h under nitrogen. The same workup described as for the isoxazolidines **5a** and **6a** afforded the isoxazolidines **5b** and **6b**. **5b** (2.70 g, 22.5%): yellowish oil; exact mass for M^+ peak, calcd m/e 497.2412, found 497.2404; $[\alpha]^{25}_D$ +43.9° (c 1.96, $CHCl_3$); IR and NMR spectra of the isoxazolidine (**5b**) were identical with those of the isoxazolidine **5a**. **6b** (3.70 g, 30.9%): yellowish oil; exact mass for M^+ peak, calcd m/e 497.2412, found 497.2412; $[\alpha]^{25}_D$ +41.3° (c 1.36, $CHCl_3$); IR and NMR spectra of the isoxazolidine **6b** were identical with those of the isoxazolidine **6a**.

(−)-4α-[3-(Ethoxycarbonyl)-2,2-(ethylenedioxy)propyl]-3β-((1*S*)-1-hydroxyethyl)azetidin-2-one (7b). This compound (**7b**) was prepared from **5b** by using the procedure described for **7a** in 20.1% yield, $[\alpha]^{25}_D$ −14.1° (c 2.23, EtOH).

(+)-1-(*tert*-Butyldimethylsilyl)-3β-[(1*S*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4α-[3-(ethoxycarbonyl)-2,2-(ethylenedioxy)propyl]azetidin-2-one (8b). This compound (**8b**) was prepared from **7b** by using the procedure described for the preparation of **8a** in 52.0% yield, $[\alpha]^{25}_D$ +28.0° (c 1.95, MeCN).

(−)-3β-[(1*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4α-[3-[[(*p*-nitrobenzyl)oxy]carbonyl]-2,2-(ethylenedioxy)-propyl]azetidin-2-one (9b) and 6α-[(2*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-(1*R*)-1-[[(*p*-nitrobenzyl)oxy]carbonyl]-propyl]-4,4-(ethylenedioxy)piperidin-2-one (10b). The azetidinone **8b** was converted into **9b** and **10b** in 66.7% and 24.0% yields, respectively, by using the procedure described for the preparation of **9a** and **10a**. **9b**: semisolid; $[\alpha]^{25}_D$ −12.7° (c 0.40, MeCN).

(−)-3β-((1*S*)-1-Hydroxyethyl)-4α-[3-[[(*p*-nitrobenzyl)-oxy]carbonyl]-2-oxopropyl]azetidin-2-one (11b). This compound (**11b**) was prepared from **10b** by using the procedure described for **11a**, in 79.8% yield, $[\alpha]^{25}_D$ −19.9° (c 0.156, $CHCl_3$).

Acknowledgment. We thank T. Ogata, M. Yuyama, T. Tanaka, H. Furuyama, M. Moriki, and J. Dogome of Hoshi University for spectral measurements, microanalysis, and manuscript preparation.

Registry No. 1, 32296-85-8; **2a**, 53933-47-4; **2b**, 67377-55-3; **3a**, 96326-21-5; **3b**, 96326-22-6; **4**, 65416-24-2; **5a**, 96347-28-3; **5b**, 96326-23-7; **6**, 96326-24-8; **7a**, 96392-33-5; **7b**, 96392-34-6; **8a**, 96326-25-9; **8b**, 96392-35-7; **9a**, 96326-26-0; **9b**, 96392-36-8; **10a**, 96326-27-1; **10b**, 96392-37-9; **11a**, 75321-07-2; **11b**, 96392-38-0; (+)-thienamycin, 59995-64-1; (−)-thienamycin, 78339-91-0; 4-nitrobenzyl bromide, 100-11-8.

3-(Acylamido)-4-phenyl-6(*E*)-(iodomethylidene)tetrahydro-2-pyranones. Synthesis of Novel Amino Acid Analogues

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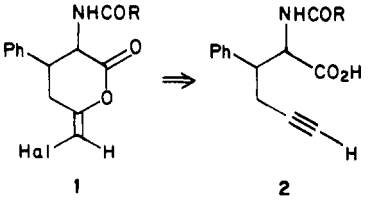
We have synthesized the 3*R**,4*R** and 3*R**,4*S** diastereomers of two 3-(acylamino)-4-phenyl-6(*E*)-(iodomethylidene)tetrahydro-2-pyranones (**13A,B** and **14A,B**) by iodolactonization of substituted 5-hexynoic acid precursors (**11A,B** and **12A,B**). Halolactonization of the 2*R**,3*R** diastereomers (**11A** and **12A**) is considerably more rapid and efficient than that of the 2*R**,3*S** diastereomers (**11B** and **12B**), presumably because of higher torsional strain in the transition states for cyclization of the latter diastereomers. The same 3*R**,4*R** precursor acids (**11A** and **12A**) can also be cyclized under mercuric ion catalysis to the protiolactones **15** or **16**, but the other diastereomers **11B** and **12B** fail to cyclize. These precursor acids are synthesized from a substituted malonic acid (**3**), either by an amination–decarboxylation sequence or by a modified Curtius rearrangement. The lack of stereoselectivity in the Curtius rearrangements of the malonate half ester is accounted for by equilibration of the readily enolizable species under the conditions of the reaction. With each sequence, a mixture of 2*R**,3*R** and 2*R**,3*S** diastereomers were obtained. The assignment of relative configuration of all the intermediates is made by correlation with the corresponding lactones and is based on the magnitude of the ^1H NMR coupling constants. These synthetic methods have permitted the preparation of several α-acylamido-β-phenyl-substituted enol and halo enol lactone systems that are close analogues of the amino acid phenylalanine. These compounds are of interest as potential mechanism-based irreversible inactivators of the serine protease α-chymotrypsin.

We have been interested in the development and synthesis of halo enol lactones as novel enzyme-activated irreversible inhibitors of serine proteases.[1] In connection with our recent investigations extending the synthesis of these halo enol lactones to α-acylamino-substituted systems that mimic the structure of α-amino acids,[1d] we have become particularly interested in the preparation of the α-acylamino-β-phenyl system **1**, as this system bears a close structural resemblance to phenylalanine derivatives which are often very good substrates for α-chymotrypsin. In previous publications, we have demonstrated that halo enol lactones can be prepared efficiently by stereoselective halolactonization of acetylenic acid precursors with electrophilic halogenating agents.[1bd] In this report we describe the use of this halolactonization methodology for the preparation of the desired α-acylamino-β-phenyl systems **1** from the requisite acetylenic amino acid precursors **2**.



