(d), 37.22 (t), 41.44 (t), 68.34 (t), 81.18 (s), 128.32, 128.43, 128.52, 128.94, 129.28, 129.73, 129.98, 130.37, 133.02 (d), 133.25 (d), 141.40 (s), 141.50 (s), 151.05 (s), 153.90 (s), 164.90 (s), 166.08 (s).

Anal. Calcd for $C_{28}H_{24}N_2O_4$: C, 74.32; H, 5.35. Found: C, 74.16; H, 5.42.

Similarly, diketone **9** was converted to quinoxaline derivative **11**: cubes from ether–hexane; mp 150 °C; NMR ($CDCl_3$) δ 1.68 (3 H, d, J = 7 Hz), 2.08 (1 H, d, J = 12 Hz), 2.31 (1 H, dd, $J_1 = J_2$ = 12 Hz), 2.51 (1 H, d, J = 12 Hz), 3.05 (1 H, dd, $J_1 = J_2$ = 12 Hz), 3.45 (1 H, m), 4.80 and 5.10 (2 H, AB, J_{AB} = 12 Hz), 7.3–8.2 (14 H, m). Irradiation at δ 3.45 caused the methyl group doublet to collapse to a singlet. All other signals were unchanged as shown by a difference spectrum.

Anal. Calcd for $C_{28}H_{24}N_2O_4$: C, 74.32, H, 5.35. Found: C, 74.27; H, 5.50.

Bis(phenylhydrazone) Derivatives 13 and 14. Diketone **1b** (50 mg, 0.13 mmol), EtOH (5 mL), and acetic acid (10.5 mL) was treated with phenylhydrazine (150 mg, 1.38 mmol). The solution was stirred and refluxed under N_2 for 5 h. The solution was cooled, diluted with H_2O, and centrifuged. The precipitate was dissolved in ether, and the solution was washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed by preparative TLC (solvent 30% EtOAc–hexane) followed by a second chromatography on a column of silica gel (100–200 mesh, 10 g) gave **13**: 20 mg; yellow plates from EtOH; mp 157–158 °C; NMR ($CDCl_3$) δ 1.15 (3 H, m), 0.9–3.1 (5 H, m), 4.75 (2 H, s), 7.0–8.3 (22 H, m); UV (95% EtOH) λ_{max} (ϵ) 232 (3.4 × 10^4), 273 (sh, 4.3 × 10^3), 282 (sh, 3.1 × 10^3), 385 (1.8 × 10^4) nm. Cyclohexane-1,2-dione bis(phenylhydrazone)[16] had UV (95% EtOH): λ_{max} (ϵ) 230 (1.3 × 10^4), 261 (1.9 × 10^4), 309 (1.1 × 10^4), 390 (1.6 × 10^4) nm.

Anal. Calcd for $C_{34}H_{32}N_4O_4$: C, 72.84; H, 5.75. Found: C, 71.73; H, 5.64.

Similarly **9** was converted to **14**: yellow noncrystalline glass; NMR ($CDCl_3$) δ 1.38 (3 H, d, J = 6 Hz), 1.1–3.3 (5 H, m), 4.76 (2 H, s), 6.8–8.3 (22 H, m).

Single-Crystal X-ray Diffraction Analysis of Quinoxaline Derivative 11. A roughly cubic crystal with dimensions of 0.8 × 0.7 × 0.5 mm was selected for study. Preliminary X-ray photographs displayed monoclinic symmetry and accurate lattice constants of a = 13.985 (3), b = 11.133 (2), and c = 14.385 (2) Å and β = 92.90 (1)° were determined from a least-squares fit of 15 diffractometer measured 2θ values. Systematic extinctions and crystal density (1.65 g/cm^3) were uniquely consistent with space group $P2_1/n$ with one molecule of formula $C_{28}H_{24}O_4N_2$ forming the asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were recorded on a computer-controlled four-circle diffractometer with a variable speed 1° ω scan and graphite-monochromated Cu K$\bar{\alpha}$ radiation (1.541 78 Å). Of the 3140 independent reflections surveyed in this manner, 2822 (90%) were judged observed ($|F_o| \geq 3\sigma(F_o)$) after correction for Lorentz, polarization, and background effects. A phasing model was found uneventfully by direct methods.[19] Block-diagonal, least-squares refinements with anisotropic heavy atoms and isotropic hydrogens have converged to a standard crystallographic residual of 0.05 for the observed reflections. Additional crystallographic parameters have been deposited with this paper as supplementary material.

Acknowledgment. We thank Drs. S. S. Welankiwar and C. A. Seymour for some preliminary experiments. Many of the ^{1}H NMR spectra were run on the Worcester Consortium Bruker WM-250 instrument at Clark University, Worcester, supported, in part, by NSF Equipment Grant No. DMR-8108697. We thank Frank Shea and Dr. Paul Engelfield for these spectra. We also thank Dr. Catherine E. Costello and Dr. Henrienna Pang, MIT, for the mass spectra at the facility supported by NIH Grant RR 00317 from the Biotechnology Resources Branch, Division of Research Resources. This work was supported by Grants No. CA 25377 (D.J.A.) and CA 24487 (J.C.) from the National Cancer Institute and by Grant No. INT 8117327 (J.C.) from the National Science Foundation.

Registry No. **1a**, 90369-58-7; **1b**, 90369-59-8; **2a**, 533-60-8; **3a**, 1004-52-0; **3b**, 90369-60-1; **4a**, 90369-61-2; **4b**, 90369-62-3; **5a**, 90369-63-4; **5b**, 90369-64-5; **6**, 90369-65-6; **7** (isomer 1), 90369-66-7; **7** (isomer 2), 90369-67-8; **8a**, 90369-68-9; **8b**, 90369-69-0; **9**, 90369-70-3; **10**, 90369-71-4; **11**, 90369-72-5; **13**, 90369-73-6; **14**, 90369-74-7; 2-hydroxy-4-methylcyclohexanone dimer, 35326-28-4; *o*-phenylenediamine, 95-54-5; leucogenenol, 29101-95-9.

