Isothiocyanate-Substituted κ-Selective Opioid Receptor Ligands Derived from *N*-Methyl-*N*-[(1*S*)-1-phenyl-2-(1-pyrrolidinyl)ethyl]phenylacetamide

S. Ananda Weerawarna, Ronda D. Davis, and Wendel L. Nelson*

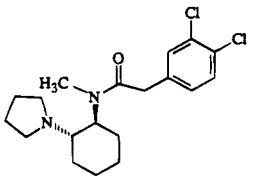
Department of Medicinal Chemistry, School of Pharmacy, University of Washington, Seattle, Washington 98195

Received May 18, 1994®

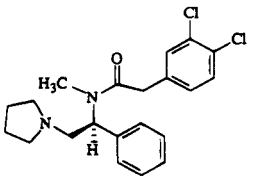
The synthesis of isothiocyanate-substituted κ-selective opioid ligands derived from *N*-methyl-*N*-[(1*S*)-1-phenyl-2-(1-pyrrolidinyl)ethyl]ethyl]phenylacetamide (**8**) and their effects in radioligand displacement assays are reported. Ligands **3**–**5** with the *S*-absolute configuration were prepared with the isothiocyanate functionality at the 2-, 3-, and 4-positions in the phenylacetamide aromatic ring. The 2-isothiocyanato-4,5-dichlorophenylacetamide **6** was prepared to evaluate the effect of 4,5-dichloro substitution in the same aromatic ring as the 2-isothiocyanate function. *N*-Methyl-*N*-[(1*S*)-1-(4-isothiocyanatophenyl)-2-(1-pyrrolidinyl)ethyl]-3,4-dichlorophenylacetamide (**7**), with the 4-isothiocyanate function in the 1-phenyl ring, was prepared for comparison with the other compounds in the series. Of the prepared ligands, **7** and **8** (IC_{50}s ≃ 1.4–1.8 nM) were approximately equal in affinity with **2** (ICI-199,441), followed by **3** and **6**. All of these compounds were more κ-selective than **2**, as well. The binding characteristics of **8** show that the previously reported 4,5-dichloro substitution is not required for high affinity and κ-selectivity. All of the synthesized isothiocyanate-substituted ligands irreversibly inhibited radioligand binding to guinea pig brain membrane preparations, including compound **2** (ICI-199,441) which had no isothiocyanate functionality.

Pharmacological studies have shown the existence of three major opioid receptor types, namely, μ, δ, and κ, in the central and peripheral nervous system of many species.[1–6] During the past decade, evidence has been accumulated, indicating that highly selective κ-opioid agonists may provide useful analgesics free from the abuse potential and the adverse side effects of μ-agonists like morphine.[7,8] Several pharmaceutical research groups have discovered highly selective enantiospecific amino amide κ-agonist analgesics[9–13] based on the structural prototype U-50,488 (**1**).

Highly selective electrophilic affinity ligands are valuable probes in the characterization of opioid receptors.[14–16] The objective of this work was to prepare single enantiomers of electrophilic opioid ligands, which contain structural features of κ-agonist **2** (ICI-199,441), as potential affinity probes to aid in the characterization of the κ-opioid receptor(s). In this series of compounds, the *S*-enantiomers show extremely high selectivity (*S*/*R* ratios > 100) at κ-receptors.[10,17] The isothiocyanate functionality is a useful electrophilic functionality to be incorporated into affinity ligands, since it has low reactivity toward water and significant reactivity toward amino and thiol groups. In this paper, we report a series of compounds in which the electrophilic isothiocyanate group is introduced at different positions in affinity ligands related to **2**.

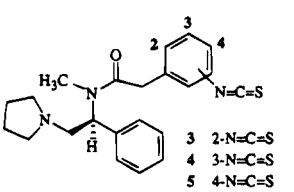


1 (S,S-enantiomer of U-50,488)

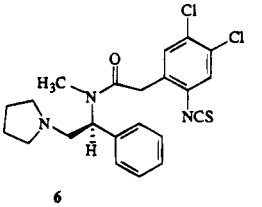


2 (ICI-199,441)

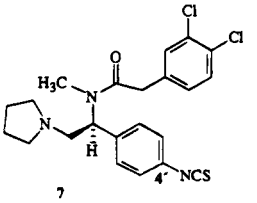
Ligands **3**–**5**, each with the *S*-absolute configuration, were prepared with the isothiocyanate function in the available 2-, 3-, and 4-positions in the phenylacetamide aromatic ring. Because the presence of two chlorine atoms in this aromatic ring in **2** has been considered important for high affinity and κ-selectivity,[10,17] more closely related analogs **6** and **7** were also prepared. Analog **7** was prepared *via* a new synthetic route to the intermediate diamines. Compound **8**, without either the isothiocyanate or chlorine substituents, was prepared for comparison.



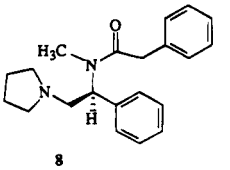
3 2-N=C=S
4 3-N=C=S
5 4-N=C=S



6



7



8

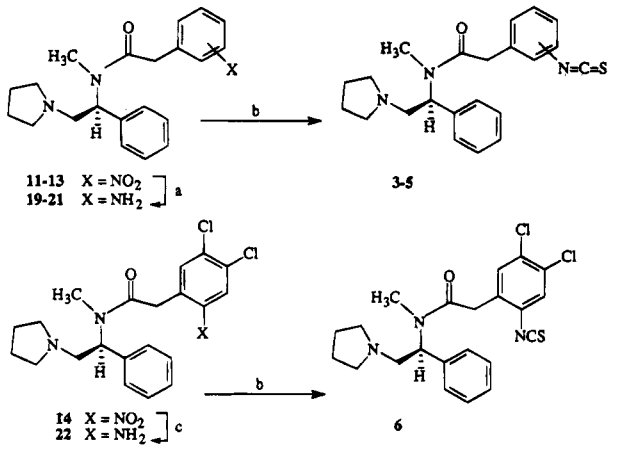
Chemistry. Compound **2** was obtained by DCC coupling of 3,4-dichlorophenylacetic acid (**9**) with (1*S*)-*N*-methyl-2-pyrrolidino-1-phenethylamine (**10**), the diamine having been prepared from (*S*)-phenylglycine as described in the literature.[10,17] The optical purity of the hydrochloride salt of **2** was >94% ee, based on its reported optical rotation.[10,17]

Compounds **3**–**5** were prepared *via* the isomeric nitrophenylacetamides **11**–**13** (Scheme 1). The nitro-substituted phenylacetamides **11**–**14** were prepared by DCC coupling of the isomeric nitrophenylacetic acids

® Abstract published in *Advance ACS Abstracts*, August 1, 1994.

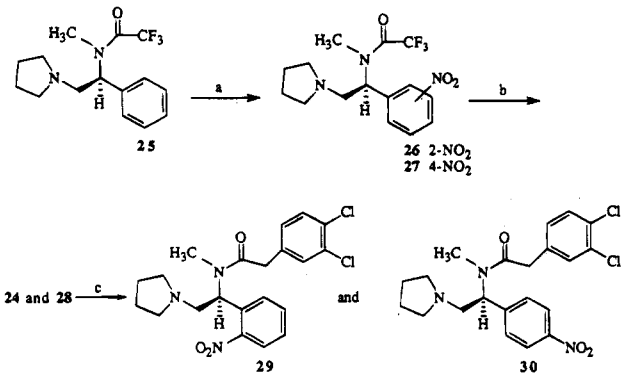
0022-2623/94/1837-2856$04.50/0

Scheme 1[a]



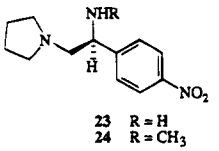
[a] Reagents: (a) H_2 (45 psi) Pd–C, MeOH, aqueous HCl; (b) di-2-pyridyl thionocarbonate; (c) H_2, PtO_2, MeOH, aqueous HCl.

Scheme 2[a]



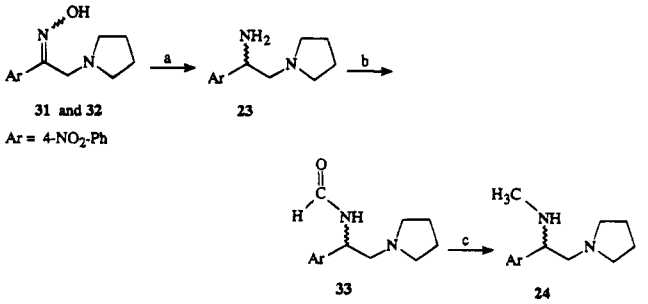
[a] Reagents: (a) concentrated $H_2SO_4/NaNO_3$; (b) hydrolysis; (c) 3,4-dichlorophenylacetyl chloride.

15–18 with the *S*-diamine **10**. Each of the three isomeric nitro-substituted aromatic amides **11–13** was reduced catalytically (Pd–C) to obtain the isomeric aromatic primary amines **19–21**. The 2-nitro-4,5-dichlorophenyl-substituted analog **14** was reduced catalytically (PtO_2) to obtain amine **22**. The corresponding electrophilic isothiocyanates **3–6** were prepared by treating the aromatic primary amines with di-2-pyridyl thionocarbonate.[18] The resulting ligands, **3** and **4**, were purified by flash column chromatography on silica gel. Two of the analogs (**5** and **6**) were unstable on silica gel and were purified by crystallization.