1 **2**

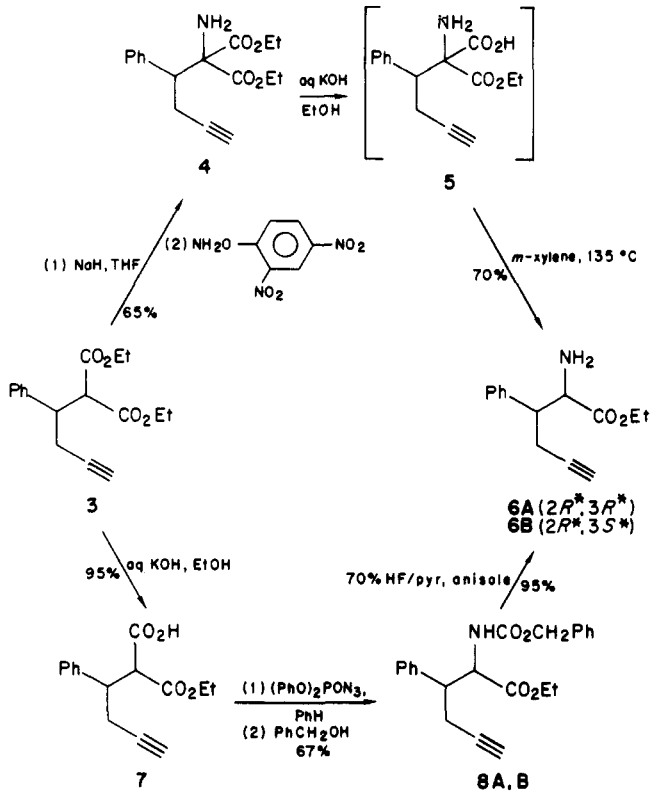
Results

Synthesis of the (3*R**,4*R**)- and (3*R**,4*S**)-3-Acetamido- and 3-Benzamido-4-phenyl-6(*E*)-(iodomethylidene)tetrahydropyranones (13A,B and 14A,B).

(1) (a) Chakravarty, P. K.; Krafft, G. A.; Katzenellenbogen, J. A. *J. Biol. Chem.* **1982**, *257*, 610. (b) Krafft, G. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 5459. (c) Daniels, S. B.; Cooney, E.; Sofia, M. J.; Chakravarty, P. K.; Katzenellenbogen, J. A. *J. Biol. Chem.* **1983**, *258*, 15046. (d) Sofia, M. J.; Chakravarty, P. K.; Katzenellenbogen, J. A. *J. Org. Chem.* **1983**, *48*, 3318.

0022-3263/85/1950-2331$01.50/0

Scheme I



Two successful routes to a 2-amino-3-phenyl-5-hexynoate precursor (**6**) of the 3-(acylamino)-4-phenyl halo enol lactones were developed (Scheme I). Both of these approaches began with the previously prepared diester **3**.[2] It should be pointed out that in the synthesis of the aminohexynoate precursor **6** and subsequent transformations to the halo enol lactones, our strategy was designed to circumvent isolation of any zwitterionic intermediates which would possibly complicate compound purification and manipulation.

The first approach, shown as the upper route in Scheme I, utilized an electrophilic amination as its key step.[3] Amination of the diester **3**, using the easily prepared 2,4-dinitrophenylhydroxylamine,[3,4] gave the amino diester **4** in 65% purified yield as a 1:1 diastereomeric mixture. Attempts to prepare the *N*-acetyl derivative (Ac_2O or AcCl, (*N*,*N*-dimethylamino)pyridine, Et_3N, and CH_2Cl_2) of the amino diester, prior to saponification of the diester and decarboxylation, proved unsuccessful, presumably due to steric factors. Therefore, the diester was carefully saponified to the half-ester **5** with 10% KOH in $EtOH/H_2O$; acidification to pH 1 followed by decarboxylation in *m*-xylene gave the amino ester **6**. This material was obtained in 71% overall yield as a 1.7:1 mixture of diastereomers (designated **A** and **B**, respectively), which were easily separated by flash chromatography. Assignment of stereochemistry to the major and minor isomers was difficult at this point. Although the resonances due to the methyl and methylene protons of the ester functionality are shifted upfield in isomer **A** by 0.16 ppm relative to isomer **B**, and therefore, indicate ester proximity to the aromatic residue, the coupling constants for the C-2 and C-3 protons of 4.5 Hz (**A**) and 6.0 Hz (**B**) are relatively similar, thus preventing reliable conformational (hence stereochemical) assignments.

An equally successful, alternative approach to the amino diester **6** starting from diester **3** utilized a modified Curtius rearrangement to introduce the amino functionality (shown as the lower route in Scheme I).[5] Careful saponification of the diester **3** gave the half-ester **7** as a 5:1 mixture of diasteromers. This mixture was subjected to modified Curtius rearrangment conditions (diphenylphosphoryl azide, Et_3N, refluxing benzene for 1.5 h, followed by trapping of the intermediate isocyanate with benzyl alcohol),[5] providing the *N*-carbobenzyloxy protected amino ester **8** in 70% yield as a 1.4:1 diastereomeric mixture. At this point, the diastereomers were easily separated by fractional crystallization with ether/hexane to give the minor diastereomer **8** as a crystalline solid (mp 103–104 °C) and the major diastereomer **8** as a clear oil. The carbobenzyloxy protecting group of each of the diastereomers was easily removed with HF/pyridine[6] to give cleanly the corresponding amino ester **6** in 95% yield. The major diastereomeric *N*-(carbobenzyloxy)amino ester provided amino ester **A**, and the minor diastereomeric *N*-(carbobenzyloxy)amino ester provided amino ester **B**. No isomerization was observed in the deprotection step.

It has been well established that the Curtius rearrangement proceeds stereoselectively with retention of configuration at the migrating carbon center.[7] Yamada[5] has also shown that the modified Curtius rearrangement of monoacids proceeds with retention of configuration at the migrating carbon center; however, the sterechemical integrity of the modified Curtius rearrangement on malonate half-esters has never been addressed. In the case of our half-ester **7**, we began with a 5:1 diastereomeric mixture of half-esters, but obtained from the Curtius rearrangement a 70% yield of a 1.4:1 diastereomeric mixture of products.

In order to investigate the stereoselectivity of this version of the Curius rearrangement, we separated the diastereomeric half-esters (**7**) cleanly by semipreparative high-pressure liquid chromatography (HPLC). In a hexane–CH_2Cl_2–*i*-PrOH–AcOH (93:5:1.8:0.2) isocratic solvent system, the major diastereomer had a retention time of 18.8 min, and the minor diastereomer 14.3 min; C_2–C_3 ^1H coupling constants were 9.0 and 9.5 Hz, respectively. When either of the pure diastereomeric half-esters was subjected to the Curtius rearrangement, a 1.4:1 mixture of diastereomeric *N*-(carbobenzyloxy)amino esters was obtained, whereas, when either pure diastereomer was simply refluxed in benzene for 1.5 h, a 3.5:1 major:minor mixture of diastereomeric half-esters (determined by analytical HPLC) was obtained. However, if either of the pure diastereomeric half-esters was refluxed in benzene with an equivalent of triethylamine for 1.5 h, a 1.6–1.5:1 major:minor mixture of diastereomeric half-esters was produced.

(2) This compound was prepared by the alkylation of diethyl sodiomalonate with the methanesulfonate of 1-phenyl-3-butyn-1-ol: Sofia, M. J.; Katzenellenbogen, J. A. *J. Med. Chem.*, submitted for publication.