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, and bond distances and bond angles for quinoxaline derivative **11** (5 pages). Ordering information is given on any current masthead page.

(19) All crystallographic calculations were done on a PRIME 850 computer operated by the Cornell Chemistry Computing Facility. Principal programs employed were as follows: REDUCE and UNIQUE, data reduction programs by M. E. Leonowicz, Cornell University, 1978; MULTAN 78 and 80, systems of computer programs for the automatic solution of crystal structures from X-ray diffraction data (locally modified to perform all Fourier calculations including Patterson syntheses) written by P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, University of York, England, 1978; BLS78A, an anisotropic block-diagonal least-squares refinement written by K. Hirotsu and E. Arnold, Cornell University, 1980; PLUTO78, a crystallographic illustration program by W. D. S. Motherwell, Cambridge Crystallographic Data Centre, 1978; and BOND, a program to calculate molecular parameters and prepare tables written by K. Hirotsu, Cornell University, 1978.

A Liquid Chromatographic Method for Resolving Chiral Lactams as Their Diastereomeric Ureide Derivatives

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Chiral type 1 lactams react with chiral isocyanates (e.g., α-phenylethyl isocyanate) to afford diastereomeric ureides that are readily separable by chromatography on silica. The elution order and sense of NMR nonequivalence of a pair of diastereomeric ureides can be used to assess relative (and hence absolute) configuration of the lactam enantiomers which are readily retrievable from the separated ureides. The enantiomeric purity and absolute configuration of these lactams may also be ascertained by NMR using chiral 2,2,2-trifluoro-1-(9-anthryl)ethanol as a chiral solvating agent.

Lactam functionality is fairly common among natural products and compounds of pharmacological interest. Consequently, the need to determine enantiomeric purity and absolute configuration of chiral lactams or, alterna-

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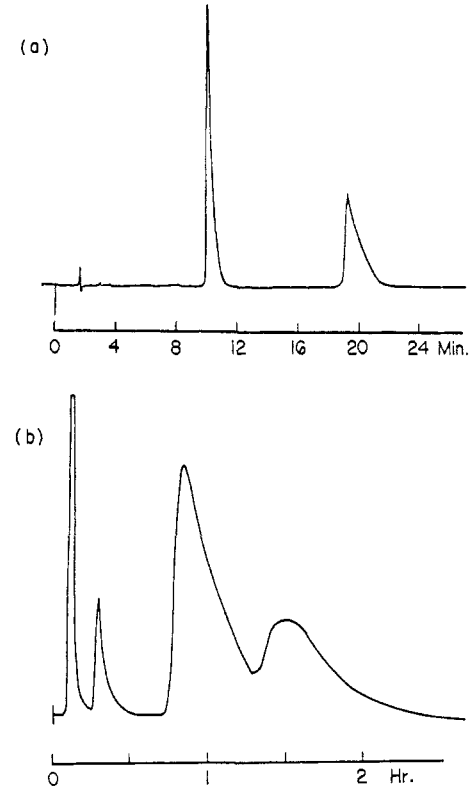
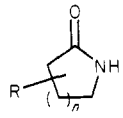


Figure 1. Chromatographic separation of diastereomeric ureide **9ab** on (a) an analytical silica gel column (5-μm Spherisorb silica gel; mobile phase, 1% isopropyl alcohol in *n*-hexane; flow rate, 2 mL/min; detector, 254 nm UV) and on (b) a preparative MPLC silica gel column (Davison 58-μm silica gel; column size, 2.5 × 30 cm; sample size, 1.8 g; mobile phase, CH_2Cl_2; flow rate, 30 mL/min; detector, 254 nm UV).

tively, to preparatively resolve such compounds is not unusual. We now describe a relatively general method whereby all three of these goals may be attained for chiral lactams of general structure **1**.



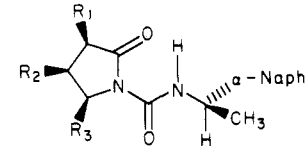
1, R = alkyl, aryl; n = 1, 2

Racemic lactams have seldom been resolved unless additional functional "handles" were present to facilitate the resolution process. The usual procedure is to resolve a lactam precursor. For example, the resolution of most racemic butyrolactams has proceeded via the fractional crystallization of diastereomeric salts derived from a γ-amino acid and various chiral reagents.[2] Such resolutions suffer from (a) the need for "trial and error" search for a suitable resolving agent, (b) uncertainty of final enantiomeric purity, (c) a general inability to predict the stereochemical outcome of the resolution, and (d) the possibility that the overall yield of resolved material will be low.

(1) Present address: Eli Lilly and Co., Tippecanoe Laboratories, Lafayette, IN 47902.

(2) (a) "Optical Resolution Procedures for Chemical Compounds"; Paul Newman, Optical Resolution Information Center, Manhattan College: Riverdale, NY 1981; Vol 2. (b) For example, see: Morlacchi, F.; Losacco, V.; Tortorella, V. *Gazz. Chim. Ital.* **1975** *105*, 349 (Resolution of 5-phenyl-2-pyrrolidone). (c) For references to the resolution of other butyrolactams via the γ-amino acid precursor, see "Stereochemistry Fundamentals and Methods"; Dagan, H. B., Ed.; Georg Thieme: Stuttgart, 1977; Vol. 4.