The synthesis of the corresponding (*S*)-4′-nitrophenyl diamine *S*-**23** and its *N*-methyl analog, *S*-**24**, was not possible *via* the synthetic route described for the preparation of **10**, due to the inaccessibility of the *S*-enantiomer of (4-nitropyhenyl)glycine. We first attempted to prepare these amines by nitration of trifluoroacetamide **25** (Scheme 2). Nitration of **25** using concentrated sulfuric acid and sodium nitrate gave a (3:1) mixture of 4′- and 2′-nitration products in moderate yield, which we were unable to separate chromatographically. Hydrolysis of the mixture of trifluoroacetamides gave the

Scheme 3[a]



[a] Reagents: (a) BH_3·THF, aqueous HCl (0 °C), then aqueous NaOH (0 °C); (b) EtOCHO; (c) BH_3·DMS/THF, aqueous HCl (0 °C), then aqueous NaOH (0 °C).

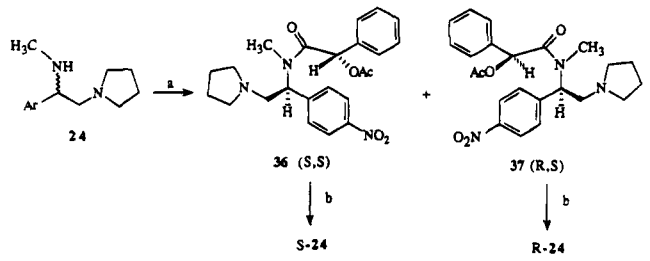
mixture of regioisomeric nitro-substituted amines *S*-**24** (4′-NO_2) and *S*-**28** (2′-NO_2), which also proved inseparable. The isomeric 3,4-dichlorophenylacetamides **29** (2′-NO_2) and **30** (4′-NO_2) were also exceedingly difficult to separate. Only a small amount of each isomer was isolated. This method was not pursued further due to the considerable difficulties in separation of the regioisomers.

Lacking the ability to reach enantiomers of **23** and/or **24** directly, we sought to obtain them as racemates and then to resolve them. The racemic 4-nitrophenyl diamines **23** and **24** were obtained from α-pyrrolidinoacetophenone oximes **31** and **32** by diborane reduction[19] followed by N-methylation through the corresponding formamide **33** and subsequent diborane–dimethyl sulfide reduction[20] (Scheme 3). Enantioselective reduction of related oxime ethers was unsuccessful,[21–24] thus requiring us to resort to resolution procedures. Preparation of diastereomeric salts of the diamines **23** and **24** with several standard optically pure acids was unsuccessful, as no crystalline salts were obtained. Formation of diastereomeric amides which could be separated and subsequently hydrolyzed was successful, however.

After thoroughly investigating many different conditions for formation and separation of a variety of diastereomeric amides, the following conditions were adopted for separation of amides formed from (*S*)-(+)-α-acetoxyphenylacetyl chloride (**34**). Similar amides have been previously separated successfully.[25–31] Formation of *S*-acid chloride **34** was accomplished from the corresponding *S*-acid **35** using oxalyl chloride in benzene or with 2 M oxalyl chloride in methylene chloride. This process occurred in 95–100% ee, as determined from the ^{1}H-NMR spectrum of amides formed for (*S*)-α-methylbenzylamine.[32] Acylation of **24** was best performed with **34** at 5 °C in methylene chloride. Although the acylation process is slow under these conditions, low-temperature conditions are required to prevent racemization of the acylating reagent through a probable ketene intermediate.[33,34] Amides **36** and **37** were successfully separated by column chromatography on neutral alumina, and subsequent hydrolysis afforded *S*-**24** (and *R*-**24**) in 94% ee.

Enantiomers of **24** were treated with DCC-activated 3,4-dichlorophenylacetic acid (**9**) to obtain the amino amides *S*-**30** and *R*-**30**. The circular dichroism (CD) spectra of *S*-**30** and *R*-**30** showed opposite Cotton effects (Figure 1). The CD spectrum of a small sample of *S*-**30** prepared by nitration of a partially racemized pyrrolidinyl amide of (*S*)-phenylglycine (Scheme 2) was also

Scheme 4[a]



[a] Reagents: (a) *S*-**34**; (b) acid hydrolysis.

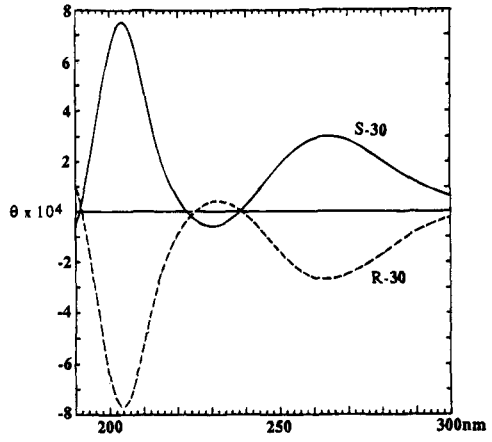
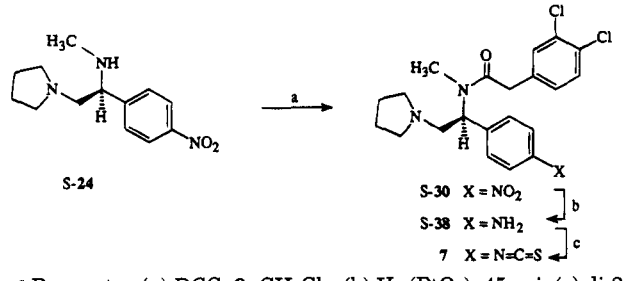


Figure 1. CD spectra of *S*-**30**·HCl and *R*-**30**·HCl in CH_3OH.

Scheme 5[a]



[a] Reagents: (a) DCC, **9**, CH_2Cl_2; (b) H_2 (PtO_2), 45 psi; (c) di-2-pyridyl thionocarbonate.

obtained for comparison. Although its CD spectrum was of diminished intensity, it gave Cotton effects identical in location and sign to that of *S*-**30** prepared from the *S*-diamine **24** which was obtained from the first eluted diastereomeric amide, **36**. These results allowed establishment of the absolute configuration of the first eluted diastereomer, **36**, to be *S*,*S* and the diamine obtained by its hydrolysis to be *S*-**24**.

Selective catalytic hydrogenation of the nitro group in amino amide *S*-**30** in acidified aqueous methanol gave the *S*-diamine **38**. Finally, the *S*-isothiocyanate **7** was prepared from the *S*-enantiomer of **38** using the thiocarbonyl transfer agent di-2-pyridyl thionocarbonate.

Biological Testing. Opioid κ-, μ-, and δ-receptor affinities for the five analogs were determined by displacement of [^{3}H]U-69,593, [^{3}H]DAMGO, and [^{3}H]-DPDPE, respectively, using a guinea pig brain membrane preparation,[35-38] and the results indicate that **7** is the most κ-selective electrophilic ligand followed by **3** and **6**. The ligands **7** and **3** and unsubstituted ligand **8** are more κ-selective than the standard **2** (ICI-199,-441). The results are in Table 1. Most had high affinity at κ-sites, with IC_{50} values in the 1−3 nM range, except the 4′-isothiocyanate **5** and the 2-isothiocyanate **6** which had lower affinities, $IC_{50} \simeq 10-15$ nM. The most κ-selective ligands among the group were **7** and **8**. Compound **7**, which was more κ-selective than **2** (ICI-199,441), showed selectivity of about 500-fold of $\kappa > \delta$ or μ. Compound **8**, with no chlorines in the arylacetamide aromatic ring, had similar affinity as **2** and had even greater selectivity than **7**, showing IC_{50} ratios of κ to δ and μ >700. The 4′-isothiocyanate **5** exhibited the lowest κ-selectivity, and the 3-isothiocyanate showed some δ-receptor affinity. The results with compound **8** indicate chlorine substituents are not required for high affinity and κ-selectivity as previously reported.[10,17] None of the new ligands had significant affinity at μ-receptors.

In the irreversibility assay,[36-38] all the ligands with isothiocyanate functionalities irreversibly inhibit [^{3}H]-U69,593 binding in guinea pig brain membrane receptors. Irreversible inhibition of radioligand binding increased with increasing concentrations of the isothiocyanate ligands **3**−**7**, as noted in the washed samples. These results suggested that the irreversible effects are associated with receptor-related processes. Surprisingly however, **2** (ICI-199,441) which has no isothiocyanate function also displayed irreversible binding characteristics. Ligand **8**, which has no chlorines in the phenylacetamide rings (and no isothiocyanate in either ring), displayed reversible binding characteristics [^{3}H]U69,-593-binding affinity returned to control values after extensive washing (Table 2).