(3) (a) Radhakrishna, A. S.; Loudon, G. M. *J. Org. Chem.* **1979**, *44*, 4836. (b) Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1. (c) Sheradsky, T.; Nir, Z. *Tetrahedron Lett.* **1969**, 77.

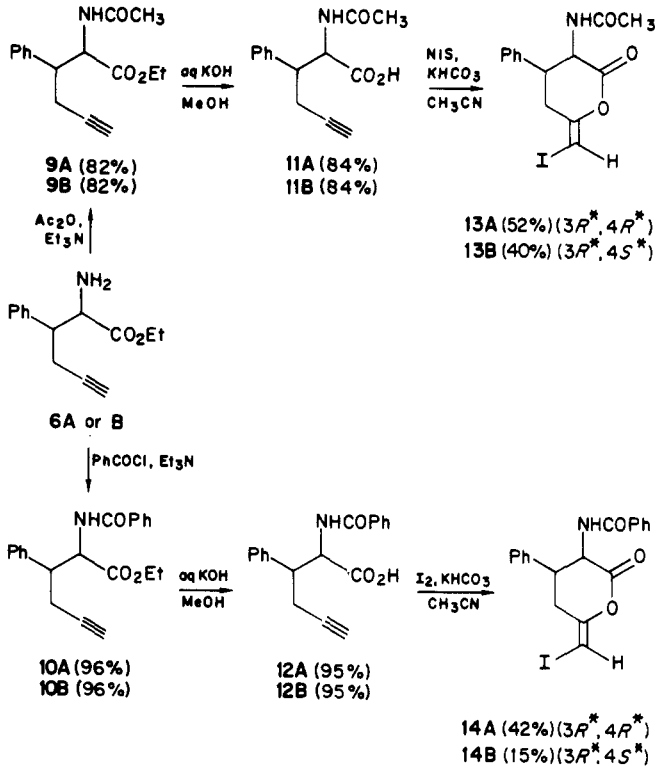
(4) (a) Ilvespaa, A. O.; Marxer, A. *Helv. Chim. Acta* **1963** *46*, 2009. (b) Tamura, Y.; Minamikawa, K.; Sumoto, K.; Fujii, S.; Ikeda, M. *J. Org. Chem.* **1973**, *38*, 1239.

(5) (a) Yamada, S.-I.; Ninomiya, K.; Shioiri, T. *Tetrahedron Lett.* **1973**, 2343. (b) Ninomiya, K.; Shiori, T.; Yamada, S.-I. *Chem. Pharm. Bull.* **1974**, *22*, 1398. (c) Ninomiya, K.; Shioiri, T.; Yamada, S.-I. *Tetrahedron* **1974**, *30*, 2151. (d) Shioiri, T.; Yamada, S.-I. *Chem. Pharm. Bull.* **1974**, *22*, 855. (e) Shioiri, T.; Yamada, S.-I. *Ibid.* **1974**, *22*, 859.

(6) Matsuura, S.; Niu, C.-H.; Cohen, J. S. *J. Chem. Soc., Chem. Commun* **1976**, 451.

(7) (a) Smith, P. A. S. In "Organic Reactions"; Adams, R., Bachmann, W. E., Fieser, L. F., Johnson, J. R., Snyder, H. R., Eds.; John Wiley and Sons: New York, 1946; Vol. 3, Chapter 9. (b) Hardy, P. M. In "Comprehensive Organic *Chemistry*"; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: New York, 1979; Chapter 23.

Scheme II



Since it was also shown that the (carbobenzyloxy)amino ester products do not isomerize under the reaction conditions, it appears that the loss of stereochemical integrity in the modified Curtius rearrangement of half-ester **7** is due to equilibration of the readily enolizable half-ester reactants.

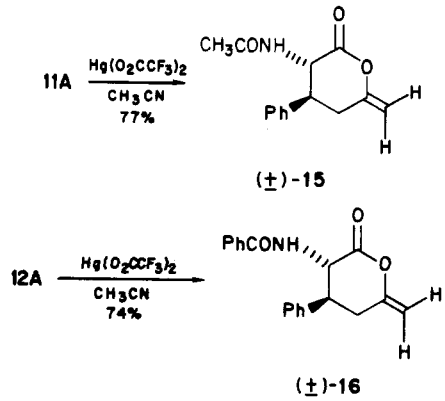
Because the free amino esters decompose slowly, possibly by autoxidation of the free amine, each of the diastereomeric amino esters (**6A,B**) was transformed into its corresponding hydrochloride salts. These diastereomeric amino ester salts were easily converted into their corresponding *N*-acetyl or *N*-benzoyl derivatives by treatment with acetic anhydride or benzoyl chloride with triethylamine (Scheme II). The esters **9A,B** and **10A,B** were then saponified to give the corresponding acids (Scheme II).

Attempts to halolactonize either of the diastereomeric *N*-acetyl derivatives with iodine in acetonitrile provided only undesirable polar products. However, lactonization with *N*-iodosuccinimide proceeded cleanly to give a 40–55% yield of the desired *N*-acetyl halo enol lactones **13A,B**. No isomerization was observed during the lactonization process.

At this point the assignment of relative lactone stereochemistry, and by correlation, the relative stereochemistry of the corresponding acyclic acids and esters could be made by an analysis of ^{1}H NMR coupling constants. The diastereomeric amino esters **6A** and **6B** provided *N*-acetyl halo enol lactones **13A** and **13B** with C_3–C_4 ^{1}H NMR coupling constants of 11.5 and 7.0 Hz, respectively. Therefore, the lactone substituents were assigned as having a trans relationship in diastereomer **A** and a cis relationship in diastereomer **B**. These lactone stereochemical assignments are consistent with similar assignments provided by Bartlett[8] for α-(acylamino)-β-methyl lactones. With the establishment of lactone relative stereochemistry,

(8) (a) Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *Tetrahedron Lett.* **1982**, *23*, 619. (b) Bartlett, P. A.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3933.

Scheme III



the acyclic precursors were given the assignments 2*R**,3*R** for diastereomer **A** and 2*R**,3*S** for diastereomer **B**.

Although halolactonization of the *N*-benzoyl acids **12A,B** with *N*-iodosuccinimide was unsuccessful, treatment with iodine gave the desired halo enol lactones **14A,B**. The trans-3,4-disubstituted *N*-benzoyl lactone **14A** proved to be soluble only in dimethyl sulfoxide and hot ethyl acetate; therefore, purification of this compound was accomplished by repeated recrystallization from ethyl acetate. Lactonization to form the isomeric *N*-benzoyl lactone **14B**, Scheme II, was extremely sluggish and inefficient (<15%), requiring separation of large amounts of starting material from the product mixture. This was accomplished by filtration through a plug of Florisil, eluting with 1% AcOH in dichloromethane.