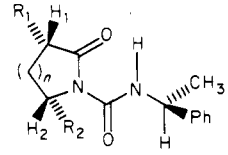
Table I. ^{1}H Nuclear Magnetic Resonance and Chromatographic Properties of Diastereomeric Ureides of (*R*)-1-(1-Naphthyl)ethyl Isocyanate



compd[a]	R_1	R_2	R_3	$\Delta\delta CH_3$ (ppm)[b]	k_1'[c]	α
3a	H	H	*p*-F-Ph	−0.06	16.6	2.47
4a	H	H	*p*-tolyl	−0.07	6.9	2.33
5a	H	H	Ph	−0.05	14.0	2.29
6a	H	Ph	H	*d*	7.7	2.04
7a	Ph	H	H	−0.02	11.9	1.84

[a] The stereochemistry represented in the drawing is that assigned to the initially eluted diastereomer. The second diastereomer, indicated as **b**, has the configuration opposite to that shown for the lactam portion of the ureides. [b] $\Delta\delta CH_3 = \delta_{CH_{3a}} - \delta_{CH_{3b}}$ where a and b refer to the first and second eluting diastereomers, respectively. [c] The chromatographic separations were performed by using 0.5% isopropyl alcohol in *n*-hexane. [d] Less than 0.01 ppm.

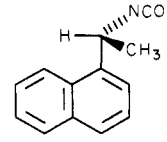
Table II. ^{1}H Nuclear Magnetic Resonance and Chromatographic Properties of Diastereomeric Ureides of (*S*)-1-Phenylethyl Isocyanate



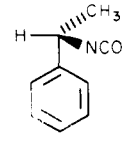
compd[a]	n	R_1	R_2	$\Delta\delta$ (ppm)[b]	k_1'[c]	α
8a	1	H	CH_3	0.05 (R_2)	10.1	1.17
9a	1	H	Ph	*d*	9.6	2.24
10a	1	H	n-C_6H_{13}	−0.05 (H_2)	5.4	1.84
11a	1	n-C_6H_{13}	H	0.03 (R_2)	8.5	1.46
12a	2	H	n-C_5H_{11}	−0.03 (H_2)	4.9	1.75

[a] The stereochemistry represented in the drawing is that assigned to the initially eluting diastereomer. The second diastereomer, indicated as **b**, has the configuration opposite to that shown for the lactam portion of the ureides. [b] NMR chemical shift difference in the functional group is shown in the parentheses. It was calculated by subtracting the chemical shift of the second eluted diastereomer from the chemical shift of the first eluted diastereomer. [c] The chromatographic separations were performed by using 0.5% isopropyl alcohol in *n*-hexane. [d] Less than 0.01 ppm in all functional groups.

In point of fact, lactams derived from primary amines (i.e., type 1 lactams) can be derivatized by isocyanates to afford ureides. Diastereomeric ureides resulting from the reaction of 1 with 1-(1-naphthyl)ethyl isocyanate (**2a**) or 1-phenylethyl isocyanate (**2b**) have been found to be



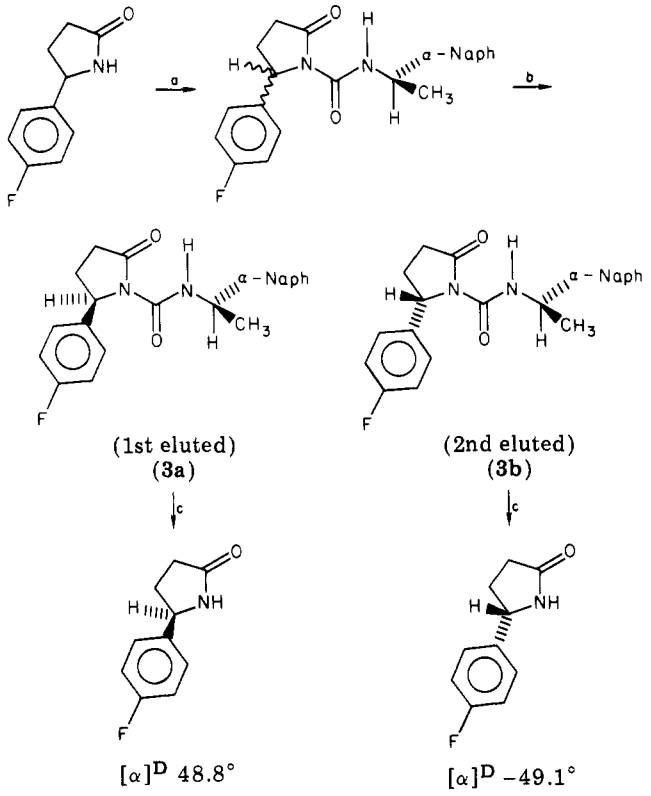
2a



2b

readily separable by liquid chromatography (Figure 1). After separation, the diastereomers may be hydrolyzed to retrieve the lactam enantiomers. The sequence of derivatization, chromatography, and retrieval is illustrated in Scheme I for 5-(4-fluorophenyl)-2-pyrrolidone. This sequence is patterned after our method for resolving primary amines (or alternatively, 2-oxazolidones) through the

Scheme I[a]



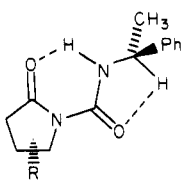
[a] (a) 2a, benzene, reflux; (b) chromatography on silica gel; (c) NaOMe, THF, reflux.

chromatographic separation of diastereomeric allophanates.[3]

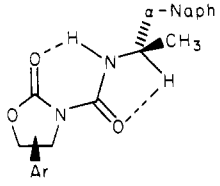
Chiral isocyanates **2a,b** react with the presently studied lactams upon heating a benzene solution of the reactants to reflux, the diastereomeric derivatives being afforded in ≥90% yield. For the present study, butyro- and valerolactams bearing alkyl or aryl substituents have been employed. The resulting diastereomeric ureides are separable by chromatography on silica. Consistent correlations of elution order, ^{1}H NMR spectral differences, and relative configurations were noted. Tables I and II present pertinent NMR and chromatographic data for the series of lactams studied. For each of the aryl-substituted butyrolactams, one notes that the chromatographic separability factor, α, is large enough to make preparative resolutions quite straightforward. For example, diastereomers **3a,b** were chromatographically separated on a homemade MPLC system and separately hydrolyzed. Specific rotations of 48.8° and −49.1° were noted for the *R* and *S* lactam enantiomers retrieved respectively from **3a** and **3b**. Ureides **4ab**, **5ab**, **6ab**, and **7ab** were similarly prepared and chromatographically examined. The magnitude of α, the chromatographic separation factor, decreases somewhat as the phenyl substituent becomes more remote from nitrogen.