It appears that the additional lipophilicity resulting from the presence of the chlorines might contribute to the continued inhibition of radioligand binding after washing, under the conditions of the experiments. Thus, some of the observed irreversible affinity of isothiocyanate ligands **6** and **7** may not be due to covalent interaction with cellular nucleophiles but instead may result from slow removal in the washing process. We are unable, on the basis of these experiments, to examine these processes independently. We are also perplexed with the low level of protection that occurred with naloxone under these conditions.

Clearly substitution in both rings can provide ligands with high affinity for κ-receptors; however, their interaction with the receptors appears to be very complex. Wash-resistant binding has been previously observed for **1** (U-50,488) at high concentrations.[39] In related work, deCosta et al. noted that structurally similar isothiocyanates related to **1** (U-50,488) also behaved differently in vitro and in vivo.[40,41] As more information becomes available about the sequence and structures of κ-opioid receptors,[42-44] additional experiments will be possible to examine the processes of ligand receptor interaction, irreversibility, and protection in greater detail.

After this work had been submitted, preparation of the regioisomeric 3′-isothiocyanato analog of **7** was reported.[45] It produced κ-antagonism of long duration in the mouse tail-flick assay and showed high affinity at κ-receptors in the radioligand displacement assay.

Experimental Section

High-field ^{1}H-NMR spectra were recorded on a Varian 300 MHz spectrometer. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. Signals from minor conformers are indicated with asterisks. ^{13}C-NMR spectra were obtained at 75.5 MHz. IR spectra were recorded as a liquid film on sodium chloride plates or in KBr with a

Table 1. Comparison of Opioid Receptor Binding against Radiolabeled Ligands in the Guinea Pig Brain Membrane Preparation[35-38,a]

compound	IC_{50} values (nM) total sites [^{3}H]bremazocine	μ-sites [^{3}H]DAMGO[b]	δ-sites [^{3}H]DPDPE[c]	κ-sites [^{3}H]U-69,593[d]
2 (4,5-dichloro) (ICI-199,441)	11	150	600	1.5
3 2-NCS (no chlorines)	58	≫1000	1060	2.3
4 3-NCS (no chlorines)	54	5100	144	3.3
5 4-NCS (no chlorines)	53	730	150	14
6 2-NCS (4,5-dichloro)	54	1250	1700	9.5
7 4′-NCS (4,5-dichloro)	430	≫1000	≫1000	1.8
8 no NCS (no chlorines)	63	≫1000	≫1000	1.4
standards				
DSLET	1040	73	1.3	600
DPDPE	>1000	>1000	1.8	>1000
U-69,593	140	1760	5000	2.1

[a] Values were obtained by probit transformation and linear regression of duplicate determinations (±10−15%) at nine concentrations (1.0−1000 nM) of displacing ligand. For compound **2**, the IC_{50} in the assay at κ-sites was obtained from triplicate determinations at five concentrations (0.22−4.7 nM). [b] [^{3}H]DAMGO or [^{3}H][D-Ala^2,MePhe^4,Gly-ol^5]enkephalin (1 nM). [c] [^{3}H]DPDPE or [^{3}H][D-Pen^2, D-Pen^5]enkephalin (1 nM). [d] [^{3}H]U-69,593 or [^{3}H]-5α,7α,8β-(−)-*N*-methyl-*N*-(1-pyrrolidinyl-1-oxaspiro[4.5]dec-8-yl)benzeneacetamide (1 nM).

Table 2. Irreversibility of κ-Opioid Receptor Binding and Protection by Naloxone[36-38,a]

compound	conc (nM)	percent specific binding[b] (%) unwashed	washed	protected
2 (4,5-dichloro) (ICI-199,441)	4.7	25	20	39
3 2-NCS (no chlorines)	2.5	74	78	87
	5	62	65	88
	10	49	57	80
4 3-NCS (no chlorines)	5	51	62	79
	10	43	45	61
	20	24	38	50
5 4-NCS (no chlorines)	20	59	53	61
	40	28	34	35
	60	27	21	27
6 2-NCS (4,5-dichloro)	10	54	46	79
	25	20	21	37
	50	11	12	34
7 4′-NCS (4,5-dichloro)	5	76	70	86
	25	46	50	56
	50	11	15	27
8 no NCS (no chlorines)	10	11	89	91

[a] The values for **2** (ICI-199,441) are averages of six separate assays (±10−20%). Results from the other ligands are the averages of triplicate determinations (±5−10%) in a single assay. Protection was by preincubation with 1 μM naloxone. [b] [^{3}H]U-69,593 (1 nM).

Perkin-Elmer 1600 Series FTIR. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Optical rotation measurements were determined on a JASCO DIP-4 digital polarimeter. Circular dichroism spectra were recorded on a JASCO 720 spectropolarimeter equipped with a Genesis Systems computer and a Hewlett-Packard 7475A plotter. Flash column chromatography was performed using Merck silica gel 60 (230−400 mesh). Microanalyses were performed by Desert Analytics, Tucson, AZ. Where indicated by the symbols of the elements, analyses were within ±0.4% of theoretical values.

***N*-Methyl-*N*-[(1*S*)-1-phenyl-2-(1-pyrrolidinyl)ethyl]-2-nitrophenylacetamide (11).** *N,N*-Dicyclohexylcarbodiimide (0.50 g, 2.4 mmol) was added to a stirred solution of 2-nitrophenylacetic acid (**15**) (0.31 g, 1.7 mmol) and dry pyridine (0.20 g, 2.5 mmol) in anhydrous methylene chloride (20 mL) at 25 °C. After the solution was stirred for 2 min, *S*-**10** (0.25 g, 1.2 mmol) in anhydrous methylene chloride (10 mL) was added and the mixture stirred for 12 h under an atmosphere of argon. The precipitated *N,N*-dicyclohexylurea was removed by filtration and washed with methylene chloride (5 mL). The filtrate was then evaporated, and the residue was subjected to silica gel flash column chromatography eluting first with ethyl acetate to remove *N,N*-dicyclohexylurea and other fast eluting byproducts and then with ethyl acetate:triethylamine (9:1) to give a pale brown solid. The product was crystallized from ether:hexane to give 0.35 g (78%) of **11** as a cream-colored solid: mp 109−111 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (d, *J* = 8.7 Hz, 1H, O_2NAr), 7.53 (d, *J* = 7.3 Hz, 1H, O_2NAr), 7.35 (m, 7H, Ar and O_2NAr), 6.05 (dd, *J* = 10.0, 6.0 Hz, 1H, ArCH), 5.20* (m, 1H, ArCH), 4.28* (s, 2H, O_2NArCH_2), 4.11 (d, *J* = 16.8 Hz, 1H, O_2NArCH_2), 4.06 (d, *J* = 16.8 Hz, 1H, O_2NArCH_2), 3.12 (dd, *J* = 13.7, 10.0 Hz, 1H, ArCHC*H*$_2$), 2.82 (s, 3H, NMe), 2.80 (dd, *J* = 13.7, 6.0 Hz, 1H, ArCHC*H*$_2$), 2.76* (s, 3H, NCH_3), 2.67 (m, 2H, pyrrolidine-NCH_2), 2.51 (m, 2H, pyrrolidine-NCH_2), 1.76 (m, 4H, pyrrolidine-CCH_2); FABMS [MH^+] 368.

***N*-Methyl-*N*-[(1*S*)-1-phenyl-2-(1-pyrrolidinyl)ethyl]-3-nitrophenylacetamide (12).** Compound **12** was prepared by a procedure analogous to the preparation of **11**. It was obtained from 3-nitrophenylacetic acid (**16**) (0.33 g, 1.8 mmol), dry pyridine (0.25 g, 3.1 mmol) in anhydrous methylene chloride (20 mL), *N,N*-dicyclohexylcarbodiimide (0.52 g, 2.5 mmol), and *S*-**10** (0.25 g, 1.22 mmol) as an oil by chromatography using ethyl acetate:triethylamine (9:1) as eluent, 0.37 g (82%): ^{1}H NMR ($CDCl_3$) δ 8.11 (s, 1H, O_2NAr), 8.08 (d, *J* = 8.2 Hz, 1H, O_2NAr), 7.70 (d, *J* = 7.6 Hz, 1H, O_2NAr), 7.46 (dd, *J* = 8.2, 7.6 Hz, 1H, O_2NAr), 7.31 (m, 5H, Ar), 6.09 (dd, *J* = 10.4, 4.9 Hz, 1H, ArCH), 5.12* (m, 1H, ArCH), 3.92 (d, *J* = 15.7 Hz, 1H, O_2NArCH_2), 3.82 (d, *J* = 15.7 Hz, 1H, O_2NArCH_2), 3.18 (dd, *J* = 13.1, 4.9 Hz, 1H, ArCHC*H*$_2$), 3.06* (m, 2H, ArCHC*H*$_2$), 2.85* (s, 3H, NMe), 2.77 (s, 3H, NMe), 2.72 (dd, *J* = 13.1, 10.4 Hz, 1H, ArCHC*H*$_2$), 2.69 (m, 2H, pyrrolidine-NCH_2), 2.50 (m, 2H, pyrrolidine-NCH_2), 1.72 (m, 4H, pyrrolidine-CCH_2); FABMS [MH^+] 368.

