potassium hydroxide (1.1 g, 19.6 mmol), and the resulting yellow oil was purified by flash column chromatography using ethyl acetate/hexane (1/1) and by recrystallization from ether/hexane: yield 0.91 g (74%); NMR ($CDCl_3$) δ 1.99 (t, 1, J = 1.9 Hz, acetylenic), 2.55–2.65 (complex, 1, CH_2 α to acetylenyl group), 2.75–2.85 (complex, 1, CH_2 α to acetylenyl group), 2.94 (dd, 1, J = 16.3, 7.2 Hz, CH_2CO$_2$H), 3.13 (dd, 1, J = 16.3, 7.4 Hz, CH_2CO$_2$H), 4.28 (quintet, 1, J = 6.7 Hz, methine), 7.30–7.57 (complex, 4, aromatic (7.30–8.12)), 7.75 (d, 1, J = 7.4 Hz), 7.87 (d, 1, J = 8.0 Hz), 8.12 (dd, 1, J = 7.7, 7.0 Hz); mass spectrum, m/z (rel intensity) 239 (M + 1, 9), 238 (M^+, 48), 199 (24), 193 (16), 178 (22), 159 (26), 154 (18), 141 (52), 127 (13); HRMS calcd for $C_{16}H_{14}O_2$ m/e 238.0994, found m/e 238.0996.

4-(1-Naphthyl)-6-methylidenetetrahydro-2-pyranone (IIIb). This compound was prepared according to method A from 3-(1-naphthyl)-5-hexynoic acid (**7b**) (0.04 g, 0.17 mmol) and mercuric trifluoroacetate (0.014 g, 0.033 mmol), and purification by flash column chromatography using ethyl acetate/hexane (1/4) gave a clear oil: yield 0.02 g (50%); NMR ($CDCl_3$) δ 2.74–2.88 (complex, 2, CH_2=CH(O)CH_2CHNp–), 2.94–3.19 (complex, 2, –CHNpCH_2CO$_2$–), 4.04 (m, 1, methine), 4.35 (s, 1, vinylic), 4.77 (s, 1, vinylic), 7.31 (d, 1, J = 7.3 Hz, aromatic (7.31–7.99)), 7.44–7.58 (complex, 3), 7.80 (d, 1, J = 8.1 Hz), 7.90 (d, 1, J = 7.5 Hz), 7.99 (d, 1, J = 8.0 Hz); mass spectrum, m/z (rel intensity) 238 (M^+, 7), 210 (15), 194 (8), 181 (100), 168 (10), 154 (11), 127 (23).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.49; H, 6.07.

Method B. Preparation of Phenylglycinol Derivatives of Acetylenic Acids via Mixed Anhydride. To a solution of acetylenic acid and triethylamine (2.2 equiv) in tetrahydrofuran (usually 5 mL per mmol of acid) was added a solution of isobutyl or n-butyl chloroformate (1.0 equiv) in tetrahydrofuran (3 mL per mmol of acid) dropwise under nitrogen at –10 °C. At the end of addition, the hydrochloric acid salt of triethylamine was precipitated, and the mixture was stirred for 15 min at –10 °C. A solution of (*R*)-2-phenylglycinol (1.0 equiv) in tetrahydrofuran (3 mL per mmol of acid) was added to the above solution and the mixture was stirred for 1 h at 0–5 °C. After the amine salt was filtered off, the solvent and unused triethylamine were evaporated in vacuo. The yield of the crude compound was quantitative, and the diastereomeric mixture of amide was separated by flash column chromatography.

Method C. Hydrolysis of the Separated Phenylglycinol Derivatives to the Acetylenic Acids. To a solution of the separated phenylglycinol derivative of the acetylenic acid in tetrahydrofuran (5 mL) was added 3–6 N aqueous sulfuric acid (5 mL) (the resulting concentration of the sulfuric acid in mixture is 1.5–3 N), and the mixture was heated to reflux for 24–48 h. Tetrahydrofuran was then removed under reduced pressure, and the remaining aqueous solution was extracted with ethyl acetate. The organic layer was washed with water and brine and dried ($MgSO_4$), and the solvent was evaporated in vacuo to yield the crude product.

***N*-((1*R*)-1-Phenyl-2-hydroxyethyl)-2-phenyl-5-hexynamide (8a).** This compound was prepared from 2-phenyl-5-hexynoic acid (**2a**) (2.5 g, 13.3 mmol), triethylamine (3.0 g, 29.6 mmol), isobutyl chloroformate (1.82 g, 13.3 mmol), and (*R*)-2-phenylglycinol (1.82 g, 13.3 mmol) according to method B. Purification by flash column chromatography using ethyl acetate/hexane (3/2)

produced equal amounts of diastereomers (2*R*)-*N*-((1*R*)-1-phenyl-2-hydroxyethyl)-2-phenyl-5-hexynamide ((*R*,*R*)-**8a**) and (2*S*)-*N*-((1*R*)-1-phenyl-2-hydroxyethyl)-2-phenyl-5-hexynamide ((*S*,*R*)-**8a**): HPLC (silica gel, hexane/methylene chloride/2-propanol 65/3.2/1.8, flow rate 1.0 mL/min), t_R = 8.6 min (*R*,*R*) and 12.1 min (*S*,*R*).