Synthesis of the Diprotio Enol Lactones (15 and 16). We were also interested in synthesizing the corresponding diprotio analogues of the halo enol lactones **13A,B** and **14A,B** by mercury lactonization of the same corresponding acetylenic acids precursors (**11A,B** and **12A,B**). We had previously used this procdure successfully to prepare diprotio analogues of simple aryl-substitued halo enol lactones.[1b,2]

Mercury lactonization of either the (2*R**,3*R**)-acetamido or -benzamido acetylenic acids (**11A**, **12A**) proceeded cleanly to give the corresponding 3,4-*trans*-diprotiolactones **15** and **16**, respectively (Scheme III). In contrast, treatment of either of the (2*R**,3*S**)-acetamido or -benzamido acetylenic acids **11B**, **12B** with $Hg(O_2CCF_3)_2$ or $Hg(OAc)_2$ gave at most a 12% yield of a 1:1 mixture of diastereomeric diprotiolactones. For the mercury lactonizations involving all of these acetylenic amino acids, standard aqueous workups[1b,2] had to be abandoned in favor of nonaqueous workups in order to circumvent inexplicable product loses.

Discussion

In studies on the lactonization of γ-olefinic-α-(acylamido) acids, Bartlett[8] attributed low lactonization yields to competing attack by the *N*-acyl moiety. In our acetylenic acids, however, the site of unsaturation is one carbon further removed from the α-acylamido group, so that cyclization upon the oxygen of the *N*-acylamido group would lead to a seven-membered ring system. Cyclization to this ring size should be disfavored relative to six-membered ring lactonization upon the carboxyl group, and thus accounts for the lack of alternative cyclization products in our system.

The lower yields in the cyclizations of the 2*R**,3*S** diastereomeric acetylenic acids (**11B** and **12B**) to the 3,4-cis lactones (40% and 15%) relative to those for the 2*R**,3*R** diastereomers (**11A** and **12A**) leading to the 3,4-trans

lactones (52% and 42%) can be attributed to greater torsional strain development in the transition state leading to the cis lactones. This same strain seems to be even more pronounced for the mercury lactonization of 2,3-substituted acetylenic acids than for the iodolactonizations since the cis diprotio lactones fail to form all together. Therefore, one may infer that mercury lactonization proceeds through a relatively late transition state compared to that for iodolactonization.

The synthetic methods presented in this report should be useful for the preparation of α-(acylamido)-substituted halomethylene lactone systems that are close analogues of amino acids and of interest as potential mechanism-based inactivators of serine proteases.

Experimental Section

General Methods. Analytical thin-layer chromatography was performed with 0.25-mm silica gel glass-backed plates with F-254 indicator (Merck). Visualization was by ultraviolet light, iodine, or phosphomolybdic acid. All column chromatography was done with the flash chromatography technique as described by Still.[9] The column packing was Woelm 32–63 μM silica gel.

Chemical shifts are reported in ppm downfield from a tetramethylsilane 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)). Mass spectrometer data are reported in the form: m/z (intensity relative to base peak = 100). Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Chemicals were obtained from the following sources: Aldrich Chemical Co. (dimethylamino)pyridine (DMAP), methanesulfonyl chloride, mercuric trifluoroacetate, 70% HF·pyridine; Alfa (Ventron) *n*-butyllithium in hexane, sodium hydride; Parish *N*-iodosuccinimide (NIS).

Tetrahydrofuran (THF) was distilled from sodium benzophenone prior to use. Acetonitrile, dichloromethane, and triethylamine were refluxed over calcium hydride and then distilled to insure dryness. The organolithium reagents were titrated periodically to determine the organic base present by using either the double titration method[10] or the single titration method with 1,10-phenanthroline as indicator.[11]

The following compound was prepared according to literature procedure: 2,4-dinitrophenylhydroxylamine.[3,4]

Diethyl 2-Amino-2-(1-phenyl-3-butynyl)malonate (4). The acetylenic diester **3** (9.0 g, 31.2 mmol) in 47 mL of THF was added over 10 min at 25 °C to a THF (47 mL) suspension of NaH (34.3 mmol) under N_2 atmosphere. The reaction was stirred for 25 min at 25 °C; then a 50-mL THF solution of 2,4-dinitrophenylhydroxylamine[3,4] (6.33 g, 32.8 mmol) was added rapidly. After another period of stirring (20 h, at 25 °C), the reaction mixture was quenched with cold water. Removal of the THF and dilution of the aqueous residue with water (~200 mL) was followed by repeated extraction with Et_2O. The combined Et_2O extracts were then washed several times with saturated aqueous $NaHCO_3$ solution. The initial water solution was brought to pH ~10 with 5% NaOH and reextracted with Et_2O. All Et_2O extracts were then combined and dried over $MgSO_4$ to give an oil after filtration and solvent removal. Purification by flash chromatography and elution with 27% EtOAc/hexane provided the amino diester **4** as a crystalline solid (62%): mp 46–49 °C; IR ($CHCl_3$) 3400, 3320, 3000, 2125, 1740, 1585 cm^{-1}; NMR ($CDCl_3$) δ 7.23 (m, 5), 4.23 (q, 2, J = 6.0 Hz), 3.95 (q, 2, J = 7.0 Hz), 3.88 (m, 1), 2.73 (m, 2), 2.03 (s (br), 2), 1.75 (t, 1, J = 1.5 Hz), 1.30 (t, 3, J = 7.0 Hz), 1.13 (t, 3, J = 7.0 Hz); mass spectrum, m/z (relative intensity) 303 (1, M^+), 264 (1), 230 (63), 174 (100), 157 (12), 129 (50).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.33; H, 6.93; H, 4.62. Found: C, 67.40; H, 6.90; N, 4.57.

Ethyl (2*R,3*R**)- and (2*R**,3*S**)-2-Amino-3-phenyl-5-hexynoate (6A,B). Method A.** The amino diester **4** (6.21 g, 20.5 mmol) was stirred at 25 °C with 150 mL of EtOH and 150 mL of H_2O. A 10% aqueous solution of KOH (40 mL) was added, and the reaction mixture was stirred at 25 °C for 1 h 20 min (carefully monitored by TLC 10% MeOH/1% AcOH/89% CH_2Cl_2). The ethanol was then removed in vacuo, and the remaining aqueous solution was diluted with water (30 mL) and chilled in an ice bath. Acidification of the chilled solution to pH ~1 with 6 N HCl followed by complete removal of the water produced a gummy residue which was stirred with absolute ethanol and filtered through sintered glass to remove undissolved solids. Removal of the ethanol from the filtrate and trituration of the resulting residue with dry Et_2O produced a white solid which was dried in vacuo. The solid was then refluxed in *m*-xylene (170 mL) for 1 h. Removal of the xylene in vacuo (8 mmHg) produced a solid which was diluted with water brought to pH 10 with 2 N NaOH and immediately extracted several times with ethyl acetate. The ethyl acetate extracts were dried over $MgSO_4$, and an oil resulted after filtration and solvent removal. Purification by flash chromatography, eluting with 1:1 EtOAc/hexane, produced separated diastereomeric amino esters **6A** (2*R**,3*R**) and **6B** (2*R**,3*S**) in a 1.7:1 ratio in 81% (3.94 g) yield.