***N*-Methyl-*N*-[(1*S*)-1-phenyl-2-(1-pyrrolidinyl)ethyl]-4-nitrophenylacetamide (13).** Compound **13** was prepared by a procedure analogous to the preparation of **11**. It was obtained from 4-nitrophenylacetic acid (**17**) (0.35 g, 1.9 mmol), dry pyridine (0.25 g, 3.1 mmol) in anhydrous methylene chloride (20 mL), *N,N*-dicyclohexylcarbodiimide (0.52 g, 2.5 mmol), and *S*-**10** (0.25 g, 1.22 mmol) as a pale brown solid by chromatography using ethyl acetate:triethylamine (9:1) as eluent, 0.31 g (69%): mp 92−93 °C; ^{1}H NMR ($CDCl_3$) δ 8.14 (d, *J* = 8.7 Hz, 2H, O_2NAr), 7.43* (d, *J* = 8.4 Hz, 2H, O_2NAr), 7.48 (d, *J* = 8.7 Hz, 2H, O_2NAr), 7.30 (m, 5H, Ar), 7.15* (d, *J* = 8.4 Hz, 2H, O_2NAr), 6.11 (dd, *J* = 10.7, 7.7 Hz, 1H, ArCH), 5.07* (m, 1H, ArCH), 3.94 (d, *J* = 15.7 Hz, 1H, O_2NArCH_2), 3.82 (d, *J* = 15.7 Hz, 1H, O_2NArCH_2), 3.21 (dd, *J* = 12.6, 10.7 Hz, 1H, ArCHC*H*$_2$), 3.02* (m, 2H, ArCHC*H*$_2$), 2.83* (s, 3H, NMe), 2.73 (s, 3H, NMe), 2.73 (m, 2H, pyrrolidine-NCH_2), 2.71 (dd, *J* = 12.6, 7.7 Hz, 1H, ArCHC*H*$_2$), 2.50 (m, 2H, pyrrolidine-NCH_2), 1.75 (m, 4H, pyrrolidine-CCH_2); FABMS [MH^+] 368.

***N*-Methyl-*N*-[(1*S*)-1-phenyl-2-(1-pyrrolidinyl)ethyl]-2-nitro-4,5-dichlorophenylacetamide (14).** Compound **14** was prepared by a procedure analogous to the preparation of **11**. It was obtained from 2-nitro-4,5-dichlorophenylacetic acid (**18**) (0.43 g, 1.7 mmol), dry pyridine (0.20 g, 2.5 mmol) in anhydrous methylene chloride (40 mL), *N,N*-dicyclohexylcarbodiimide (0.55 g, 2.6 mmol), and *S*-**10** (0.25 g, 1.22 mmol) as a pale yellow solid by flash column chromatography using ethyl acetate:triethylamine (19:1) as the eluent. The product was crystallized from ether:hexane to give 0.38 g (71%) of **14**: mp 117−119 °C; ^{1}H NMR ($CDCl_3$) δ 8.18 (s, 1H, O_2NAr), 7.44 (s, 1H, O_2NAr), 7.30 (m, 5H, Ar), 5.97 (dd, *J* = 10.2, 7.9 Hz, 1H,

ArCH), 5.12* (m, 1H, ArCH), 4.23* (s, 2H, $ArCH_2$), 4.05 (d, J = 17.1 Hz, 1H, O_2NArCH_2), 4.00 (d, J = 17.1 Hz, 1H, O_2NArCH_2), 3.12 (dd, J = 12.6, 10.2 Hz, 1H, $ArCHCH_2$), 2.81 (s, 3H, NMe), 2.76* (s, 3H, NMe), 2.74 (dd, J = 12.6, 7.9 Hz, 1H, $ArCHCH_2$), 2.66 (m, 2H, pyrrolidine-NCH_2), 2.49 (m, 2H, pyrrolidine-NCH_2), 1.79 (m, 4H, pyrrolidine-CCH_2); FABMS [MH^+ (^{35}Cl, ^{37}Cl and ^{35}Cl, ^{35}Cl)] 438, 436.

***N*-Methyl-*N*-[(1*S*)-1-phenyl-2-(1-pyrrolidinyl)ethyl]-phenylacetamide (8).** In an analogous procedure, from phenylacetic acid (0.26 g, 1.9 mmol), dry pyridine (0.20 g, 2.5 mmol) in anhydrous methylene chloride (20 mL), *N,N*-dicyclohexylcarbodiimide (0.52 g, 2.5 mmol), and *S*-**10** (0.25 g, 0.32 mmol), 0.32 g (81%) of **8** was obtained as an oil after chromatography eluting eith ethyl acetate:triethylamine (9:1): $[\alpha]^{30}_D$ = +112.2° (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.28 (m, 10H, Ar), 6.12 (dd, J = 11.4 Hz, 7.3H, ArCH), 5.08* (m, 1H, ArCH), 3.83 (d, J = 15.1 Hz, 1H, $ArCH_2$), 3.75 (d, J = 15.1 Hz, 1H, $ArCH_2$), 3.12 (dd, J = 12.7, 11.4 Hz, 1H, $ArCHCH_2$), 2.90* (m, 2H, $ArCHCH_2$), 2.78* (s, 3H, NMe), 2.73 (dd, J = 12.7, 7.3, 1H, $ArCHCH_2$), 2.69 (m, 2H, pyrrolidine-NCH_2), 2.68 (s, 3H, NMe), 2.45 (m, 2H, pyrrolidine-NCH_2), 1.73 (m, 4H, pyrrolidine-CCH_2); ^{13}C NMR ($CDCl_3$) δ 171.07, 138.86, 134.97, 128.50, 128.27, 128.15, 127.37, 127.10, 126.30, 55.15, 54.20, 53.27, 41.59, 30.06, 23.64; IR (neat) 1639 cm^{-1}. Anal. ($C_{21}H_{26}N_2O$·0.25H_2O) C, N; H: calcd, 8.17; found, 7.69.

***N*-Methyl-*N*-[(1*S*)-1-phenyl-2-(1-pyrrolidinyl)ethyl]-3,4-dichlorophenylacetamide (2).** Compound **2** was prepared by a procedure analogous to the preparation of **11**. It was obtained from 3,4-dichlorophenylacetic acid (**9**) (0.36 g, 1.4 mmol), dry pyridine (0.21 g, 2.6 mmol) in anhydrous methylene chloride (20 mL), *N,N*-dicyclohexylcarbodiimide (0.53 g, 2.5 mmol), and *S*-**10** (0.25 g, 1.2 mmol) as an oil by chromatography using ethyl acetate:triethylamine (9:1) as eluent. The product was treated with dry HCl in ether, and after evaporation of the ether, it was crystallized from methanol:ethyl acetate to give 0.37 g (69%) of *S*-**2**·HCl as a white solid: mp 225 °C (lit[17] mp 225–226 °C); $[\alpha]^{24}_D$ = +121.8° (c = 1.0, $CHCl_3$).

***N*-Methyl-*N*-[(1*S*)-1-phenyl-2-(1-pyrrolidinyl)ethyl]-2-aminophenylacetamide (19).** Compound **11** (0.30 g, 0.8 mmol) in methanol (100 mL), 10 mL of 15% aqueous HCl, and 50 mg of 5% Pd–C was reduced under a hydrogen atmosphere (45 psi) for 8 h. The residue, after removal of the catalyst by filtration and evaporation, was dissolved in chloroform (25 mL), washed with saturated aqueous $NaHCO_3$, dried (anhydrous Na_2SO_4), filtered, and evaporated to give a pale brown solid. The resulting amine was then crystallized from chloroform:hexane to give 0.21 g (75%) of **19** as an off-white sticky solid: HCl salt, mp 184–186 °C; ^1H NMR (free base) ($CDCl_3$) δ 7.21 (m, 5H, Ar), 7.04 (m, 2H, Ar), 6.68 (m, 2H, Ar), 6.06 (dd, J = 11.2, 7.2 Hz, 1H, ArCH), 5.30* (m, 1H, ArCH), 3.70 (d, J = 14.6 Hz, 1H, $ArCH_2$), 3.62 (d, J = 14.6 Hz, 1H, $ArCH_2$), 3.09 (dd, J = 12.8, 11.2 Hz, 1H, $ArCHCH_2$), 3.00* (m, 2H, $ArCHCH_2$), 2.81 (s, 3H, NMe), 2.74* (s, 3H, NMe), 2.69 (dd, J = 12.8, 7.2 Hz, 1H, $ArCHCH_2$), 2.63 (m, 2H, pyrrolidine-NCH_2), 2.44 (m, 2H, pyrrolidine-NCH_2), 1.67 (m, 4H, pyrrolidine-CCH_2); FABMS [MH^+] 338.