As previously noted,[3,4] isocyanate **2a** is slightly more efficacious as a chromatographic resolving agent (compare the α's for **5ab** and **9ab**) than is **2b**. However, the latter is usually quite adequate and its lower cost and greater accessibility will usually cause it to be the reagent of choice. As Table II indicates, isocyanate **2b** affords chromatographically separable ureide diastereomers from alkyl-substituted lactams. Since (*S*)-**2b** was used, the absolute configuration of the initially eluted diastereomer is expected to differ from that of the ureides derived from (*R*)-**2a**. Again, the magnitudes of the observed α's depend somewhat on the positions of the ring substituents as well as the substituents themselves. The magnitude of α seems directly related to the ability of these substituents to interact with the adsorbent surface. These interactions may be either bonding or repulsive and the elution order of the diastereomers will be influenced by the nature of these interactions.[5] For the presently studied lactams, these interactions are repulsive and the elution orders may be understood in terms of differences in the effective bulk of the substituents on either face of the lactam.

The arguments advanced to support the contention that these diastereomeric ureides extensively populate the conformation shown in **13** and that this type of confor-



13



14

mation determines the relative NMR and chromatographic behavior of the diastereomers are basically the same arguments as those advanced earlier for diastereomeric allophanates of the type shown in **14**.[3] The least adsorbed diastereomer is shown in both **13** and **14**.

The elution order of the diastereomers was related to their stereochemistry by retrieving the optically active lactams from the ureide diastereomers. For example, hydrolysis of initially eluted diastereomer **8a** afforded dextrorotatory 5-methyl-2-pyrrolidone, previously assigned the *R* configuration.[6] This configurational assignment, the one expected on the basis of the chromatographic and NMR arguments advanced, was further supported by comparison of observed and reported[6] CD spectra. The enantiomeric purity and absolute configuration of a number of 3-aryl lactams can be determined by HPLC on a previously reported chiral stationary phase.[7]

Use of the NMR chiral solvating agent (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol also allows one to adduce the absolute configuration of lactams such as 5-methyl-2-pyrrolidone.[8] Figure 2 shows the NMR spectra of (a) racemic 5-methyl-2-pyrrolidone and (b) 5-methyl-2-pyrrolidone enriched in the *S* enantiomer (obtained from the second eluted diastereomer of ureide 8). In solution, the major solvation interactions between (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol and 5-methyl-2-pyrrolidone are suggested to be hydrogen bonding between the alcohol hydroxy and the carbonyl oxygen of the lactam and interaction of the electron-deficient N–*H* with the anthryl π-system as shown in Figure 3. In solvation model **15a**, the methyl of (*S*)-5-methyl-2-pyrrolidone is held over the

(3) Pirkle, W. H.; Simmons, K. A. *J. Org. Chem.* **1983**, *48*, 2520.
(4) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, 42, 1839.

(5) If one of the lactam substituents were polar (e.g., cyano, carbethoxy), one would expect this substituent to bind to the silica. Hence, the diastereomer having this substituent most "exposed" would be expected to be the one most strongly retained by the column. In other words, "polar" and "small" substituents influence elution order in the same sense. Implicit here is the assumption that the polar substituent is not altering the conformational behavior of the ureide.
(6) (a) Urry, D. W. *J. Phys. Chem.* **1968**, *72*, 3035. (b) Cervinka, O.; Hub, L.; Snatzke, F.; Snatzke, G. *Collect. Czech. Chem. Commun.* **1973**, *38*, 897.
(7) Pirkle, W. H.; Finn, J. M.; Hamper, B. C.; Schreiner, J.; Pribish, J. "Asymmetric Reactions and Processes in Chemistry", Eliel, E. L., Otsuka, S., Ed.; American Chemical Society; Washington, DC, 1982, ACS Symp. Ser., No. 185, p 245.
(8) (a) Pirkle, W. H.; Sikkenga, D. L. *J. Org. Chem.* **1977**, *42*, 1370. (b) Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1982**, *13*, 263.

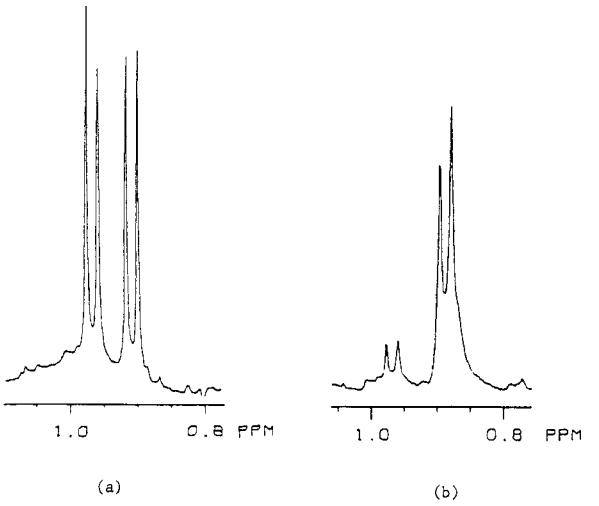
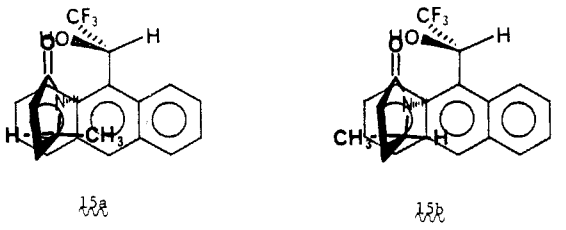


Figure 2. Proton NMR spectra (360-MHz, $CDCl_3$) of (a) racemic 5-methyl-2-pyrrolidone and (b) *S*-enriched 5-methyl-2-pyrrolidone (obtained from the second eluted diastereomer of ureide **8**) in the presence of a 5-fold excess of (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol.