(*R*,*R*)-**8a** (less polar product; R_f = 0.50, ethyl acetate/hexane/acetic acid (60/40/1): mp 116–117 °C (recrystallized from ether/hexane); NMR ($CDCl_3$) δ 1.9–2.4 (complex, 6, O*H*, CH_2CH_2–, acetylenic), 3.67 (t, 1, *J* = 8.8 Hz, –C*H*PhCONH–), 3.73 (t, 2, *J* = 8.0 Hz, CH_2OH), 4.98 (m, 1, NHC*H*PhCH$_2$OH), 6.27 (d, 1, *J* = 6.6 Hz, –N*H*–), 7.24, 7.35 (complex, 10, aromatic); mass spectrum, *m*/*z* (rel intensity) 307 (M^+, 1), 277 (15), 276 (72), 255 (10), 173 (6), 143 (17), 128 (13), 121 (22), 106 (100), 103 (30), 91 (69), 77 (13), 65 (8).

Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.79; H, 6.75; N, 4.63.

(*S*,*R*)-**8a** (more polar product; R_f = 0.44, ethyl acetate/hexane/acetic acid 60/40/1): mp 127–127.5 °C (recrystallized from ether); NMR ($CDCl_3$) δ 1.9–2.45 (complex, 6, O*H*, $-CH_2CH_2$–, acetylenic), 3.70 (t, 1, *J* = 7.3 Hz, –C*H*PhCONH–), 3.85 (t, 2, *J* = 6.5 Hz, CH_2OH), 5.03 (dt, 1, *J* = 6.6, 4.6 Hz, NHC*H*PhCH$_2$OH), 6.16 (d, 1, *J* = 6.6 Hz, –N*H*–), 7.03, 7.24, 7.33 (complex, 10, aromatic); mass spectrum, same as that of (*R*,*R*)-**8a** with minor differences in intensity.

Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.88; H, 6.84; N, 4.64.

(2*R*)-2-Phenyl-5-hexynoic Acid ((*R*)-2a). (*R*,*R*)-**8a** (1.0 g, 3.25 mmol) was hydrolyzed by method C with 1.5 N aqueous sulfuric acid by reflux for 48 h. The resulting yellow oil was purified by flash column chromatography using ethyl acetate/hexane (1/2) and by recrystalljzation from ether/hexane: yield 0.42 g (69%); mp 78.5–80 °C; $[\alpha]^{25}_D$ –146.4° (*c* 1, C_2H_5OH); NMR ($CDCl_3$) δ 2.00 (t, 1, *J* = 1.9 Hz, acetylenic), 2.0–2.35 (complex, 4, $-CH_2CH_2$–), 3.80 (t, 1, *J* = 7.7 Hz, methine), 7.32 (s, 5, aromatic).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57;, H, 6.43. Found: C, 76.65; H, 6.46.

(2*S*)-2-Phenyl-5-hexynoic Acid ((*S*)-2a). (*S*,*R*)-**8a** (1.0 g, 3.25 mmol) was hydrolyzed by the same procedure as for (*R*,*R*)-**8a**: yield 0.4 g (65%); mp 78–79.5 °C; $[\alpha]^{25}_D$ +134.3° (*c* 1, C_2H_5OH); NMR, same as that of (*R*)-**2a**.

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.71; H, 6.55.

(3*R*)-3-Phenyl-6-methylidenetetrahydro-2-pyranone ((*R*)-IIa). This compound was prepared from (2*R*)-2-phenyl-5-hexynoic acid ((*R*)-**2a**) (0.1 g, 0.53 mmol) and mercuric trifluoroacetate (0.023 g, 0.054 mmol) according to method A and purified by flash column chromatography using ethyl acetate/hexane (1/3): yield 0.065 g (65%); NMR, same as that of IIa; HRMS calcd for $C_{12}H_{12}O_2$ *m*/*e* 188.0838, found *m*/*e* 188.0840.

(3*S*)-3-Phenyl-6-methylidenetetrahydro-2-pyranone ((*S*)-IIa). This compound was prepared from (2*S*)-2-phenyl-5-hexynoic acid ((*S*)-**2a**) (0.1 g, 0.53 mmol) by the same procedure as for (*R*)-IIa: yield 0.073 g (73%); NMR, same as that of IIa; HRMS calcd for $C_{12}H_{12}O_2$ *m*/*e* 188.0838, found *m*/*e* 188.0840.

***N*-((1*R*)-1-Phenyl-2-hydroxyethyl)-2-(1-naphthyl)-5-hexynamide (8b).** This compound was prepared from 2-(1-naphthyl)-5-hexynoic acid (**2b**) (2.0 g, 8.39 mmol), triethylamine (2.0 g, 19.8 mmol), *n*-butyl chloroformate (1.15 g, 8.42 mmol), and (*R*)-2-phenylglycinol (1.15 g, 8.38 mmol) according to method B. Purification by flash column chromatography using ethyl acetate/hexane (3/2) produced a 1:1 mixture of two diastereomers, (2*R*)-*N*-((1*R*)-1-phenyl-2-hydroxyethyl)-2-(1-naphthyl)-5-hexynamide ((*R*,*R*)-**8b**) and (2*S*)-*N*-((1*R*)-1-phenyl-2-hydroxyethyl)-2-(1-naphthyl)-5-hexynamide ((*S*,*R*)-**8b**): HPLC (silica gel, hexane/methylene chloride/2-propanol 65/33.2/1.8, flow rate 1.0 mL/min), t_R = 10.1 min (*R*,*R*) and 13.5 min (*S*,*R*).