***N*-Methyl-*N*-[(1*S*)-1-phenyl-2-(1-pyrrolidinyl)ethyl]-3-aminophenylacetamide (20).** In a procedure analogous to the preparation of **19**, catalytic hydrogenation of **12** (0.32 g, 0.90 mmol) in methanol (100 mL) and 10 mL of 15% aqueous HCl with 50 mg of 5% Pd–C at 45 psi (8 h) followed by basic workup afforded **20** as a pale brown solid. Crystallization from ether:hexane gave 0.23 g (78%) of **20** as a cream-colored solid: mp 94–95 °C; ^1H NMR (C_6D_6) δ 7.29 (d, J = 7.4 Hz, 2H, Ar), 7.10 (m, 4H, Ar), 6.70 (d, J = 7.9 Hz, 1H, Ar), 6.54 (s, 1H, Ar), 6.40 (dd, J = 9.9, 4.8 Hz, 1H, ArCH), 6.29 (d, J = 7.8 Hz, 1H, Ar), 5.09* (m, 1H, ArCH), 3.84* (d, J = 14.6 Hz, 1H, $ArCH_2$), 3.73* (d, J = 14.6 Hz, 1H, $ArCH_2$), 3.57 (d, J = 15.1 Hz, 1H, $ArCH_2$), 3.52 (d, J = 15.1 Hz, 1H, $ArCH_2$), 2.89* (s, 3H, NMe), 2.89 (dd, J = 12.5, 9.9 Hz, 1H, $ArCHCH_2$), 2.66 (m, 2H, pyrrolidine-NCH_2), 2.49 (dd, J = 12.5, 4.8 Hz, 1H, $ArCHCH_2$), 2.39 (s, 3H, NMe), 2.32 (m, 2H, pyrrolidine-NCH_2), 1.57 (m, 4H, pyrrolidine-CCH_2); FABMS [MH^+] 338.

***N*-Methyl-*N*-[(1*S*)-phenyl-2-(1-pyrrolidinyl)ethyl]-4-aminophenylacetamide (21).** In a procedure analogous to the preparation of **19**, catalytic hydrogenation of **13** (0.25 g, 0.70 mmol) in methanol (100 mL) and 10 mL of 15% aqueous HCl with 50 mg of 5% Pd–C at 45 psi (8 h) followed by basic workup afforded crude **21**. Crystallization from ether:hexane gave 0.16 g (71%) of **21** as a pale brown solid: mp 152–153 °C; ^1H NMR ($CDCl_3$) δ 7.28 (m, 5H, Ar), 7.06 (d, J = 7.9 Hz, 2H, Ar), 6.61 (d, J = 7.9 Hz, 2H, Ar), 6.11 (dd, J = 10.0, 5.8 Hz, 1H, ArCH), 5.10* (m, 1H, ArCH), 3.71 (d, J = 15.0 Hz, 1H, $ArCH_2$), 3.64 (d, J = 15.0 Hz, 1H, $ArCH_2$), 3.10 (dd, J = 12.7, 10.0 Hz, 1H, $ArCHCH_2$), 2.90* (m, 2H, $ArCHCH_2$), 2.80* (s, 3H, NMe), 2.72 (dd, J = 12.7, 5.8 Hz, 1H, $ArCHCH_2$), 2.68 (s, 3H, NMe), 2.47 (m, 4H, pyrrolidine-NCH_2), 1.74 (m, 4H, pyrrolidine-CCH_2); FABMS [MH^+] 338.

***N*-Methyl-*N*-[(1*S*)-1-phenyl-2-(1-pyrrolidinyl)ethyl]-2-amino-4,5-dichlorophenylacetamide (22).** In a procedure analogous to the preparation of **19**, catalytic hydrogenation of **14** (0.30 g, 0.69 mmol) in methanol (150 mL) and 20 mL of 15% aqueous HCl with 80 mg of PtO_2 at an initial pressure of 45 psi (10 h) followed by basic workup gave **22** as a brown solid. The product was crystallized from chloroform:hexane to give 0.18 g (64%) of **22** as a pale brown solid: mp 196–198 °C; ^1H NMR ($CDCl_3$) δ 7.26 (m, 5H, Ar), 7.08 (s, 1H, Ar), 6.98* (s, 1H, Ar), 6.76 (s, 1H, Ar), 6.72* (s, 1H, Ar), 6.03 (dd, J = 9.8, 7.3 Hz, 1H, ArCH), 5.20* (m, 1H, ArCH), 3.64 (d, J = 14.9 Hz, 1H, $ArCH_2$), 3.53 (d, J = 14.9 Hz, 1H, $ArCH_2$), 3.25 (dd, J = 13.1, 9.8 Hz, 1H, $ArCHCH_2$), 3.04* (m, 2H, $ArCHCH_2$), 2.87* (s, 3H, NMe), 2.80 (s, NMe), 2.71 (dd, J = 13.1, 7.3 Hz, 1H, $ArCHCH_2$), 2.65 (m, 2H, pyrrolidine-NCH_2), 2.54 (m, 2H, pyrrolidine-NCH_2), 1.68 (m, 4H, pyrrolidine-CCH_2).

***N*-Methyl-*N*-[(1*S*)-1-phenyl-2-(1-pyrrolidinyl)ethyl]-2-isothiocyanatophenylacetamide (3).** To a solution of **19** (0.15 g, 0.44 mmol) in dry methylene chloride (20 mL) was added di-2-pyridyl thionocarbonate (0.11 g, 0.47 mmol) at ambient temperature. After the mixture had been stirred under argon for 12 h, it was washed with saturated aqueous sodium bicarbonate solution and dried (anhydrous Na_2SO_4) and the solvent was evaporated. The product was isolated chromatographically using ethyl acetate and then with ethyl acetate:triethylamine (19:1) as eluents to give 0.12 g (73%) of **3** as an oil: $[\alpha]^{24}_D$ = +81.4° (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.18–7.41 (m, 9H, Ar), 6.11 (dd, J = 9.5, 4.5 Hz, 1H, ArCH), 5.09* (m, 1H, ArCH), 3.93* (s, 2H, $ArCH_2$), 3.85 (d, J = 16.2 Hz, 1H, $ArCH_2$), 3.77 (d, J = 16.2 Hz, 1H, $ArCH_2$), 3.16 (dd, J = 12.4, 9.5 Hz, 1H, $ArCHCH_2$), 3.07* (m, 2H, $ArCHCH_2$), 2.82* (s, 3H, NMe), 2.78 (dd, J = 12.4, 4.5 Hz, 1H, $ArCHCH_2$), 2.76 (s, NMe), 2.73 (m, 2H, pyrrolidine-NCH_2), 2.50 (m, 2H, pyrrolidine-NCH_2), 1.76 (m, 2H, pyrrolidine-CCH_2); ^{13}C NMR ($CDCl_3$) δ 169.63, 138.52, 138.30, 135.98, 131.78, 130.27, 128.26, 127.77, 127.48, 127.23, 126.80, 126.38, 55.23, 54.26, 53.59, 37.54, 30.04, 23.67; IR (neat) 2095, 1843 cm^{-1}. Anal. ($C_{22}H_{25}N_3OS$·0.5H_2O) C, H, N.

***N*-Methyl-*N*-[(1*S*)-1-phenyl-2-(1-pyrrolidinyl)ethyl]-3-isothiocyanatophenylacetamide (4).** In a procedure analogous to the preparation of **3**, the amine **20** (0.18 g, 0.53 mmol) in dry methylene chloride (10 mL) and di-2-pyridyl thionocarbonate (0.13 g, 0.56 mmol) were stirred at ambient temperature under argon for 12 h. The product was isolated chromatographically using ethyl acetate and then with ethyl acetate:triethylamine (19:1) as eluents to give 0.13 g (65%) of **4** as an oil: $[\alpha]^{29}_D$ = +95.1° (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.09–7.40 (m, Ar), 6.11 (dd, J = 10.7, 4.6 Hz, 1H, ArCH), 5.05* (m, 1H, ArCH), 3.81 (d, J = 15.6 Hz, 1H, $ArCH_2$), 3.72 (d, J = 15.6 Hz, 1H, $ArCH_2$), 3.19 (dd, J = 12.7, 10.7 Hz, 1H, $ArCHCH_2$), 3.00* (m, 2H, $ArCHCH_2$), 2.80* (s, 3H, NMe), 2.75 (dd, J = 12.7, 4.6 Hz, 1H, $ArCHCH_2$), 2.72 (s, 3H, NMe), 2.69 (m, 2H, pyrrolidine-NCH_2), 2.50 (m, 2H, pyrrolidine-NCH_2), 1.77 (m, 4H, pyrrolidine-CCH_2); ^{13}C NMR ($CDCl_3$) δ 170.25, 138.56, 136.96, 134.85, 131.13, 129.36, 128.52, 128.29, 127.38, 125.86, 123.87, 55.15, 54.30, 53.49, 40.88, 30.04, 23.46; IR (neat) 2112, 1634 cm^{-1}. Anal. ($C_{22}H_{25}N_3OS$·0.25H_2O) C, H, N.