15a **15b**

Figure 3. The diastereomeric solvation model proposed to account for the chemical shift nonequivalance of the enantiomers of 5-methyl-2-pyrrolidone in the presence of (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

center of the anthryl system where it is heavily shielded. However, in solvate **15b**, the methyl of the *R* enantiomer protrudes beyond the edge of the anthryl system and is relatively less shielded. Hence, the origin and sense of chemical shift nonequivalance is explained.

In conclusion, diastereomeric ureides show distinctive differences in their chromatographic and NMR properties which may be used to determine relative and, hence, absolute configurations of the lactam enantiomers. This, and the ease of chromatographic separability of the diastereomers, makes the present approach quite attractive for the resolution of lactams.

Experimental Section

Melting points were taken on a Büchi apparatus and are uncorrected. Proton NMR spectra were recorded on a Varian EM-390 or HR-220 spectrometer. IR spectra were recorded on a Beckman IR-12, Perkin-Elmer 137, or Perkin-Elmer 237B spectrophotometer. Routine mass spectra were obtained on a Varian MAT CH-5 spectrometer and high-resolution electron-impact mass spectra were obtained on a Varian Model 731 mass spectrometer. Optical rotations were determined on a Rudolf Autopol III at 589 nm. Preparative medium-pressure liquid chromatography was performed on Ventron silica gel (average particle size, 58 μm). Analytical high-pressure liquid chromatography was performed by using an Altex 100 pump, an Altex Model 210 injector, and Altex Model 253 dual wavelength (254 nm and 280 nm) detector, and a slurry-packed 5-μm Spherisorb silica gel 4.6 × 250 mm column. All lactams used in the reaction with isocyanates were prepared according to known procedures[9] or were available from prior studies.

(9) (a) Rosenmund, K. W.; Engels, P. *Arch. Pharm. (Weinheim, Ger.)* **1951**, *284*, 16. (b) Koelsch, C. F.; Stratton, C. H. *J. Am. Chem. Soc.* **1944**, *66*, 1883. (c) Widequist, S. *Ark. Kemi, Mineral. Geol.* **1948**, *26*, 1. (d) Sinnreich, J.; Elad, D. *Tetrahedron* **1968**, *24*, 4509.

Reaction of Aryl-2-pyrrolidones with (*R*)-(−)-1-(1-Naphthyl)ethyl Isocyanate. As a representative example, the synthesis of diastereomeric ureides **5ab** is described. A solution of racemic 5-phenyl-2-pyrrolidone (170 mg, 1.06 mmol) and (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (220 mg, 1.10 mmol) in 10 mL of dry benzene was heated to reflux for 24 h, cooled to room temperature, and concentrated under reduced pressure. The residue was dissolved in 5 mL of CH_2Cl_2 and filtered, and the mixture of diastereomers was subsequently chromatographically resolved (silica gel, 1:1 hexane:CH_2Cl_2). All diastereomeric ureides reported herein were isolated in ca. 90–95% yield.

***N*-[(*R*)-1-(1-Naphthyl)ethyl]-5-phenyl-2-pyrrolidone-1-carboxamide (5a).** This high-R_f diastereomer is a colorless solid: mp 125–126 °C (hexane–ethyl acetate); ^1H NMR ($CDCl_3$) δ 1.63 (d, 3 H, CH_3), 1.85–1.95 (m, 1 H, PhCHCH_xH_y), 2.40–2.61 (m, 2 H, C(O)CH_aH_b, PhCHCH_xH_y), 2.77–2.84 (m, 1 H, C(O)CH_aH_b), 5.38–5.41 (m, 1 H, PhCH), 5.79–5.86 (m, 1 H, NCH), 7.19–8.13 (m, 12 H, Ar H), 9.05 (d, 1 H, NH); IR (KBr) 3442, 3292, 1727 (CO), 1541, 1380, 1342, 1231, 801, 782 cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 358 (M^+, 15), 197 (12), 182 (40), 171 (14), 170 (100), 161 (10), 160 (11), 155 (18), 153 (17), 128 (11), 127 (18), 117 (15), 77 (11), 28 (16). Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.09; H, 6.15; N, 7.82. Found: C, 77.34; H, 6.02; N, 7.79.

***N*-[(*R*)-1-(1-Naphthyl)ethyl]-5-phenyl-2-pyrrolidone-1-carboxamide (5b).** This low-R_f diastereomer is a colorless viscous oil: ^1H NMR ($CDCl_3$) δ 1.68 (d, 3 H, $CHCH_3$), 1.72–1.78 (m, 2 H, PhCHCH_2), 2.35–2.59 (m, 2 H, C(O)CH_2), 5.43 (d of d, 1 H, PhCH), 5.69–5.86 (m, 1 H, NCH), 7.06–7.97 (m, 12 H, Ar H), 8.91 (d, 1 H, NH); IR (KBr) 3446, 3308, 1722 (CO), 1535, 1382, 1343, 1237, 803, 781 cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 358 (M^+, 22), 182 (26), 171 (13), 170 (100), 155 (11).