(*R*,*R*)-**8b** (less polar product; R_f = 0.52, ethyl acetate/hexane/acetic acid 60/40/1): mp 125–126 °C (recrystallized from ether/hexane); NMR ($CDCl_3$) δ 2.06 (t, 1, *J* = 1.9 Hz, acetylenic, 2.10–2.38 (complex, 4, $-CH_2CH_2$–, O*H*), 2.53–2.64 (m, 1, $-CH_2CH_2$–), 3.69 (d, 2, *J* = 5.0 Hz, CH_2OH), 4.46 (t, 1, *J* = 6.8 Hz, –C*H*NpCONH–), 5.06 (dt, 1, *J* = 8.2, 5.0 Hz, –NHC*H*PhCH$_2$OH), 6.06 (d, 1, *J* = 8.2 Hz, –N*H*–), 7.08 (d, 2, *J* = 7.7 Hz, aromatic (7.08–8.14)), 7.26 (d, 3, *J* = 7.7 Hz), 7.46–7.61 (complex, 4), 7.82 (d, 1, *J* = 8.0 Hz), 7.92 (d, 1, *J* = 9.2 Hz), 8.14 (d, 1, *J* = 9.0 Hz); mass spectrum, *m*/*z* (rel intensity) 307 (M^+, 1), 277 (15), 276 (72), 255 (10), 173 (6), 143 (17), 128 (13), 121 (22), 106 (100), 103 (30), 91 (69), 77 (13), 65 (8).

Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.55; H, 6.54; N, 3.85.

(*S*,*R*)-**8b** (more polar product; R_f = 0.45, ethyl acetate/hexane/acetic acid 60/40/1): mp 151.5–153.5 °C (recrystallized from benzene); NMR ($CDCl_3$) δ 2.07 (t, 1, *J* = 1.9 Hz, acetylenic), 2.09–2.35 (complex, 4, $-CH_2CH_2$–, O*H*), 2.50–2.60 (m, 1, $-CH_2CH_2$–), 3.76 (m, 2, CH_2OH), 4.48 (t, 1, *J* = 6.8 Hz, –C*H*NpCONH–), 5.04 (m, 1, NHC*H*PhCH$_2$OH), 6.07 (d, 1, *J* = 8.0 Hz, –N*H*–), 6.86 (d, 2, *J* = 8.7 Hz, aromatic (6.86–8.10)), 7.15 (d, 3, *J* = 7.6 Hz), 7.41–7.54 (complex, 4), 7.80 (d, 1, *J* = 7.7 Hz), 7.90 (m, 1), 8.10 (m, 1); mass spectrum, same as that of (*R*,*R*)-**8b** with minor differences in intensity.

Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.59; H, 6.55; N, 3.88.

(2*R*)-2-(1-Naphthyl)-5-hexynoic Acid ((*R*)-2b). (*R*,*R*)-**8b** (1.0 g, 2.80 mmol) was hydrolyzed by method C with 2 N aqueous sulfuric acid by reflux for 48 h. The resulting yellow oil was purified by flash column chromatography using ethyl acetate/hexane (1/2): yield 0.37 g (56%); NMR ($CDCl_3$) δ 2.04 (t, 1, *J* = 1.9 Hz, acetylenic), 2.10–2.55 (complex, 4, $-CH_2CH_2$–), 4.66 (t, 1, *J* = 7.3 Hz, methine), 7.4–7.6 (complex, 4, aromatic (7.4–8.16)), 7.80–7.88 (complex, 2), 7.97 (d, 0.5, *J* = 8.7 Hz), 8.16 (d, 0.5, *J* = 8.7 Hz).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.33; H, 6.07.

(2*S*)-2-(1-Naphthyl)-5-hexynoic Acid ((*S*)-2b). (*S*,*R*)-**8b** (1.0 g, 2.80 mmol) was hydrolyzed by the same procedure as (*R*,*R*)-**8b**: yield 0.33 g (50%); NMR same as that of (*R*)-**2b**; HRMS calcd for $C_{16}H_{14}O_2$: *m*/*e* 238.0994, found: *m*/*e* 238.0998.

(3*R*)-(1-Naphthyl)-6-methylidenetetrahydro-2-pyranone ((*R*)-IIb). This compound was prepared from (2*R*)-2-(1-naphthyl)-5-hexynoic acid ((*R*)-**2b**) (0.2 g, 0.84 mmol) and mercuric trifluoroacetate (0.039 g, 0.092 mmol) according to method A and purified by flash column chromatography using ethyl acetate/hexane (1/4): yield 0.092 g (46%); NMR ($CDCl_3$) δ 2.74–2.88 (complex, 2, CH_2=CH(O)CH_2CHNp–), 2.94–3.19 (complex, 2, –CHNpCH_2CO_2–), 4.04 (m, 1, methine), 4.35 (s, 1, vinylic), 4.77 (s, 1, vinylic), 7.31 (d, 1, *J* = 7.3 Hz, aromatic (7.31–7.99)), 7.44–7.58 (complex, 3), 7.80 (d, 1, *J* = 8.1 Hz), 7.90 (d, 1, *J* = 7.5 Hz), 7.99 (d, 1, *J* = 8.0 Hz); HRMS calcd for $C_{16}H_{14}O_2$ *m*/*e* 238.0994, found *m*/*e* 238.0996.