***N*-Methyl-*N*-[(1*S*)-1-phenyl-2-(1-pyrrolidinyl)ethyl]-4-isothiocyanatophenylacetamide (5).** In a procedure analogous to the preparation of **3**, the amine **21** (0.15 g, 0.44 mmol) in dry methylene chloride (10 mL) and di-2-pyridyl thionocarbonate (0.11 g, 0.47 mmol) at ambient temperature were stirred under argon for 12 h. A pale brown solid was isolated

after evaporation of the solvents. Because it was unstable on silica gel, the product was crystallized from chloroform:hexane, giving 0.10 g (60%) of **5** as an off-white solid: mp 86–88 °C; $[\alpha]^{30}_D$ = +98.3° (*c* = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.29 (m, 7H, Ar), 7.14 (d, *J* = 8.3 Hz, 2H, Ar), 6.10 (dd, *J* = 10.3, 6.3 Hz, 1H, ArCH), 5.05* (m, 1H, ArCH), 3.81 (d, *J* = 15.6 Hz, 1H, $ArCH_2$), 3.72 (d, *J* = 15.6 Hz, 1H, $ArCH_2$), 3.17 (dd, *J* = 13.1, 10.3 Hz, 1H, $ArCHCH_2$), 3.00* (m, 2H, $ArCHCH_2$), 2.80* (s, 3H, NMe), 2.75 (dd, *J* = 13.1, 6.3 Hz, 1H, $ArCHCH_2$), 2.70 (s, 3H, NMe), 2.68 (m, 2H, pyrrolidine-NCH_2), 2.48 (m, 2H, pyrrolidine-NCH_2), 1.74 (m, 4H, pyrrolidine-CCH_2); ^{13}C NMR ($CDCl_3$) δ 170.39, 138.56, 136.33, 134.58, 132.85, 129.84, 120.23, 127.33, 127.25, 125.53, 55.06, 54.21, 53.41, 40.93, 30.01, 23.67; IR (neat) 2105, 1634 cm^{-1}. Anal. ($C_{22}H_{25}N_3OS{\cdot}0.5H_2O$) C, H, N.

***N*-Methyl-*N*-[(1*S*)-1-phenyl-2-(1-pyrrolidinyl)ethyl]-2-isothiocyanato-4,5-dichlorophenylacetamide Hydrochloride (6).** In a procedure analogous to the preparation of **3**, the amine **22** (0.16 g, 0.39 mmol) in dry methylene chloride (10 mL) and di-2-pyridyl thionocarbonate (0.10 g, 0.43 mmol) were stirred at ambient temperature under argon for 12 h. An oil was obtained which was not chromatographed because it was unstable on silica gel. The crude product was treated with dry HCl in ether and crystallized from chloroform:ether to give 90 mg (49%) of **6** as a white solid: mp 202–203 °C; ^1H NMR ($CDCl_3$) δ 7.71 (s, 1H, Ar), 7.39 (m, 3H, Ar), 7.34 (s, 1H, Ar), 7.27 (m, 2H, Ar), 6.39 (dd, *J* = 11.4, 3.4 Hz, 1H, ArCH), 4.38 (d, *J* = 16.6 Hz, 1H, $ArCH_2$), 4.08 (m, 2H, pyrrolidine-NCH_2), 3.97 (dd, *J* = 13.2, 11.4 Hz, 1H, $ArCHCH_2$), 3.76 (d, *J* = 16.6 Hz, 1H, $ArCH_2$), 3.23 (dd, *J* = 13.2, 3.4 Hz, 1H, $ArCHCH_2$), 2.96 (s, 3H, NMe), 2.91 (m, 2H, pyrrolidine-NCH_2), 2.31 (m, 2H, pyrrolidine-CCH_2), 2.03 (m, 2H, pyrrolidine-CCH_2); IR (KBr) 2057, 1639 cm^{-1}; HRFAB calcd [MH^+] 448.1017, found 448.1008. Anal. ($C_{22}H_{23}N_3OSCl_2{\cdot}HCl{\cdot}0.25H_2O$) C, H; N: calcd, 8.67; found, 7.75.

α-Pyrrolidino-4-nitroacetophenone Oximes 31 and 32. To a solution of a mixture of α-bromo- and α-chloroacetophenone oxime[46,47] (1:1.6) (20.0 g, 87.1 mmol) in dry methylene chloride (300 mL) at 0 °C was added 20 mL of pyrrolidine (0.24 mol) over 10 min. The mixture was allowed to warm to ambient temperature and stirred under argon for 4 h, after which it was washed with saturated aqueous sodium bicarbonate solution, dried (anhydrous Na_2SO_4), and evaporated under reduced pressure. The product was crystallized from benzene:hexane to give 18.2 g (84%) of a mixture of **31** and **32** as a pale pink solid. A portion was fractionally crystallized from benzene:hexane to give **31** first and subsequently **32** from the mother liquor. The major isomer, **31**, was obtained as a pale pink solid: mp 126–127 °C; ^1H NMR ($CDCl_3$) δ 8.22 (d, *J* = 8.9, 2H, O_2NAr), 7.68 (d, *J* = 8.9, 2H, O_2NAr), 3.49 (s, HO-N=C-CH_2), 2.54 (m, 4H, pyrrolidine-NCH_2), 1.74 (m, 4H, pyrrolidine-NCH_2); ^{13}C NMR ($CDCl_3$) δ 153.21, 139.03, 129.26, 123.10, 59.36, 54.09, 23.55. The minor isomer, **32**, was also obtained as a pale pink solid: mp 143–145 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 9.0 Hz, 2H, O_2NAr), 7.82 (d, *J* = 9.0 Hz, 2H, O_2NAr), 3.93 (s, 2H, HO-N=C-CH_2), 2.71 (m, 4H, pyrrolidine-NCH_2), 1.88 (m, 4H, pyrrolidine-CCH_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ 152.15, 147.74, 141.65, 126.68, 123.49, 53.88, 52.18, 23.71.

1-[2-(4-Nitrophenyl)-2-aminoethyl]pyrrolidine (23). To a well-stirred solution of the mixed oxime isomers **31** and **32** (15.52 g, 62.3 mmol) in 100 mL of dry THF at 0 °C maintained under an inert atmosphere of argon was added 200 mL of 1 M BH_3–THF complex in THF over 30 min. The mixture was refluxed for 24 h and cooled to 0 °C, and 10 mL of water was added cautiously. Next, ice cold concentrated HCl (15 mL) was added cautiously in portions. When the evolution of hydrogen was complete, the mixture was refluxed for 15 min. Then the mixture was cooled and evaporated. The residual acidic aqueous mixture was washed with ether and cooled to 0 °C and the precipitated boric acid removed by filtration. The cold acidic solution was then made alkaline with 6 M NaOH solution and extracted with methylene chloride (2 × 200 mL). The combined methylene chloride solution was dried (anhydrous Na_2SO_4) and evaporated to give 12.3 g (84%) of racemic **23** as a viscous oil: ^1H NMR ($CDCl_3$) δ 8.17 (d, *J* = 8.7 Hz, 2H, O_2NAr), 7.57 (d, *J* = 8.7 Hz, 2H, O_2NAr), 4.20 (dd, *J* = 10.3, 5.0 Hz, 1H, O_2NArCH), 2.71 (dd, *J* = 12.1, 10.3 Hz, 1H, $O_2NArCHCH_2$), 2.63 (m, 2H, pyrrolidine-NCH_2), 2.49 (m, 2H, pyrrolidine-NCH_2), 2.37 (dd, *J* = 2, 12.1, 5.0 Hz, 1H, $O_2NArCHCH_2$), 1.78 (m, 4H, pyrrolidine-CCH_2); IR (neat) 3443, 1513, 1346 cm^{-1}; FABMS [MH^+] 236.

1-[2-(4-Nitrophenyl)-2-formamidoethyl]pyrrolidine (33). Ethyl formate (50 mL) was added to **23** (10.50 g, 44.6 mmol), and the solution was stirred for 24 h at ambient temperature under argon. The mixture was then evaporated, and the residue was dissolved in 200 mL of methylene chloride. The methylene chloride solution was washed with a saturated solution of sodium bicarbonate, dried (anhydrous Na_2SO_4), and evaporated to give a sticky solid. The product was crystallized from benzene:hexane to give 10.20 g (87%) of formamide **33** as a pink solid: mp 65–66 °C; ^1H NMR ($CDCl_3$) δ 8.26 (s, 1H, CHO), 8.14 (d, *J* = 8.7 Hz, 2H, O_2NAr), 7.47 (d, *J* = 8.7 Hz, 2H, O_2NAr), 7.36 (d, *J* = 6.1 Hz, 1H, NH), 5.00 (m, 1H, O_2NArCH), 2.85 (dd, *J* = 12.6, 9.5 Hz, 1H, $O_2NArCHCH_2$), 2.63 (dd, *J* = 12.6, 5.2 Hz, 1H, $O_2NArCHCH_2$), 2.53 (m, 2H, pyrrolidine-NCH_2), 2.47 (m, 2H, pyrrolidine-NCH_2), 1.74 (m, 4H, pyrrolidine-CCH_2).