Method B. The (carbobenzyloxy)amino ester **8A** or **8B** (0.205 g, 0.56 mmol) and 0.4 mL of anisole were stirred with CH_2Cl_2 (5 mL) in a 50-mL polyethylene reaction vessel and cooled to 0 °C. A 70% HF·pyridine solution (5 mL) was then added, and the reaction mixture was stirred for 3 h at 25 °C. The reaction mixture was then transferred to a 250-mL polyethylene beaker, cooled to 0 °C, and brought to pH 8 or 9 with saturated aqueous $NaHCO_3$ solution (~170 mL). This alkaline solution was then extracted with CH_2Cl_2, and the organic extract was washed with saturated aqueous $NaHCO_3$ and water, dried over $MgSO_4$, and filtered to give a yellow oil after solvent removal. Purification by flash chromatography, eluting with 1:1 EtOAc/hexane, produced 0.130 g (84%) of amino esters **6A** and **6B**.

(2*R**,3*R**)-**6A** (major diastereomer): IR ($CHCl_3$) 3300, 3020, 2120, 1735 cm^{-1}; NMR ($CDCl_3$) δ 7.20 (s (br), 5), 4.10 (q, 2, J = 7.0 Hz), 3.88 (d, 1, J = 4.5 Hz), 3.35 (m, 1), 2.73 (AB quartet, 1, $\Delta\nu$ = 5.6 Hz, J = 16.5 Hz, with each line appearing as a doublet, J = 2 Hz), 2.65 (AB quartet, 1, $\Delta\nu$ = 5.6 Hz, J = 16.5 Hz, with each line appearing as a doublet, J = 2 Hz), 1.97 (t, 1, J = 2.0 Hz), 1.32 (s, 2), 1.20 (t, 3, J = 7.0 Hz); mass spectrum, m/z (relative intensity) 231 (2, M^+), 202 (1), 158 (100), 157 (4), 154 (1), 129 (48), 102 (100), 74 (100).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.73; H, 7.36; N, 6.06. Found: C, 72.96; H, 7.49; H, 6.03.

(2*R**,3*S**)-**6B** (minor diastereomer): IR ($CHCl_3$) 3400, 3320, 3000, 2125, 1735, 1610 cm^{-1}; NMR ($CDCl_3$) δ 7.23 (s, 5), 3.97 (q, 2, J = 7.0 Hz), 3.70 (d, 1, J = 6.0 Hz), 3.13 (m, 1), 2.20 (m, 2), 1.90 (t, 1, J = 2.0 Hz), 1.60 (s, 2), 1.07 (t, 3, J = 7.0 Hz); mass spectrum, m/z (relative intensity) 231 (6, M^+), 202 (1), 158 (100), 157 (11), 154 (2), 129 (90), 102 (100), 74 (100).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.73; H, 7.36; N, 6.06. Found: C, 72.97; H, 7.42; N, 5.74.

(2*R,3*R**)- and (2*R**,3*S**)-2-Carbethoxy-3-phenyl-5-hexynoic Acid (7).** Diester **3** (0.750 g, 2.60 mmol) was stirred at 25 °C with 38 mL of EtOH, 38 mL of H_2O, and 4.7 mL of 10% aqueous KOH for 50 min. The EtOH was then removed in vacuo, and the remaining aqueous solution was diluted with 30 mL of water and cooled to 0 °C. Acidification to pH ~1 with 6 N HCl and repeated extraction with ethyl acetate followed by drying of the organic extract over $MgSO_4$, filtration, and solvent removal provided 0.70 g of a clear oil. Purification by flash chromatography, eluting with 1% AcOH/5% MeOH/94% CH_2Cl_2, provided 0.69 g of a clear oil as a mixture of diastereomeric half-esters **7**.

Diastereomeric half-esters were separated by semipreparative HPLC with a Whatman M9 10/50 semipreparative silica gel column eluting with an isocratic solvent system (93% hexane/2% *i*-PrOH containing 10% AcOH/5% CH_2Cl_2) at a flow rate of 4.2 mL/min. Peaks were detected by UV absorption at 256 nm and had retention times of 14.34 min (minor diastereomer) and 18.75 min (major diastereomer).

Major diastereomer **7**: mp 85–86.5 °C; IR (film) 3700–2500, 3300, 2125, 1740 (br), 1610 cm^{-1}; NMR ($CDCl_3$) δ 10.03 (s (br), 1), 7.25 (s, 5), 3.92 (q, 2, J = 7.0 Hz), 3.90 (d, 1, J = 4.5 Hz), 3.62

(9) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(10) Whitesides, G. M.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379.
(11) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

(m, 1), 2.70 (m, 2), 1.98 (t, 1, J = 2.0 Hz), 0.97 (t, 3, J = 7.0 Hz); mass spectrum, m/z (relative intensity) 216 (1), 215 (3), 187 (6), 131 (79), 129 (22), 128 (100), 77 (30).

Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.23; H, 6.15. Found: C, 69.09; H, 5.91.

Minor diastereomer **7**: mp 83–84.5 °C; IR (film) 3700–2500, 3300, 2125, 1740 (br), 1610 cm^{-1}; NMR ($CDCl_3$) δ 10.10 (s (br), 1), 7.25 (s, 5), 4.20 (q, 2, J = 7.0 Hz), 3.90 (d, 1, J = 10.0 Hz), 3.60 (m, 1), 2.63 (m, 2), 1.93 (t, 1, J = 2.0 Hz), 1.27 (t, 3, J = 7.0 Hz); mass spectrum, m/z (relative intensity) 216 (1), 215 (2), 187 (4), 131 (78), 129 (22), 128 (100), 77 (33).

Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.23; H, 6.15. Found: C, 69.24; H, 5.85.

Isomerization Studies of (2*R,3*R**)- and (2*R**,3*S**)-2-Carbethoxy-3-phenyl-5-hexynoic Acid (7).** Each pure diastereomeric half-ester **7**, 2*R**,3*R** or 2*R**,3*S**, was stirred in benzene (3 mL) with and without triethylamine (1 equiv) at 80 °C for 1.5 h under N_2 atmosphere. All volatile components were removed in vacuo, and the remaining residue was dissolved in CH_2Cl_2. Diastereomeric ratios were determined by HPLC with a Varian SI-5 analytical silica gel column eluting with an isocratic solvent composition of 80% hexane/3% *i*-PrOH containing 1% AcOH/17% CH_2Cl_2 at a flow rate of 1 mL/min and detecting at 256 nm: major diastereomer retention time = 16.5 min; minor diastereomer retention time = 10.13 min. Peak areas were determined by electronic integration with a Hewlett-Packard Model 3390A integrator-plotter.