(3*S*)-3-(1-Naphthyl)-6-methylidenetetrahydro-2-pyranone ((*S*)-IIb, (*S*)-αNp6H). This compound was prepared from (2*S*)-2-(1-naphthyl)-5-hexynoic acid ((*S*)-**2b**) (0.2 g, 0.84 mmol) by the same procedure as for (*R*)-IIb: yield 0.106 g (53%); NMR same as that of (*R*)-IIb; HRMS calcd for $C_{16}H_{14}O_2$ *m*/*e* 238.0994, found *m*/*e* 238.0995.

***N*-((1*R*)-1-Phenyl-2-hydroxyethyl)-3-phenyl-5-hexynamide (9a).** This compound was prepared from 3-phenyl-5-hexynoic acid (**7a**) (2.5 g, 13.3 mmol), triethylamine (3.0 g, 29.6 mmol), isobutyl chloroformate (1.82 g, 13.3 mmol), and (*R*)-2-phenylglycinol (1.82 g, 13.3 mmol) according to method B. Purification by flash column chromatography using ethyl acetate/hexane (4/1) produced equal amounts of diastereoisomers (3*R*)-*N*-((1*R*)-1-phenyl-2-hydroxyethyl)-3-phenyl-5-hexynamide ((*R*,*R*)-**9a**) and (3*S*)-*N*-((1*R*)-1-phenyl-2-hydroxyethyl)-3-phenyl-5-hexynamide ((*S*,*R*)-**9a**): HPLC (silica gel, hexane/methylene chloride/2-propanol 65/33.2/1.8, flow rate 1.5 mL/min), t_R = 14.4 min (*R*,*R*) and 26.4 min (*S*,*R*).

(*R*,*R*)-**9a** (less polar product; R_f = 0.41, ethyl acetate/hexane/acetic acid (60/40/1): mp 97.5–98.5 °C (recrystallized from ether/hexane); NMR ($CDCl_3$) δ 1.99 (t, 1, *J* = 1.9 Hz, acetylenic), 2.43 (t, 1, *J* = 6.8 Hz, O*H*), 2.53 (m, 3, $-CH_2$CHPhCH_2–), 2.84 (dd, 1, *J* = 12.6, 7.3 Hz, $-CH_2$CHPhCH_2–), 3.38 (quintet, 1, *J* = 7.7 Hz, –C*H*PhCH$_2$CONH–), 3.56–3.66 (m, 2, CH_2OH), 4.89 (m, 1, –CONHC*H*Ph–), 6.11 (d, 1, *J* = 8.0 Hz, –N*H*–), 7.11 (d, 2, *J* = 7.3 Hz, aromatic (7.11–7.4)), 7.2–7.4 (complex, 8); mass spectrum, *m*/*z* (rel intensity) 307 (M^+, 1), 276 (23), 129 (9), 128 (19), 107 (11), 106 (100), 104 (14), 103 (16), 91 (15), 77 (16), 67 (23).

Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.99; H, 6.73; N, 4.53.

(*S*,*R*)-**9a** (more polar product; R_f = 0.33, ethyl acetate/hexane/acetic acid (60/40/1): mp 104.5–105 °C (recrystallized from

benzene); NMR ($CDCl_3$) δ 2.01 (t, 1, J = 1.9 Hz, acetylenic), 2.51–2.58 (complex, 3, $-CH_2-$ α to acetylenyl group, O*H*), 2.84 (dd, 2, J = 15.5, 7.3 Hz, $-CH_2CONH-$), 3.36 (quintet, 1, J = 7.7 Hz, $-CHPhCH_2CONH-$), 3.72 (d, 2, J = 5.8 Hz, CH_2OH), 4.89 (m, 1, $-CONHCHPh-$), 6.26 (d, 1, J = 7.5 Hz, N*H*–), 6.88 (m, 2, aromatic (6.88–7.31)), 7.19–7.31 (complex, 8); mass spectrum, same as that of (*R*,*R*)-**9a** with minor differences in intensity.

Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.06; H, 6.81; N, 4.61.

(3*R*)-3-Phenyl-5-hexynoic Acid ((*R*)-7a). (*R*,*R*)-**9a** (1.0 g, 3.25 mmol) was hydrolyzed by method C with 3 N aqueous sulfuric acid by reflux for 24 h. The resulting yellow oil was purified by flash column chromatography using ethyl acetate/hexane (1/2): yield 0.55 g (90%); NMR, same as that of **7a**; HRMS calcd for $C_{12}H_{12}O_2$ m/e 188.0838, found m/e 188.0843.

(3*S*)-3-Phenyl-5-hexynoic Acid ((*S*)-7a). (*S*,*R*)-**9a** (1.0 g, 3.25 mmol) was hydrolyzed by the same method as (*R*,*R*)-**9a**: yield 0.53 g (87%); NMR, same as that of **7a**; HRMS calcd for $C_{12}H_{12}O_2$ m/e 188.0838, found m/e 188.0841.

(4*R*)-4-Phenyl-6-methylidenetetrahydro-2-pyranone ((*R*)-IIIa). This compound was prepared from (3*R*)-3-phenyl-5-hexynoic acid ((*R*)-**7a**) (0.1 g, 0.53 mmol) and mercuric trifluoroacetate (0.023 g, 0.054 mmol) according to method A and purified by flash column chromatography using ethyl acetate/hexane (1/3): yield 0.06 g (60%); NMR ($CDCl_3$) δ 2.54–2.78 (complex, 2, CH_2=CH(O)CH_2CHPh), 2.78–3.06 (complex, 2, $-CHPhCH_2CO_2-$), 3.22 (m, 1, methine), 4.35 (s, 1, vinylic), 4.74 (s, 1, vinylic), 7.2–7.4 (complex, 5, aromatic); HRMS calcd for $C_{12}H_{12}O_2$ m/e 188.0838, found m/e 188.0841.