1-[2-(4-Nitrophenyl)-2-(methylamino)ethyl]pyrrolidine (24). To a well-stirred solution of crude formamide **33** (9.80 g, 32.2 mmol) in 100 mL of dry THF at 0 °C was added 55 mL of a 2 M borane–dimethyl sulfide complex in THF under an inert atmosphere of argon. The mixture was then refluxed for 2 h and the dimethyl sulfide removed by distillation. The mixture was cooled to 0 °C and 5 mL of water added cautiously followed with 15 mL of ice-cooled concentrated HCl in small portions. The mixture was refluxed for 15 min to complete the hydrolysis and then evaporated to remove THF. The aqueous acidic solution was washed with ether. The aqueous acidic solution was cooled in ice and the precipitated boric acid removed by filtration. The solution was then basified with 6 M NaOH solution with ice bath cooling and extracted with methylene chloride (2 × 200 mL), dried (anhydrous Na_2SO_4), and evaporated to give 6.6 g (81%) of **24** as a viscous oil which solidified: mp 53–54 °C; ^1H NMR (C_6D_6) δ 7.93 (d, *J* = 8.8 Hz, 2H, O_2NAr), 7.18 (d, *J* = 8.8 Hz, 2H, O_2NAr), 3.40 (dd, *J* = 10.8, 3.6 Hz, 1H, O_2NArCH), 2.55 (dd, *J* = 12.7, 10.8 Hz, 1H, $O_2NArCHCH_2$), 2.38 (m, 2H, pyrrolidine-NCH_2), 2.24 (m, 2H, pyrrolidine-NCH_2), 2.11 (s, 3H, NMe), 1.99 (dd, *J* = 12.0, 10.8 Hz, 1H, $O_2NArCHCH_2$), 1.56 (m, 4H, pyrrolidine-CCH_2); FABMS [MH^+] 250.

(*S*)-(+)-α-Acetoxyphenylacetyl Chloride (*S*-34). To a stirred solution of 2 M oxalyl chloride in methylene chloride (200 mL) at 0 °C was added (*S*)-(+)-α-acetoxyphenylacetic acid (*S*-**35**) (5.0 g, 25.7 mmol) in five portions over 10 min. Then the solution was allowed to warm to ambient temperature and stirred until reaction was complete (10 h). Progress of the reaction was assessed hourly by rotary evaporation of small samples at room temperature and determination of the proton NMR spectrum of the mixture. When the reaction was complete, the solution was evaporated at room temperature to remove all traces of excess oxalyl chloride to obtain 5.23 g (96%) of *S*-**34** as a colorless oil of optical purity over 97% ee.

Procedure for Optical Purity Determination of *S*-34. To a solution of *S*-**34** (0.05 g, 0.24 mmol) in 3 mL of chloroform at 0 °C were added 40 mL of pyridine and (*S*)-(−)-α-methylbenzylamine (35 mg, 0.29 mmol). The mixture was then stirred at ambient temperature for 30 min and washed with 10% aqueous HCl to remove pyridine and excess amine. The chloroform solution was then dried (anhydrous Na_2SO_4) and evaporated. The proton NMR spectrum was determined in C_6D_6. With pure *S*-**34**, a single doublet for the *N*-methyl protons was observed at δ 1.22. Repeating the above procedure using racemic **34**, we observed two doublets for the diastereomeric *N*-methyl protons centered at δ 1.22 and 1.17. Integral ratios for the two doublets gave the enantiomeric purity of the *S*-**34** prepared.

***N*-Methyl-*N*-[(1*S*)-1-(4-nitrophenyl)-2-(1-pyrrolidinyl)-ethyl]-(*S*)-α-acetoxyphenylacetamide (36) and *N*-Methyl-*N*-[(1*R*)-1-(4-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]-(*S*)-α-acetoxyphenylacetamide (37).** To a stirred solution of *S*-**34** in dry methylene chloride at 0 °C was added pyridine (1.60 g,

20.2 mmol) and **24** (3.21 g, 12.9 mmol) in 20 mL of dry methylene chloride. The mixture was maintained at 5 °C for 16 h under argon. The mixture then was washed with saturated sodium bicarbonate solution, dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was flash chromatographed on grade II neutral alumina eluting with hexane:ethyl acetate (6:4) to give 1.65 g (30%) of *S,S*-**36** followed by 1.52 g (28%) of *S,R*-**37**. Compound *S,S*-**36** was obtained as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 8.21 (d, J = 8.8 Hz, 2H, O_2NAr), 7.95* (d, J = 8.9 Hz, 1H, O_2NAr), 7.55 (m, 2H, Ar), 7.53 (d, J = 8.8 Hz, 2H, O_2NAr), 7.41 (m, 3H, Ar), 6.85* (d, J = 8.9 Hz, 2H, O_2NAr), 6.45* (s, 1H, ArC*H*OAc), 6.24 (s, 1H, ArC*H*OAc), 6.16 (dd, J = 10.5, 5.5 Hz, 1H, O_2-NArCH), 5.15* (m, 1H, O_2NAr), 3.30* (m, 2H, $O_2NArCHCH_2$), 3.05 (dd, J = 12.4, 10.5 Hz, 1H, $O_2NArCHCH_2$), 2.83 (dd, J = 12.4, 5.5 Hz, 1H, $O_2NArCHCH_2$), 2.69 (s, 3H, NMe), 2.65 (m, 2H, pyrrolidine-NCH_2), 2.43 (m, 2H, pyrrolidine-NCH_2), 2.22 (s, 3H, OAc), 2.16* (s, 3H, OAc), 1.69 (4, m, pyrrolidine-CCH_2); ^{13}C NMR ($CDCl_3$) δ 170.67, 168.74, 146.92, 145.93, 133.08, 129.05, 128.59, 128.38, 128.10, 123.47, 73.56, 54.74, 54.00, 53.46, 29.49, 23.58, 20.78; FABMS [MH$^+$] 426. The second compound, *S,R*-**37**, was also obtained as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 8.24* (d, J = 8.5 Hz, 2H, O_2NAr), 8.08 (d, J = 8.7 Hz, 2H, O_2NAr), 7.75* (d, J = 8.5 Hz, 2H, O_2NAr), 7.45 (m, 5H, Ar), 7.34 (d, J = 8.7 Hz, 2H, O_2NAr), 6.23 (s, 1H, ArC*H*OAc), 6.16* (s, 1H, ArC*H*OAc), 5.98 (dd, J = 8.7, 7.4 Hz, 1H, O_2NArCH), 4.99* (m, 1H, O_2NArCH), 3.05 (dd, J = 12.3, 8.7 Hz, 1H, $O_2NArCHCH_2$), 2.97 (dd, J = 7.4, 12.3 Hz, 1H, $O_2NArCHCH_2$), 2.85* (s, 3H, NMe), 2.74 (s, 3H, NMe), 2.66 (m, 2H, pyrrolidine-NCH_2), 2.58 (m, 2H, pyrrolidine-NCH_2), 2.18 (s, 3H, OAc), 2.15* (s, 3H, OAc), 1.79 (m, 4H, pyrrolidine-CCH_2); ^{13}C NMR ($CDCl_3$) δ 170.13, 168.31, 146.74, 146.32, 133.18, 129.30, 128.79, 128.38, 128.00, 123.23, 73.62, 55.40, 54.44, 53.86, 30.02, 23.57, 20.74; FABMS [MH$^+$] 426.

1-[(2*S*)-2-(4-Nitrophenyl)-2-(methylamino)ethyl]pyrrolidine (*S*-24). To diastereomeric amide *S,S*-**36** (1.12 g, 2.63 mmol) was added 5 mL of concentrated hydrochloric acid, and the mixture was refluxed for 12 h under argon. The mixture was then cooled in an ice bath and made alkaline with solid sodium bicarbonate added in portions. The basic solution was extracted with methylene chloride (2 × 25 mL), dried (Na_2SO_4), and evaporated to give 0.35 g (53%) of *S*-**24** as an oil of optical purity over 95% ee.

Procedure for Optical Purity Determination of Amines *S*-24 and *R*-24. To a solution of racemic **24** in $CDCl_3$ in an NMR tube was added 2 equiv of pure (*S*)-(+)-α-acetoxyphenylacetic acid (*S*-**35**) at ambient temperature and the proton NMR spectrum recorded. The aromatic protons adjacent to the nitro group for the diastereomeric salts separated into two doublets appearing at δ 8.17 and 8.07, the most downfield doublet representing the *S,S*-salt and the other the *S,R*-salt. The procedure was repeated using the amine *S*-**24** obtained by hydrolysis of *S,S*-**36**. The integral ratio of the two signals gave the enantiomeric purity of *S*-**24**: $[\alpha]^{24}_D$ = +28.0° (c = 0.5, MeOH).

1-[(2*R*)-2-(4-Nitrophenyl)-2-(methylamino)ethyl]pyrrolidine (*R*-24). To the second eluted diastereomeric amide, *S,R*-**37** (1.32 g, 3.10 mmol), was added 5 mL of concentrated hydrochloric acid, and the mixture was refluxed for 12 h under argon. The mixture was then cooled in an ice bath and basified with solid sodium bicarbonate added in portions. The basic solution was extracted with methylene chloride (2 × 25 mL), dried (Na_2SO_4), and evaporated to give 0.39 g (50%) of *R*-**24** as an oil of optical purity over 95% ee: $[\alpha]^{24}_D$ = −28.1° (c = 0.5, MeOH).