***N*-[(*R*)-1-(1-Naphthyl)ethyl]-4-phenyl-2-pyrrolidone-1-carboxamides (6ab).** This mixture is a colorless solid: mp 88–95 °C (hexane); ^1H NMR ($CDCl_3$) δ 1.66 (d, 3 H, $CH_{3a,b}$), 2.56–2.95 (m, 2 H, C(O)CH_2), 3.30–3.51 (m, 1 H, PhCH), 3.61–3.80 (m, 1 H, NCH_xH_y), 4.14–4.32 (m, 1 H, NCH_xH_y), 5.77–5.95 (m, 1 H, NCH), 7.00–8.11 (m, 12 H, Ar H), 8.85 (br d, 1 H, NH); IR (KBr) 3450, 3314, 1725 (CO), 1540, 1460, 1388, 1246, 1200, 803, 782, 718 cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 358 (M^+, 23), 343 (17), 197 (14), 182 (46), 171 (15), 170 (100), 155 (17), 153 (13), 128 (13), 104 (17), 91 (10). Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.09; H, 6.15; N, 7.82. Found: C, 77.28; H, 6.14; N, 7.56.

***N*-[(*R*)-1-(1-Naphthyl)ethyl]-3-phenyl-2-pyrrolidone-1-carboxamide (7a).** This high-R_f diastereomer is a colorless solid: mp 147–148 °C (hexane); ^1H NMR ($CDCl_3$) δ 1.63 (d, 3 H, CH_3), 1.98–2.19 (m, 1 H, PhCHCH_xH_y), 2.23–2.42 (m, 1 H, PhCHCH_xH_y), 3.55–3.77 (m, 2 H, NCH_2), 3.91–4.05 (m, 1 H, PhCH), 5.78–5.91 (m, 1 H, NHC*H*), 7.11–8.10 (m, 12 H, Ar H), 8.90 (d, 1 H, NH); IR (KBr) 3442, 3300, 1719 (CO), 1540, 1385, 1251, 1187, 805, 785 cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 358 (M^+, 18), 343 (12), 182 (34), 171 (14), 170 (100), 155 (24), 153 (18), 127 (17), 91 (20), 57 (29), 43 (71). Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.09; H, 6.15; N, 7.82. Found: C, 76.89; H, 6.04; N, 7.46.

***N*-[(*R*)-1-(1-Naphthyl)ethyl]-3-phenyl-2-pyrrolidone-1-carboxamide (7b).** This low-R_f diastereomer is a colorless oil: ^1H NMR ($CDCl_3$) δ 1.65 (d, 3 H, CH_3), 2.02–2.24 (m, 1 H, PhCHCH_xH_y), 2.34–2.50 (m, 1 H, PhCHCH_xH_y), 3.66–3.84 (m, 2 H, NCH_2), 3.93–4.07 (m, 1 H, PhCH), 5.79–5.94 (overlapping quartets, 1 H, NCH), 7.11–8.11 (m, 12 H, Ar H), 8.89 (d, 1 H, NH); IR (KBr) 3442, 3316, 1725 (CO), 1539, 1385, 1250, 1188, 805, 782 cm^{-1}; mass spectrum (10 eV), *m/e* (relative intensity) 358 (M^+, 38), 343 (22), 270 (20), 197 (29), 182 (14), 171 (14), 170 (100), 163 (21), 161 (12), 118 (12), 107 (49). Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.09; H, 6.15; N, 7.82. Found: C, 76.84; H, 6.38; N, 7.46.

***N*-[(*R*)-1-(1-Naphthyl)ethyl]-5-(4-methylphenyl)-2-pyrrolidone-1-carboxamide (4a).** This high-R_f diastereomer is a colorless solid: mp 118–120 °C (hexane); ^1H NMR ($CDCl_3$) δ 1.60 (d, 3 H, CH_3), 1.80–2.89 (m, 4 H, ArCH(CH_2)$_2$), 2.32 (s, 3 H, $ArCH_3$), 5.25–5.36 (m, 1 H, ArCH), 5.70–5.84 (m, 1 H, NCH), 6.95–8.11 (m, 11 H, Ar H), 9.00 (d, 1 H, NH); IR (KBr) 3450, 3319, 1722 (CO), 1522, 1380, 1339, 1237, 802, 780 cm^{-1}; mass spectrum (10 eV), *m/e* (relative intensity) 372 (M^+, 22), 197 (10), 177 (27), 174 (12), 171 (15), 170 (100), 155 (15), 154 (10).

***N*-[(*R*)-1-(1-Naphthyl)ethyl]-5-(4-fluorophenyl)-2-pyrrolidone-1-carboxamide (3a).** This high-R_f diastereomer

is a colorless solid: mp 129.5–131 °C (hexane–benzene); ^{1}H NMR ($CDCl_3$) δ 1.62 (d, 3 H, CH_3), 1.74–2.89 (m, 4 H, $C(O)(CH_2)_2$), 5.17–5.38 (m, 1 H, ArCH), 5.63–5.88 (overlapping quartets, 1 H, NCH), 6.82–8.18 (m, 11 H, Ar H), 9.02 (d, 1 H, NH); IR (KBr) 3308, 1733 (CO), 1540, 1378, 1334, 1235, 846, 781 cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 376 (M^+, 14), 197 (22), 182 (69), 178 (13), 171 (14), 170 (100), 155 (25), 153 (16), 135 (17), 128 (17), 127 (22), 77 (11), 28 (19). Anal. Calcd for $C_{23}H_{21}FN_2O_2$: C, 73.40; H, 5.59; F, 5.05; N, 7.45. Found: C, 73.80; H, 5.63; N, 7.07; F, 4.93.

***N*-[(*R*)-1-(1-Naphthyl)ethyl]-5-(4-fluorophenyl)-2-pyrrolidone-1-carboxamide (3b).** This low-R_f diastereomer is a viscous oil: ^{1}H NMR ($CDCl_3$) δ 1.68 (d, 3 H, CH_3), 1.94–2.70 (m, 4 H, $C(O)(CH_2)_2$), 5.30–5.48 (m, 1 H, ArCH), 5.65–5.88 (overlapping quartets, 1 H, NCH), 6.80–8.04 (m, 11 H, Ar H), 8.88 (d, 1 H, NH); IR (KBr) 3310, 1720 (CO), 1535, 1338, 1234, 1162, 782 cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 376 (M^+, 1), 220 (16), 206 (27), 182 (35), 137 (28), 121 (69), 119 (80), 117 (100), 107 (27), 91 (66), 82 (20), 77 (27), 65 (26).