(4*S*)-4-Phenyl-6-methylidenetetrahydro-2-pyranone ((*S*)-IIIa). This compound was prepared from (3*S*)-3-phenyl-5-hexynoic acid ((*S*)-**7a**) (0.1 g, 0.53 mmol) by the same procedure as (*R*)-IIIa: yield 0.062 g (62%); NMR, same as that of (*R*)-IIIa; HRMS calcd for $C_{12}H_{12}O_2$ m/e 188.0838, found m/e 188.0840.

***N*-((1*R*)-1-Phenyl-2-hydroxyethyl)-3-(1-naphthyl)-5-hexynamide (9b).** This compound was prepared from 3-(1-naphthyl)-5-hexynoic acid (**7b**) (1.0 g, 4.20 mmol), triethylamine (0.98 g, 9.65 mmol), isobutyl chloroformate (0.57 g, 4.20 mmol), and (*R*)-2-phenylglycinol (0.58 g, 4.20 mmol) according to method B. Purification by flash column chromatography using ethyl acetate/hexane (4/1) produced a 1:1 mixture of two diastereomers, (3*R*)-*N*-((1*R*)-1-phenyl-2-hydroxyethyl)-3-(1-naphthyl)-5-hexynamide ((*R*,*R*)-**9b**) and (3*S*)-*N*-((1*R*)-1-phenyl-2-hydroxyethyl)-3-(1-naphthyl)-5-hexynamide ((*S*,*R*)-**9b**): HPLC (silica gel, hexane/methylene chloride/2-propanol 65/33.2/1.8, flow rate 1.5 mL/min), t_R = 14.2 min (*R*,*R*) and 23.3 min (*S*,*R*).

(*R*,*R*)-**9b** (less polar product; R_f = 0.42, ethyl acetate/hexane/acetic acid 60/40/1): NMR ($CDCl_3$) δ 1.97 (t, 1, J = 2.4 Hz, acetylenic), 2.51 (t, 1, J = 4.9 Hz, O*H*), 2.61–2.75 (complex, 3, $-CH_2CHNpCH_2-$), 2.94 (dd, 1, J = 14.2, 7.4 Hz, $-CH_2CHNpCH_2-$), 3.50 (dd, 2, J = 9.6, 4.9 Hz, CH_2OH), 4.29 (quintet, 1, J = 6.3 Hz, $-CHNpCH_2CONH-$), 4.86 (m, 1, NHC*H*PhCH$_2$OH), 6.25 (d, 1, J = 7.0 Hz, N*H*–), 7.03 (m, 2, aromatic (7.03–8.13)), 7.20–7.28 (complex, 3), 7.40–7.51 (complex, 4), 7.73 (m, 1), 7.85 (m, 1), 8.13 (d, 1, J = 8.0 Hz); mass spectrum, m/z (rel intensity) 307 (M^+, 1), 276 (23), 129 (9), 128 (19), 107 (11), 106 (100), 104 (14), 103 (16), 91 (15), 77 (16), 67 (23).

Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.61; H, 6.42; N, 3.85.

(*S*,*R*)-**9b** (more polar product; R_f = 0.34, ethyl acetate/hexane/acetic acid 60/40/1): NMR ($CDCl_3$) δ 2.01 (t, 1, J = 2.5 Hz, acetylenic), 2.64–2.83 (complex, 4, $-CH_2CHNpCH_2-$, O*H*), 2.95 (dd, 1, J = 14.2, 7.3 Hz, $-CH_2CHNpCH_2-$), 3.70 (t, 2, J = 5.0 Hz, CH_2OH), 4.31 (quintet, 1, J = 6.6 Hz, $-CHNpCH_2CONH-$), 4.88 (dt, 1, J = 6.8, 5.0 Hz, NHC*H*PhCH$_2$OH), 6.18 (d, 1, J = 6.8 Hz, N*H*–), 6.89 (t, aromatic (6.89–8.11)), 7.15 (d, 3, J = 3.6 Hz), 7.39–7.51 (complex, 4), 7.75 (d, 1, J = 7.4 Hz), 7.85 (m, 1), 8.11 (d, 1, J = 7.1 Hz); mass spectrum, same as that for (*R*,*R*)-**9b** with minor differences in intensity.

Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.54; H, 6.56; N, 3.99.

(3*R*)-3-(1-Naphthyl)-5-hexynoic Acid ((*R*)-7b). (*R*,*R*)-**9b** (1.0 g, 2.80 mmol) was hydrolyzed by method C with 3 N aqueous sulfuric acid by reflux for 24 h. The resulting yellow oil was purified by flash column chromatography using ethyl acetate/hexane (15/85): yield 0.54 g (81%); NMR, same as that for **7b**.

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.37; H, 6.09.

(3*S*)-3-(1-Naphthyl)-5-hexynoic Acid ((*S*)-7b). (*S*,*R*)-**9b** (1.0 g, 2.80 mmol) was hydrolyzed by the same procedure as for (*R*,*R*)-**9b**: yield 0.50 g (75%); NMR same as that for **7b**.