Ethyl (2*R,3*R**)- and (2*R**,3*S**)-2-[(Carbobenzyloxy)amino]-3-phenyl-5-hexynoate (8A,B).** A diastereomeric mixture of half-esters **7** (0.639 g, 2.46 mmol) was refluxed in benzene (20 mL) with (diphenylphosphoryl)azide (0.680 g, 2.46 mmol) and triethylamine (0.250 g, 2.70 mmol) under N_2 atmosphere for 1.5 h. The reaction mixture was then cooled to 25 °C, and a benzene solution (20 mL) of benzyl alcohol (0.293 g, 2.70 mmol) was added. The reaction mixture was then refluxed for 15 h. The reaction was cooled to 25 °C; the benzene was removed in vacuo, and the remaining residue was dissolved in ethyl acetate and washed with 5% HCl, H_2O, and saturated aqueous $NaHCO_3$ solution. The organic extract was then dried over $MgSO_4$ and filtered to give a yellow oil after solvent removal. Flash chromatography, eluting with 25% EtOAc/hexane, provided 0.620 g (70%) of a 1.4:1 mixture of diastereomeric (carbobenzyloxy)amino esters **8**. Diastereomers were separated by fractional crystallization from diethyl ether and hexane.

(2*R**,3*R**)-**8A** (major diastereomer): IR (film) 3420, 3300, 3020, 2125, 1720 (br), 1580 cm^{-1}; NMR ($CDCl_3$) δ 7.30 (s, 5), 7.17 (m, 5), 5.03 (s, 2), 4.98 (m, 1), 4.05 (q, 2, J = 7.0 Hz), 3.50 (m, 1), 2.63 (m, 2), 1.92 (t, 1, J = 2.0 Hz), 1.17 (t, 3, J = 7.0 Hz); mass spectrum, m/z (relative intensity), 326 (26), 292 (7), 236 (1), 215 (7), 214 (33), 129 (63), 91 (100); mass spectrum (FD), m/z (relative intensity) 365 (28, M^+).

Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.33; H, 6.30; N, 3.84. Found: C, 71.98; H, 6.26; N, 3.89.

(2*R**,3*R**)-**8B** (minor diastereomer): IR ($CHCl_3$) 3460, 3340, 3040, 2140, 1730 (br), 1520 cm^{-1}; NMR ($CDCl_3$) δ 7.36 (s, 5), 7.23 (s (br), 5), 5.38 (d (br), 1, J = 9.0 Hz), 5.10 (s, 2), 4.70 (dd, 1, J = 9.0 Hz, J = 6.0 Hz), 4.00 (q, 2, J = 7.0 Hz), 3.27 (m, 1), 2.77 (m, 2), 1.93 (t, 1, J = 2.0 Hz), 1.05 (t, 3, J = 7.0 Hz); mass spectrum, m/z (relative intensity) 292 (5), 236 (1), 215 (4), 214 (22), 129 (34), 91 (100).

Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.33; H, 6.30; N, 3.84. Found: C, 71.96; H, 6.05; N, 3.88.

Ethyl (2*R,3*R**)-2-Acetamido-3-phenyl-5-hexynoate (9A).** The amino ester **6A** (2*R**,3*R**) (0.31 g, 1.35 mmol) was stirred in dry CH_2Cl_2 (25 mL) with triethylamine (0.273 g, 2.7 mmol) at 25 °C under N_2 atmosphere for 10 min. Addition of acetic anhydride (0.15 g, 1.48 mmol) at 25 °C was followed by stirring for 16 h. The CH_2Cl_2 was then removed in vacuo, and the remaining residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with 5% HCl, saturated $NaHCO_3$ solution, and H_2O, dried over $MgSO_4$, and filtered, and solvent was removed to give a white solid which was recrystallized from ethyl acetate/hexane to give ester **9A** (82%): mp 90–92 °C; IR (KBr) 1735, 1660 cm^{-1}; NMR ($CDCl_3$) δ 7.25 (m, 5), 5.70 (d (br), 1, J = 9.0 Hz), 5.15 (dd, 1, J = 9.0 Hz, J = 4.5 Hz), 4.22 (q, 2, J = 7.0 Hz), 3.60 (m, 1), 2.67 (m, 2), 2.03 (s, 3), 1.98 (t, 1, J = 2.0 Hz), 1.33 (t, 3, J = 7.0 Hz); mass spectrum, m/z (relative intensity) 273 (1, M^+), 215 (3), 200 (11), 145 (21), 144 (5), 129 (52), 77 (11).

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.33; H, 6.96; N, 5.13. Found: C, 70.35; H, 6.96; N, 4.89.

Ethyl (2*R,3*S**)-2-Acetamido-3-phenyl-5-hexynoate (9B).** The *N*-acetylamino ester **9B** (2*R**,3*S**) was prepared in 82% yield from amino ester **6B** according to the procedure described for compound **9A**: mp 121.5–123.5 °C; IR (KBr) 3380, 3300, 3010, 1750, 1660 cm^{-1}; NMR ($CDCl_3$) δ 7.20 (m, 5), 6.03 (d (br), 1, J = 9.0 Hz), 4.92 (dd, 1, J = 9.0 Hz, J = 7.0 Hz), 3.97 (q, 2, J = 7.0 Hz), 3.20 (m, 1), 2.70 (m, 2), 2.02 (s, 3), 1.92 (t, 1, J = 2.0 Hz), 1.03 (t, 3, J = 7.0 Hz); mass spectrum, m/z (relative intensity) 273 (2, M^+), 215 (5), 214 (30), 200 (16), 145 (27), 144 (5), 129 (58), 102 (100), 77 (11); HRMS calcd for $C_{16}H_{19}NO_3$ m/z 273.1367, found m/z 273.1366.

Ethyl (2*R,3*R**)-2-Benzamido-3-phenyl-5-hexynoate (10A).** The amino ester **6A** (2*R**,3*R**) (0.20 g, 0.75 mmol) was stirred in dry CH_2Cl_2 (1 mL/13 mg) with triethylamine (1.3 equiv) for 10 min at 25 °C under N_2 atmosphere. Benzoyl chloride (1 equiv) was then added, and the reaction was stirred at 25 °C for 2–3 h. The reaction was then quenched with water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was then washed with 5% HCl, saturated $NaHCO_3$ solution, and H_2O and dried over $MgSO_4$ to give a white solid on solvent removal. Purification by recrystallization from ethyl acetate/hexane provided the benzamido ester (2*R**,3*R**)-**10A** in 96% yield: mp 128–130 °C; IR ($CHCl_3$) 3425, 3300, 3000, 2120, 1735, 1670, 1600 cm^{-1}; NMR ($CDCl_3$) δ 7.67 (m, 2), 7.30 (m, 8), 6.30 (d (br), 1, J = 9.0 Hz), 5.27 (dd, 1, J = 9.0 Hz, J = 4.0 Hz), 4.18 (q, 2, J = 7.0 Hz), 3.63 (m, 1), 2.73 (m, 2), 1.93 (t, 1, J = 2.0 Hz), 1.27 (t, 3, J = 7.0 Hz); mass spectrum, m/z (relative intensity) 335 (1, M^+), 262 (5), 215 (2), 214 (11), 206 (5), 129 (4), 105 (100).

Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.22; H, 6.27; N, 4.18. Found: C, 75.30; H, 6.23; N, 4.29.

Ethyl (2*R,3*S**)-2-Benzamido-3-phenyl-5-hexynoate (10B).** The benzamido ester **10B** (2*R**,3*S**) was prepared in 96% yield from amino ester **6B** (2*R**,3*S**) according to the procedure described for ester **10A**: mp 152–153.5°C; IR (KBr) 3360, 3245, 2980, 1740, 1645 cm^{-1}; NMR ($CDCl_3$) δ 7.76 (m, 2), 7.35 (m, 8), 6.75 (d (br), 1, J = 9.0 Hz), 5.15 (dd, 1, J = 9.0 Hz, J = 7.0 Hz), 4.05 (q, 2, J = 7.0 Hz), 3.40 (q, 1, J = 8.0 Hz), 2.83 (m, 2), 1.95 (t, 1, J = 2.0 Hz), 1.10 (t, 3, J = 7.0 Hz); mass spectrum, m/z (relative intensity) 335 (21, M^+), 262 (22), 215 (14), 214 (85), 206 (32), 129 (13), 105 (100).

Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.22; H, 6.27; N, 4.14. Found: C, 75.27; H, 6.35; N, 4.11.

(2*R,3*R**)-2-Acetamido-3-phenyl-5-hexynoic Acid (11A).** The acetamido ester **9A** (2*R**,3*R**) in MeOH/H_2O (30 mL/0.1 g) was stirred with 10% aqueous KOH (1 mL/0.02 g) for 3 h at 25 °C. The methanol was then removed in vacuo, and the resulting aqueous solution was cooled in an ice bath and acidified to pH ~1 with 6 N HCl. The acidified solution was then extracted with ethyl acetate, which was then dried over $MgSO_4$ and filtered to give a white solid on solvent removal. Recrystallization from ethyl acetate/hexane provided pure acid **11A** (2*R**,3*R**) (84%): mp 141–142 °C; IR (KBr) 3700–2400, 3300, 3040, 2120, 1730, 1640 (br), 1540 (br) cm^{-1}; NMR (200 MHz, $CDCl_3$ + Me_2SO-d_6) δ 7.26 (m, 5), 6.39 (d (br), 1), 5.03 (m, 1), 3.56 (m, 1), 2.65 (m, 2), 1.97 (s (br), 4); mass spectrum, m/z (relative intensity) 245 (1, M^+), 200 (1), 187 (2), 168 (6), 129 (100), 117 (18), 116 (2), 77 (11), 39 (5).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.57; H, 6.12; N, 5.71. Found: C, 68.58; H, 6.14; N, 5.71.

(2*R,3*S**)-2-Acetamido-3-phenyl-5-hexynoic Acid (11B).** The acetamido acid **11B** (2*R**,3*S**) was prepared in 84% yield from the ester **9B** according to the general procedure described for compound **11A**: mp 141–142.5 °C; IR (KBr) 3700–2400, 3340, 3280, 1705, 1655, 1515 cm^{-1}; NMR (200 MHz, $CDCl_3$ + Me_2SO-d_6) δ 7.59 (d (br), 1, J = 9.4 Hz), 7.27 (s, 5), 4.81 (t, 1, J = 8.0 Hz), 3.31 (m, 1), 2.66 (m, 2), 1.98 (s, 4); mass spectrum, m/z (relative intensity) 245 (1, M^+), 200 (1), 187 (2), 168 (6), 129 (100), 117 (18), 116 (2), 77 (14), 39 (8).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.57; H, 6.12; N, 5.71. Found: C, 68.32; H, 6.26; N, 5.59.

(2*R,3*R**)-2-Benzamido-3-phenyl-5-hexynoic Acid (12A).** The benzamido acid **12A** was prepared from the corresponding

ester **10A** in 95% yield according to the procedure described for the acetamido acid **12A**: mp 174.5–176.5 °C; IR (KBr) 3700–2400, 3280, 2120, 1720 (br), 1645 (br), 1600 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 7.65 (m, 2), 7.37 (m, 3), 7.23 (s, 5), 6.50 (d (br), 2, J = 9.0 Hz), 5.18 (dd, 1, J = 9.0 Hz, J = 4.5 Hz), 3.65 (m, 1), 2.72 (m, 2), 1.97 (t, 1, J = 2.0 Hz); mass spectrum, m/z (relative intensity) 307 (1, M^+), 262 (1), 187 (1), 186 (5), 179 (16), 178 (1), 129 (31), 105 (100), 77 (47); HRMS calcd for $C_{19}H_{17}NO_3$ m/z 307.1176, found m/z 307.1192.

(2*R,3*S**)-2-Benzamido-3-phenyl-5-hexynoic Acid (12B).** The benzamido acid **12B** (2*R**,3*S**) was prepared from the corresponding ester **10B** in 95% yield according to the procedure described for the acetamido acid **11A**: mp 177.5–178.5 °C; IR (Nujol) 3295, 3860, 1705, 1605, 1530 cm^{-1}; NMR (200 MHz, Me_2SO-d_6) δ 8.72 (d, 1, J = 8.3 Hz), 7.87 (m, 2), 7.50 (m, 3), 7.28 (m, 5), 4.76 (t, 1, J = 8.8 Hz), 3.41 (m, 2), 2.63 (m, 2); mass spectrum, m/z (relative intensity) 307 (2, M^+), 262 (1), 186 (5), 179 (17), 129 (39), 105 (100), 77 (62).

Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.27; H, 5.54; N, 4.56. Found: C, 73.95; H, 5.59; N, 4.51.

(3*R,4*R**)-3-Acetamido-4-phenyl-6(*E*)-(iodomethylidene)tetrahydro-2-pyranone (13A).** The acid **11A** (0.060 g, 0.25 mmol) was stirred in CH_3CN (20 mL) under N_2 atmosphere until all of the solid dissolved. *N*-Iodosuccinimide (0.056 g, 0.25 mmol) and $KHCO_3$ (0.025 g, 0.25 mmol) were then added sequentially at 25 °C. The reaction was stirred for 4 h, after which it was quenched with 5% $Na_2S_2O_3$ and stirred for 5–10 min. The CH_3CN was removed in vacuo, the resulting aqueous solution was extracted several times with CH_2Cl_2, which was then dried over Na_2SO_4 and filtered, and the solvent removed to give a white solid. Purification by flash chromatography eluting with 1:1 ethyl acetate/hexane, and crystallization from benzene/hexane gave the iodo lactone **13A** (0.047 g, 52%): mp 79–81 °C; IR (film) 3280 (br), 3070, 1770, 1655, 1535 cm^{-1}; NMR ($CDCl_3$) δ 7.26 (m, 5), 6.08 (s (br), 1), 5.83 (d (br), 1, J = 8.0 Hz), 4.80 (dd, 1, J = 11.5 Hz, J = 8.0 Hz), 3.10 (m, 2), 1.83 (s, 3); mass spectrum, m/z (relative intensity) 371 (5, M^+), 312 (1), 244 (4), 231 (1), 115 (9), 59 (3), 43 (100); HRMS calcd for $C_{14}H_{14}NO_3I$ m/z 371.0018, found m/z 371.0009.