5-(4-Fluorophenyl)-2-pyrrolidone. This lactam was prepared by the same procedure used for the synthesis of 5-phenyl-2-pyrrolidone[9a] and was obtained as a faintly yellow solid: mp 134–135 °C (benzene); ^{1}H NMR ($CDCl_3$) δ 1.76–2.73 (m, 4 H, $(CH_2)_2$), 4.60–4.80 (m, 1 H, ArCH), 6.89–7.42 (m, 4 H, Ar H); IR (CCl_4) 3176 (NH), 1695 (CO), 1510, 1340, 1278, 1221, 1160, 1088, 1018 cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 179 (M^+, 100), 178 (67), 159 (38), 135 (40), 124 (71), 122 (58), 95 (20), 84 (20), 55 (29). Anal. Calcd for $C_{10}H_{10}FNO$: C, 67.04; H, 5.59; F, 10.61; N, 7.82. Found: C, 67.33; H, 5.48; F, 10.30; N, 7.47.

***N*-[(*S*)-1-Phenylethyl]-5-methyl-2-pyrrolidone-1-carboxamide (8a).** This high-R_f diastereomer is a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.35 (d, 3 H), 1.52 (d, 3 H), 1.60–1.72 (m, 1 H), 2.06–2.25 (m, 1 H), 2.41–2.54 (m, 1 H), 2.65–2.82 (m, 1 H), 4.35–4.49 (m, 1 H), 4.96–5.09 (m, 1 H), 7.22–7.34 (m, 5 H), 8.87 (d, 1 H); IR (neat) 3250, 1930, 1705, 1520, 1370, 1230, 768, 700 cm^{-1}; high-resolution mass spectrum, calcd for $C_{14}H_{18}N_2O_2$ 246.1368, found 246.1386.

***N*-[(*S*)-1-Phenylethyl]-5-methyl-2-pyrrolidone-1-carboxamide (8b).** This low-R_f diastereomer is a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.30 (d, 3 H) 1.51 (d, 3 H), 1.58–1.69 (m, 1 H), 2.13–2.27 (m, 1 H), 2.41–2.55 (m, 1 H), 2.63–2.80 (m, 1 H) 4.43–4.53 (m, 1 H), 4.99–5.12 (m, 1 H), 7.21–7.34 (m, 5 H), 8.88 (d, 1 H); IR (neat) 3250, 1930, 1700, 1530, 1370, 1230, 766, 698 cm^{-1}; high-resolution mass spectrum, calcd for $C_{14}H_{18}N_2O_2$ 246.1368, found 246.1386.

***N*-[(*S*)-1-Phenylethyl]-5-phenyl-2-pyrrolidone-1-carboxamide (9a).** This high-R_f diastereomer is a colorless solid: mp 97–100 °C; ^{1}H NMR ($CDCl_3$) δ 1.52 (d, 3 H) 1.87–1.96 (m, 1 H), 2.44–2.79 (m, 3 H), 4.95–5.08 (m, 1 H), 5.43–5.46 (m, 1 H) 7.11–7.32 (m, 10 H), 8.91 (d, 1 H); IR (Nujol) 3230, 1705, 1680, 1510, 1230, 759, 704 cm^{-1}; high-resolution mass spectrum, calcd for $C_{19}H_{20}N_2O_2$ 308.1525, found 308.1534.

***N*-[(*S*)-1-Phenylethyl]-5-phenyl-2-pyrrolidone-1-carboxamide (9b).** This low-R_f diastereomer is a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.52 (d, 3 H), 1.86–1.99 (m, 1 H), 2.40–2.81 (m, 3 H), 4.95–5.08 (m, 1 H), 5.43–5.47 (m, 1 H), 7.11–7.31 (m, 10 H), 8.91 (d, 1 H); IR (neat) 3240, 2990, 2930, 1720, 1700, 1525, 1225, 764, 700 cm^{-1}; high-resolution mass spectrum, calcd for $C_{19}H_{20}N_2O_2$ 308.1525, found 308.1531.

***N*-[(*S*)-1-Phenylethyl]-5-hexyl-2-pyrrolidone-1-carboxamide (10a).** This high-R_f diastereomer is a pale yellow liquid: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H), 1.22–1.62 (m, 9 H), 1.52 (d, 3 H), 1.79–1.94 (m, 2 H), 2.00–2.16 (m, 1 H), 2.41–2.54 (m, 1 H), 2.62–2.79 (m, 1 H), 4.23–4.31 (m, 1 H), 4.96–5.08 (m, 1 H), 7.14–7.34 (m, 5 H), 8.90 (d, 1 H); IR (neat) 3290, 2910, 1720, 1520, 1230, 762 700 cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 316 (M^+, 0.1), 301 (0.2), 248 (22), 233 (3), 205 (10), 120 (12), 105 (30), 86 (100), 84 (80), 77 (8), 58 (32), 43 (44), 31 (60), 29 (26).

***N*-[(*S*)-1-Phenylethyl]-5-hexyl-2-pyrrolidone-1-carboxamide (10b).** This low-R_f diastereomer is a pale yellow liquid: ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H), 1.23–1.60 (m, 9 H), 1.51 (d, 3 H), 1.76–1.85 (m, 2 H), 2.05–2.20 (m, 1 H), 2.42–2.56 (m, 1 H), 2.61–2.74 (m, 1 H), 4.27–4.36 (m, 1 H), 4.98–5.11 (m, 1 H), 7.16–7.35 (m, 5 H), 8.89 (d, 1 H); IR (neat) 3290, 2920, 1720, 1540, 1235, 767, 700 cm^{-1}; high-resolution mass spectrum, calcd for $C_{19}H_{28}N_2O_2$ 316.2151, found 316.2158.