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.44; H, 5.97.

(4*R*)-4-(1-Naphthyl)-6-methylidenetetrahydro-2-pyranone ((*R*)-IIIb). This compound was prepared from (3*R*)-3-(1-naphthyl)-5-hexynoic acid ((*R*)-**7b**) (0.2 g, 0.84 mmol) and mercuric trifluoroacetate (0.046 g, 0.108 mmol) according to method A and purified by flash column chromatography using ethyl acetate/hexane (1/3): yield 0.138 g (69%); NMR same as that for IIIb; HRMS calcd for $C_{16}H_{14}O_2$ m/e 238.0994, found m/e 238.0995.

(4*S*)-4-(1-Naphthyl)-6-methylidenetetrahydro-2-pyranone ((*S*-IIIb). This compound was prepared from (3*S*)-3-(1-naphthyl)-5-hexynoic acid ((*S*)-**7b**) (0.2 g, 0.84 mmol) by the same procedure as (*R*)-IIIb: yield 0.146 g (73%); NMR same as that for IIIb; HRMS calcd for $C_{16}H_{14}O_2$ m/e 238.0994, found m/e 238.0997.

(*S*)-(Isopropylideneamino)-2-(methoxymethyl)pyrrolidine ((*S*)-11). The hydrazone, prepared from SAMP (2.00 g, 15.4 mmol) according to a literature procedure,[15d] was obtained in 88% yield (2.30 g): bp 34 °C/0.8 mm; NMR ($CDCl_3$) δ 3.40 (d, 1, J = 8 Hz), 3.34 (s, 3, CH_3O), 3.21 (m, 2, $-CH_2N-$), 3.10 (m, 1), 2.40 (quartet, 1, J = 8.8 Hz, $-CHN-$), 2.00 (m, 1), 1.93 (d, 6, J = 4 Hz, CH_3C=), 1.79 (m, 2), 1.65 (m, 1); mass spectrum, m/z (rel intensity) 170 (M^+, 7), 126 (5), 125 (100), 56 (13); IR ($CHCl_3$) 2950, 2890, 2820, 1711, 1435, 1361, 1226, 1098 cm^{-1}.

Anal. Calcd for $C_9H_{18}N_2O$: C, 63.49; H, 10.65; N, 16.46. Found: C, 63.02; H, 10.31; N, 16.50.

(*R*,*S*)-1-[[3-Phenyl-4-(carboxymethyl)-1-methylbutylidene]amino]-2-(methoxymethyl)pyrrolidine ((*R*,*S*)-12). The hydrazone (*S*)-**11** (0.85 g, 5.0 mmol) dissolved in 5 mL of THF was metalated at 0 °C with *n*-butyllithium according to the literature procedure.[15b] The resulting solution was cooled to −78 °C and methyl cinnamate (0.892 g dissolved in 2.5 mL of THF, 5.5 mmol) was added dropwise over a 15-min period. Stirring was continued for 6 h at −78 °C, followed by 1 h at −64 °C; 1 h at −46 to −20 °C; and 0.5 h at −10 to 0 °C. The reaction mixture was then poured into a saturated ammonium chloride solution and extracted with ether. The combined ether extracts were then dried (Na_2SO_4) and concentrated to give the crude product (1.58 g, 95%), which was used without further purification. Purity could be improved by distillation (150 °C/0.3 mm): NMR ($CDCl_3$) δ 7.22 (m, 5, C_6H_5), 3.56 (s, 3, CH_3OC=O), 3.46 (m, 2), 3.30 (s, 3, CH_3OCH_2), 3.16 (m, 3), 2.98 (m, 1), 2.67 (d, 2, J = 7 Hz), 2.56 (quartet, 2, J = 11 Hz), 1.93 (m, 2), 1.82 (s, 3, CH_3C=N), 1.69 (m, 2); mass spectrum, m/z (rel intensity) 332 (M^+, 3), 288 (19), 287 (100), 220 (11), 188 (17), 160 (43), 145 (27), 131 (25), 117 (32); IR ($CHCl_3$) 4215, 3024, 1730, 1226, 910 cm^{-1}; HRMS calcd for $C_{19}H_{28}N_2O_3$ m/e 332.2099, found m/e 332.2092.

(*R*)-Methyl 5-Oxo-3-phenylhexanoate ((*R*)-10b). This procedure follows general methods published by Enders.[15a,e] In order to prevent exposure to the carcinogenic SAMP nitrosamine formed in this reaction, all manipulations were done in a fume hood while wearing gloves and all glassware was cleaned in an HBr/HOAc bath[30] after use. The hydrazone (*R*,*S*)-**12** (1.00 g, 3.01 mmol) was dissolved in 10 mL of methylene chloride and cooled to −78 °C under O_2. Ozone was then bubbled through the solution for 15 min, during which time the solution color changed from orange to clear green. The reaction was warmed to room temperature under O_2 and concentrated to an orange oil (1.21 g). The white solid, (*R*)-**10b** (0.338 g, 51%), was isolated by flash column chromatography using ether/hexane (1/2): mp 47 °C; NMR ($CDCl_3$) δ 7.29 (m, 2), 7.21 (m, 3), 3.68 (quintet, 1, J = 7 Hz), 3.59 (s, 3, CH_3OC=O), 2.83 (d of AB quartet, 2, J_1 = 7 Hz, $\Delta\delta$ = 0.04, J_2 = 17 Hz, $CH_2CO_2CH_3$), 2.65 (d of AB quartet, 2, J_1 = 8 Hz, $\Delta\delta$ = 0.07, J_2 = 15 Hz, CH_2COCH_3), 2.06 (s, 3, CH_3CO); mass spectrum, m/z (rel intensity) 220 (M^+, 26), 189 (34), 160 (100), 147 (42), 145 (46), 131 (31); IR ($CHCl_3$) 3025, 2401, 1724, 1437, 1363, 1020 cm^{-1}.