(3*R,4*S**)-3-Acetamido-4-phenyl-6(*E*)-(iodomethylidene)tetrahydro-2-pyranone (13B).** The iodo lactone **13B** was prepared in 40% yield from the acid **11B** according to the procedure for lactone **13A**: mp 167–169.5 °C; IR (Nujol) 3330 (br), 1770, 1660, 1620, 1515 cm^{-1}; NMR ($CDCl_3$) δ 7.28 (m, 3), 7.05 (m, 2), 6.19 (t, 1, J = 1.5 Hz), 5.90 (d (br), 1, J = 7.0 Hz), 4.90 (t, 1, J = 7.0 Hz), 3.87 (m, 1), 3.43 (m, 1), 2.98 (m, 1), 1.97 (s, 3); mass spectrum, m/z (relative intensity) 371 (6, M^+), 244 (7), 231 (2), 115 (22), 58 (3), 43 (100); HRMS calcd for $C_{14}H_{14}NO_3I$ m/z 371.0018, found m/z 371.0013.

(3*R,4*R**)-3-Benzamido-4-phenyl-6(*E*)-(iodomethylidene)tetrahydro-2-pyranone (14A).** The acid **12A** (2*R**,3*R**) (0.10 g, 0.36 mmol) was stirred in CH_3CN (30 mL) at 25 °C under N_2 atmosphere until dissolved. Iodine (0.182 g, 0.72 mmol) and $KHCO_3$ (0.033 g, 0.36 mmol) were added sequentially, and the reaction was stirred for 22 h with protection from light. The reaction was then worked up as for lactone **11A**. Purification by repeated crystallization from ethyl acetate gave a 42% yield of lactone **14A** (3*R**,4*R**): mp 189–190 °C dec; IR (Nujol) 3425, 1755, 1660, 1620, 1515 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 8.75 (d, 1, J = 8.0 Hz), 7.63 (m, 2), 7.30 (m, 8), 6.03 (s (br), 1), 4.92 (dd, 1, J = 11.5 Hz, J = 8.0 Hz), 3.53 (m, 1), 3.03 (m, 1); mass spectrum, m/z (relative intensity) 433 (4), 306 (3), 156 (7), 127 (1), 105 (100), 77 (39), 44 (45).

Anal. Calcd for $C_{19}H_{16}NO_3I$: C, 52.68; H, 3.69; N, 3.23; I, 29.33. Found: C, 52.38; H, 3.71; N, 3.10; I, 29.14.

(3*R,4*S**)-3-Benzamido-4-phenyl-6(*E*)-(iodomethylidene)tetrahydro-2-pyranone (14B).** Iodo lactone **14B** was prepared in 15% yield from acid **12B** according to the procedure described for iodo lactone **14A**. Purification was accomplished by first passing a 1% $AcOH/CH_2Cl_2$ solution of crude product through a Florisil plug and eluting with two column volumes of solvent. The resulting solid was crystallized from ethyl acetate/hexane: mp 167–168 °C; IR (Nujol) 3360, 1765, 1650, 1630, 1510 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 7.64 (m, 2), 7.38 (m, 6), 7.11 (m, 2), 6.48 (d (br), 1, J = 6.35 Hz), 6.28 (t, 1, J = 1.60 Hz), 5.12 (t, 1, J = 6.35 Hz), 4.07 (m, 1), 3.52 (ddd, 1, J = 17.8 Hz, J = 8.26 Hz, J = 1.27 Hz), 3.10 (dt, 1, J = 17.8 Hz, J = 1.90 Hz); mass spectrum, m/z (relative intensity) 433 (30, M^+), 306 (11), 105 (78); HRMS calcd for $C_{19}H_{16}NO_3I$ m/z 433.0163, found m/z 433.0169.

(3*R,4*R**)-3-Acetamido-4-phenyl-6-methylidenetetrahydro-2-pyranone (15).** Solid mercuric trifluoroacetate (0.017 g, 0.041 mmol) was added to a solution of acid **11A** (0.10 g, 0.41 mmol) in dry CH_3CN (20 mL) under N_2 atmosphere at 25 °C. The reaction was stirred for 4 h at 25 °C; the CH_3CN was removed in vacuo, and the resulting residue was immediately subjected to flash chromatography with 60% ethyl acetate/hexane. The desired lactone **15** was obtained as a white crystalline solid (0.077 g, 77%): mp 57–60 °C; IR ($CHCl_3$) 3440, 3010, 1765, 1670 cm^{-1}; NMR ($CDCl_3$) δ 7.22 (m, 5), 6.53 (d, 1, J = 8.0 Hz), 4.73 (s (br), 1), 4.70 (dd, 1, J = 11.5 Hz, J = 8.0 Hz), 4.40 (s (br), 1), 3.33 (m, 1), 2.83 (m, 1), 1.80 (s, 3); mass spectrum, m/z (relative intensity) 245 (4, M^+), 203 (1), 202 (1), 187 (5), 186 (5), 130 (3), 115 (6), 59 (10), 58 (5), 43 (75).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.57; H, 6.12; N, 5.71. Found: C, 68.25; H, 6.39; N, 5.55.

(3*R,4*R**)-3-Benzamido-4-phenyl-6-methylidenetetrahydro-2-pyranone (16).** Solid mercuric trifluoroacetate (0.008 g, 0.018 mmol) was added to a solution of acid **12A** (0.054 g, 0.18 mmol) in dry CH_3CN (10 mL) under N_2 atmosphere at 25 °C. After 2 h of stirring, H_2S was bubbled through the reaction followed by an additional 10 min of stirring. The yellow precipitate was removed by filtration; the CH_3CN solution was concentrated to a volume of 2 mL and then filtered again through a Celite pad in a fine sintered glass funnel. After solvent removal, the resulting white solid was recrystallized repeatedly from ethyl acetate to give lactone **16** (74%) as a white powder: mp 201–203 °C; IR (Nujol) 3320, 1760, 1670, 1640, 1530 cm^{-1}; NMR (200 MHz, Me_2SO-d_6) δ 8.95 (d, 1, J = 8.0 Hz), 7.68 (m, 2), 7.41 (m, 3), 7.23 (m, 5), 4.85 (m, 1), 4.65 (s (br), 1), 4.46 (s (br), 1), 3.51 (m, 1), 3.13 (t (br), 1, J = 13 Hz), 2.78 (m, 1); mass spectrum, m/z (relative intensity) 307 (6, M^+), 186 (2), 130 (4), 105 (100), 77 (64), 44 (10).

Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.27; H, 5.54; N, 4.56. Found: C, 74.48; H, 5.60; N, 4.47.

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