***N*-[(*S*)-1-Phenylethyl]-3-hexyl-2-pyrrolidone-1-carboxamide (11a).** This high-R_f diastereomer is a pale yellow liquid: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3 H), 1.27–1.60 (m, 9 H), 1.52 (d, 3 H), 1.60–1.73 (m, 1 H), 1.82–1.91 (m, 1 H), 2.11–2.26 (m, 1 H), 2.55–2.64 (m, 1 H), 3.55–3.66 (m, 1 H), 3.85–3.95 (m, 1 H), 4.98–5.11 (m, 1 H), 7.24–7.34 (m, 5 H), 8.86 (d, 1 H); IR (neat) 3250, 2900, 1720, 1540, 1250, 766, 700 cm^{-1}; high-resolution mass spectrum, calcd for $C_{19}H_{28}N_2O_2$ 316.2151, found 316.2157.

***N*-[(*S*)-1-Phenylethyl]-3-hexyl-2-pyrrolidone-1-carboxamide (11b).** This low-R_f diastereomer is a pale yellow liquid: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H), 1.28–1.60 (m, 9 H), 1.52 (d, 3 H), 1.60–1.70 (m, 1 H), 1.80–1.90 (m, 1 H), 2.14–2.25 (m, 1 H), 2.55–2.67 (m, 1 H), 3.56–3.69 (m, 1 H), 3.82–3.93 (m, 1 H), 4.97–5.10 (m, 1 H), 7.24–7.35 (m, 5 H), 8.85 (d, 1 H); IR (neat) 3250, 2890, 1720, 1535, 1250, 765, 700 cm^{-1}; high-resolution mass spectrum, calcd for $C_{19}H_{28}N_2O_2$ 316.2151, found 316.2151.

***N*-[(*S*)-1-Phenylethyl]-6-pentyl-2-piperidone-1-carboxamide (12a).** This high-R_f diastereomer is a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H), 1.29 (br s, 6 H), 1.51 (d, 3 H), 1.61–1.79 (m, 4 H), 1.86–1.94 (m, 2 H), 2.49–2.57 (m, 2 H), 4.60–4.66 (m, 1 H), 4.94–5.07 (m, 1 H), 7.23–7.39 (m, 5 H), 9.94 (d, 1 H); IR (neat) 3190, 2890, 1690, 1680, 1510, 1390, 1180, 765, 700 cm^{-1}; high-resolution mass spectrum calcd for $C_{19}H_{28}N_2O_2$ 316.2151, found 316.2160.

***N*-[(*S*)-1-Phenylethyl]-6-pentyl-2-piperidone-1-carboxamide (12b).** This low-R_f diastereomer is a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3 H), 1.24 (br s, 6 H), 1.50 (d, 3 H), 1.57–1.67 (m, 2 H), 1.71–1.82 (m, 2 H), 1.86–1.96 (m, 2 H), 2.51–2.57 (m, 2 H), 4.64–4.68 (m, 1 H), 4.96–5.09 (m, 1 H), 7.24–7.34 (m, 5 H), 9.92 (d, 1 H); IR (neat) 3220, 2910, 1705, 1690, 1510, 1182, 767, 702 cm^{-1}; high-resolution mass spectrum, calcd for $C_{19}H_{28}N_2O_2$ 316.2151, found 316.2155.

Ureide Hydrolysis. The hydrolysis of *N*-[(*R*)-1-(1-naphthyl)ethyl]-5-(4-fluorophenyl)-2-pyrrolidone-1-carboxamide (**3a**) is described. A solution of diastereomerically pure (^{1}H NMR) **3a** (4.25 g, 11.3 mmol) and sodium methoxide (2.16 g, 40 mmol) in 300 mL of THF was refluxed for 48 h and subsequently allowed to cool to room temperature. A saturated solution of NH_4Cl (100 mL) and 3 N HCl (100 mL) were successively added, and the organic phase was subsequently separated, washed with brine, and dried ($MgSO_4$). After filtration and concentration, the residue was chromatographed on silica gel with EtOAc as the mobile phase. The desired lactam was collected as the low-R_f fraction and, after recrystallization, 1.02 g (50%) of the enantiomerically and analytically pure 2-pyrrolidone was obtained: $[\alpha]^{22}_D$ 48.8° (*c* 4.35, CH_2Cl_2) for the high-R_f lactam; $[\alpha]^{22}_D$ −49.1° (*c* 2.27, CH_2Cl_2) for the low-R_f lactam.

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Registry No. **2a**, 42340-98-7; **2b**, 14649-03-7; (±)-**3** (lactam), 90432-58-9; **3a**, 90432-63-6; **3b**, 90432-64-7; (±)-**4** (lactam), 90432-59-0; **4a**, 90432-65-8; **4b**, 90432-66-9; (±)-**5** (lactam), 56523-57-0; **5a**, 90432-67-0; **5b**, 90432-68-1; (±)-**6** (lactam), 61548-72-9; **6a**, 90432-69-2; **6b**, 90432-70-5; (±)-**7** (lactam), 78772-72-2; **7a**, 90432-71-6; **7b**, 90432-72-7; (±)-**8** (lactam), 62182-32-5; **8a**, 90432-73-8; **8b**, 90432-74-9; **9a**, 90432-75-0; **9b**, 90460-02-9; (±)-**10** (lactam), 90432-60-3; **10a**, 90432-76-1; **10b**, 90432-77-2; (±)-**11** (lactam), 90432-61-4; **11a**, 90432-78-3; **11b**, 90432-79-4; (±)-**12** (lactam), 90432-62-5; **12a**, 90432-80-7; **12b**, 90432-81-8.