(30) Eisenbrand, V. G.; Prenssmann, R. *Arzneim. Forsch.* **1970**, *10*, 1513.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.55; H, 7.48.

(*S*)-Methyl 5-Oxo-3-phenylhexanoate ((*S*)-10b). This compound was prepared from (*R*)-11 (1.70 g, 10 mmol) by the same procedure used for (*R*)-**10b**. The NMR spectrum of the product (1.00 g, 45%) is identical to (*R*)-**10b**: mp 47 °C.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.94; H, 7.43.

(*R*)-5-Oxo-3-phenylhexanoic Acid ((*R*)-10a). Method D. The ester (*R*)-**10b** (0.205 g, 0.93 mmol) was dissolved in a solution prepared from 4 mL of 5% KOH and 8 mL of methanol and stirred for 45 min. The reaction solution was then poured into 50 mL of 10% sodium bicarbonate and washed with ether. The aqueous phase was then acidified with HCl and extracted with ethyl acetate. The combined ethyl acetate extracts were washed (saturated NH_4Cl), dried ($MgSO_4$), and concentrated to a white solid (0.17 g, 89%). Recrystallization from ether provided analytically pure product: mp 93–94 °C; NMR ($CDCl_3$) δ 7.27 (m, 5, C_6H_5), 3.68 (m, 1), 2.82 (m, 2, $CH_2CO_2CH_3$), 2.69 (d of AB qt, 2, J_1 = 8 Hz, $\Delta\delta$ = 0.07, J_2 = 15 Hz, CH_2COCH_3), 2.06 (s, 3); mass spectrum, *m/z* (rel intensity) 206 (M^+, 13), 188 (23), 160 (100), 147 (20), 145 (38), 107 (14); IR (KBr) 3104, 1730, 1683, 1492, 1451, 1398, 1149, 1078 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.57; H, 6.52.

Method E. The acid (*R*)-**7a** (28 mg, 149 μmol) was combined with HgO (5.2 mg, 24 μmol), concentrated H_2SO_4 (50 μL), and water (0.75 mL). The mixture was stirred and heated to 70 °C for 1 h, then poured into 20 mL 20% sodium bicarbonate, and washed with ether. The aqueous phase was then acidified with HCl and extracted with ethyl acetate. The combined ethyl acetate extracts were washed (saturated NH_4Cl), dried ($MgSO_4$), and concentrated to a white solid (22 mg, 77%). The product, >95% pure by GC, gave MS and NMR spectra identical with the product prepared by the preceding method: HRMS calcd for $C_{12}H_{14}O_3$ *m/e* 206.0943, found *m/e* 206.0949.

(*S*)-5-Oxo-3-phenylhexanoic ((*S*)-10a). This compound was prepared from (*S*)-**10b** (0.5 g, 2.27 mmol) by method D. The NMR spectrum of the product, 0.43 g of light brown crystals (92%), was identical with that of (*R*)-**10a**. Recrystallization from ether provided analytically pure material.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.90; H, 7.05.

(*R*/*S*)-5-Oxo-3-phenylhexanoic Acid ((*R*/*S*)-10a). This compound was prepared from (*R*/*S*)-**7a** (40 mg, 213 μmol) by method E, yielding a white solid (30 mg, 68%). The product, >99% pure by GC, gave MS and NMR spectra identical with those of (*R*)- and (*S*)-**24**: HRMS calcd for $C_{12}H_{14}O_3$ *m/e* 206.0943, found *m/e* 206.0949.

(3*R*)-*N*-((1*R*)-1-Phenyl-2-hydroxyethyl)-5-oxo-3-phenylhexanamide ((*R*,*R*)-13). According to method B, acid (*R*)-**10a** (22 mg, 108 μmol) was converted to the phenylglycinol amide (*R*,*R*)-**13**, a white solid (25.2 mg, 71%). The de of the product was shown by HPLC to be >99%: mp 121–124 °C; NMR ($CDCl_3$) δ 7.28 (m, 3), 7.14 (d, 2, J = 7 Hz), 5.94 (d, 1, J = 6 Hz, N*H*), 4.93 (m, 1, C*H*NH), 3.69 (m, 3), 2.92 (d, 1, J = 7.5 Hz), 2.82 (d, 1, J = 7.0 Hz), 2.59 (d, 1, J = 7.0 Hz), 2.52 (d, 1, J = 7.5 Hz), 2.08 (s, 3, CH_3CO), 0.90 (s, 1); mass spectrum, *m/z* (rel intensity) 325 (M^+, 13), 295 (18), 294 (36), 264 (16), 189 (17), 131 (25), 106 (100); IR (KBr) 3318, 3021, 1710, 1639, 1530, 1399, 753 cm^{-1}; HRMS calcd for $C_{20}H_{23}NO_3$ *m/e* 325.1678, found *m/e* 325.1674.

(3*S*)-*N*-((1*R*)-1-Phenyl-2-hydroxyethyl)-5-oxo-3-phenylhexanamide ((*S*,*R*)-13). This compound was prepared from (*S*)-**10a** according to the procedure for (*R*,*R*)-**13**. The product (18 mg, 51%) was shown to have >93% de by HPLC: mp 107–110 °C; NMR ($CDCl_3$) δ 7.25 (m, 3), 7.03 (m, 2), 6.02 (d, 1, J = 7.2 Hz, N*H*), 4.95 (m, 1, –C*H*NH–), 3.78 (d, 2, J = 5.4 Hz, CH_2OH), 3.67 (quintet, 1, J = 7.2 Hz, PhC*H*), 2.88 (m, 2), 2.56 (m, 2), 2.07 (s, 3, CH_3CO), 0.91 (s, 1); HRMS calcd for $C_{20}H_{23}NO_3$ *m/e* 325.1678, found *m/e* 325.1684.

***N*-((1*R*)-1-Phenyl-2-hydroxyethyl)-5-oxo-3-phenylhexanamide (13).** This compound was prepared from (*R*/*S*)-**10a** according to the procedure for (*R*,*R*)-**13**. The product was shown to co-elute on HPLC with a mixture of (*R*,*R*)- and (*S*,*R*)-**25**: NMR ($CDCl_3$) δ 7.25 (m, 3), 7.03 (m, 2), 6.02 (d, 1, J = 7.2 Hz), 4.95 (m, 1), 3.78 (d, 2, J = 5.4 Hz), 3.67 (quintet, 1, J = 7.2 Hz), 2.88 (m, 2, –CH_2CON–), 2.56 (m, 2, CH_2COCH_3), 2.07 (s, 3, CH_3CO), 0.91 (s, 1); HRMS calcd for $C_{20}H_{23}NO_3$ *m/e* 325.1678, found *m/e* 325.1681.

(+)-2-(1-Naphthyl)-5-hexynoic Acid, (–)-Cinchonidine Salt. Acid **2b** (5.40 g, 22.7 mmol) and (–)-cinchonidine (6.67 g, 22.7 mmol, $[\alpha]^{25}_D$ (*c* 1.97, absolute ethanol) –103.9°) were dissolved in 700 mL of boiling 95% ethanol, and the solution was slowly allowed to cool to room temperature. After several crystals had formed (48 h), the solution was refrigerated at 4 °C for 1 week. The crystals were collected and washed with cold 95% ethanol and recrystallized from 95% ethanol 4 times (until a constant optical rotation was obtained to give 1.27 g (11%) of (+)-**2b**, (–)-cinchonidine salt as colorless crystals with a melting point greater than 200 °C, $[\alpha]^{25}_D$ (*c* 0.568, absolute ethanol) –39.85°.

Anal. Calcd for $C_{33}H_{36}N_2O$: C, 78.92; H, 6.81; N, 5.26. Found: C, 78.87; H, 6.99; N, 5.39.

(+)-2-(1-Naphthyl)-5-hexynoic Acid ((+)-2b). The (–)-cinchonidine salt of acid (+)-**2b** (1.00 g, 1.87 mmol) was decomposed in 50 mL of 6 N sulfuric acid and the acidic solution extracted with two 50-mL portions of ether. The combined organic extracts were washed with water and saturated sodium chloride, dried over anhydrous magnesium sulfate, and filtered, and the solvent was evaporated to give 0.43 g (96%) of 89% optically pure (+)-**2b** (see text for assignment of absolute configuration and optical purity) as colorless crystals: $[\alpha]^{25}_D$ (*c* 1.05, absolute ethanol) +116°; mp 79–81 °C. The spectroscopic properties of (+)-**2b** were the same as those for (*S*)-**2b** (vide ante).

(+)-2-(1-Naphthyl)hexanoic Acid ((+)-16). Acid (+)-**2b** (0.20 g, 0.84 mmol) was dissolved in 10 mL of absolute ethanol, 20 mg of palladium on carbon added, the vessel evacuated, and the solution stirred under a slight positive pressure of hydrogen gas. After 3 h the theoretical amount of hydrogen had been taken up (37.6 mL, 1.68 mmol), the palladium catalyst was filtered off, and the solvent was removed to give 0.19 g (93%) of a clear oil: $[\alpha]^{25}_D$ (*c* 1.06, absolute ethanol) +70.2°; NMR ($CDCl_3$) δ 0.85 (t, 3, J = 6.4 Hz, CH_3), 1.18–1.40 (m, 4, CH_2CH_2), 1.86–1.96 (m, 1, NpCHCH_2), 2.17–2.28 (m, 1, NpCHCH_2), 4.36 (t, 1, J = 7.2 Hz, methine), 7.38–7.55 (m, 4), 7.72–7.85 (m, 3), 8.11 (d, J = 7.5 Hz); mass spectrum, *m/z* (rel intensity) 243 (17), 242 (100, M^+), 197 (14), 186 (5.7), 141 (20); IR (Nujol mull) 1710 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}O_2$: C, 84.91; H, 8.02. Found: C, 85.06; H, 7.91.

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Supplementary Material Available: Atomic numbering schemes, tables of atomic coordinates, thermal parameters, bond lengths, and bond angles for compound (*S*,*R*)-**9a** (11 pages). Ordering information is given on any current masthead page.