***N*-Methyl-*N*-[(1*S*)-1-(4-nitrophenyl)-2-(1-pyrrolidinyl)-ethyl]-3,4-dichlorophenylacetamide (30).** To a stirred solution of 3,4-dichlorophenylacetic acid (**9**) (0.40 g, 1.6 mmol) and dry pyridine (0.20 g, 2.5 mmol) in anhydrous methylene chloride (20 mL) was added *N,N*-dicyclohexylcarbodiimide (0.42 g, 2.0 mmol) at 25 °C. After the solution was stirred for 2 min, *S*-**24** (0.23 g, 0.9 mmol) in anhydrous methylene chloride (10 mL) was added and the mixture was stirred for 12 h under an atmosphere of argon. The *N,N*-dicyclohexylurea precipitate was removed by filtration and washed with methylene chloride (5 mL). The filtrate was then evaporated, and the residue was submitted to flash column chromatography on silica gel eluting first with ethyl acetate to remove *N,N*-dicyclohexylurea and other fast eluting byproducts and then with ethyl acetate: triethylamine (9:1) to give 0.31 g (71%) of *S*-**30** as an oil: ^{1}H NMR ($CDCl_3$) δ 8.15 (d, J = 8.8 Hz, 2H, O_2NAr), 7.47 (d, J = 8.8 Hz, 2H, O_2NAr), 7.37 (d, J = 8.3 Hz, 1H, Ar), 7.35 (s, 1H, Ar), 7.14 (d, J = 8.3 Hz, 1H, Ar), 6.09 (dd, J = 10.2, 6.1 Hz, 1H, ArCH), 5.10* (m, 1H, ArCH), 3.78 (d, J = 15.5 Hz, 1H, $ArCH_2$), 3.70 (d, J = 15.5 Hz, 1H, $ArCH_2$), 3.11 (dd, J = 12.3, 10.2 Hz, 1H, $ArCHCH_2$), 2.81 (dd, J = 12.3, 6.1 Hz, 1H, $ArCHCH_2$), 2.76 (s, 3H, NMe), 2.66 (m, 2H, pyrrolidine-NCH_2), 2.51 (m, 2H, pyrrolidine-NCH_2), 1.75 (m, 4H, pyrrolidine-CCH_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.46, 147.12, 146.28, 134.83, 132.48, 130.93, 130.69, 130.36, 128.35, 128.27, 123.60, 55.30, 54.31, 53.55, 40.36, 30.57, 23.75; IR (neat) 1640, 1519, 1347 cm^{-1}. A portion of the free base was treated with dry HCl in ether and evaporated to give *S*-**30**·HCl as a pale brown solid. *S*-**30**·HCl was crystallized from methanol:ethyl acetate to obtain an off-white solid: $[\alpha]^{25}_D$ = +176.4° (c = 0.11, MeOH); mp 262–264 °C dec; FABMS [MH$^+$ (^{35}Cl, ^{37}Cl and ^{35}Cl, ^{35}Cl)] 438, 436; CD (c = 0.107, MeOH), $[\theta]_{350}$ +2670, $[\theta]_{264}$ + 30 300, $[\theta]_{238}$ 0, $[\theta]_{230}$ −5800, $[\theta]_{222}$ 0 deg cm^2 dmol^{-1}.

Compound *R*-**30** was prepared from *R*-**24** by the same procedure. *R*-**30**·HCl: $[\alpha]^{26}_D$ = −176.1°; mp 262–263 °C dec; FABMS [MH$^+$ (^{35}Cl, ^{37}Cl and ^{35}Cl, ^{35}Cl)] 438, 436; CD (c = 0.11, MeOH) $[\theta]_{350}$ +2670, $[\theta]_{305}$ 0, $[\theta]_{263}$ −26 800, $[\theta]_{238}$ 0, $[\theta]_{231}$ +4290, $[\theta]_{224}$ 0 deg cm^2 dmol^{-1}.

***N*-Methyl-*N*-[(1*S*)-1-(4-aminophenyl)-2-(1-pyrrolidinyl)ethyl]-3,4-dichlorophenylacetamide (*S*-38).** A solution of *S*-**30** (0.22 g, 0.45 mmol) in methanol (150 mL), 15% aqueous HCl (20 mL), and 0.08 g of PtO_2 was reduced under 45 psi of hydrogen atmosphere (initial pressure) for 10 h. The catalyst was then removed by filtration and the solution evaporated under reduced pressure. The residue was dissolved in chloroform (30 mL), washed with saturated aqueous $NaHCO_3$, dried (anhydrous Na_2SO_4), filtered, and evaporated to give a brown solid. Crystallization from ether:hexane gave 0.15 g (73%) of *S*-**38** as a pale brown solid; the HCl salt crystallized from chloroform–ether: mp 162–165 °C; ^{1}H NMR (free base) ($CDCl_3$) δ 7.36 (s, 1H, Ar), 7.34 (d, J = 6.7 Hz, 1H, Ar), 7.14 (d, J = 6.7 Hz, 1H, Ar), 7.07 (d, J = 8.3 Hz, 2H, O_2-NAr), 6.62 (d, J = 8.3 Hz, 2H, O_2NAr), 6.00 (dd, J = 11.1, 4.9 Hz, 1H, ArCH), 4.95* (m, 1H, ArCH), 3.75 (d, J = 15.6 Hz, 1H, $ArCH_2$), 3.67* (d, J = 15.6 Hz, 1H, $ArCH_2$), 3.14 (dd, J = 12.2, 11.1 Hz, 1H, $ArCHCH_2$), 2.92* (m, 2H, $ArCHCH_2$), 2.76* (s, 3H, NMe), 2.71 (m, 2H, pyrrolidine-NCH_2), 2.67 (s, 3H, NMe), 2.60 (dd, J = 12.2, 4.9 Hz, 1H, $ArCHCH_2$), 2.48 (m, 2H, pyrrolidine-NCH_2), 1.74 (m, 4H, pyrrolidine-NCH_2); IR (neat) 3341, 1628 cm^{-1}.

***N*-Methyl-*N*-[(1*S*)-1-(4-isothiocyanatophenyl)-2-(1-pyrrolidinyl)ethyl-3,4-dichlorophenylacetamide (7).** To a solution of *S*-**38** (0.15 g, 0.44 mmol) in dry methylene chloride (10 mL) was added di-2-pyridyl thionocarbonate (0.11 g, 0.47 mmol) at ambient temperature. The mixture was stirred under an atmosphere of argon for 12 h. Then the mixture was washed with saturated aqueous sodium bicarbonate solution, dried (anhydrous Na_2SO_4), and evaporated under reduced pressure at ambient temperature. The product was then submitted to flash column chromatography on silica gel eluting first with ethyl acetate and then with ethyl acetate:triethylamine (19:1) to give 0.12 g (55%) of *S*-**7** as an oil: $[\alpha]^{25}_D$ = +85.9° (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 2H, Ar), 7.27 (m, 2H, Ar), 7.15 (m, 3H, Ar), 6.04 (dd, J = 8.7, 4.5 Hz, 1H, ArCH), 5.00* (m, 1H, ArCH), 3.76 (d, J = 15.3 Hz, 1H, $ArCH_2$), 3.67 (d, J = 15.3 Hz, 1H, $ArCH_2$), 3.09 (dd, J = 13.7, 8.7 Hz, 1H, $ArCHCH_2$), 2.76 (dd, J = 13.7, 4.5 Hz, 1H, $ArCHCH_2$), 2.70 (s, 3H, NMe), 2.67 (m, 2H, pyrrolidine-NCH_2), 2.49 (m, 2H, pyrrolidine-NCH2), 1.75 (m, 4H, pyrrolidine-CCH_2); ^{13}C NMR (CD_3CN) δ 171.04, 139.90, 137.64, 135.01, 131.86, 130.89, 130.49, 130.37, 130.04, 129.63, 126.39, 55.96, 54.62, 54.25, 40.31, 30.75, 24.26; IR (neat) 2105, 1639 cm^{-1}. Anal. ($C_{22}H_{23}N_3OSCl_2$·0.25H_2O) C, H, N.

***N*-Methyl-*N*-[(1*S*)-1-(phenyl)-2-(1-pyrrolidinyl)ethyl]-trifluoroacetamide Hydrocyloride (25).** To a solution of trifluoroacetic anhydride (2.57 g, 12.24 mmol) in methylene chloride (50 mL) at 0 °C were added pyridine (0.97 g, 12.24

mmol) and then *S*-**10** (1.25 g, 6.12 mmol) in 10 mL of methylene chloride. The mixture was then stirred at ambient temperature for 12 h. The solution was then basified with saturated aqueous sodium bicarbonate solution (2 × 50 mL), dried (Na_2SO_4), and evaporated. The crude product was subjected to flash column chromatography on silica using ethyl acetate:triethylamine (8:2) as eluent to give **25** as an oil. The product was treated with dry HCl ether, and the solvent evaporated to give 1.32 g (64%) of **25** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.41 (m, 3H, Ar), 7.27 (m, 2H, Ar), 6.03 (dd, J = 10.7, 3.8 Hz, 1H, ArCH), 4.25 (dd, J = 13.2, 10.7 Hz, 1H, ArCHCH_2), 3.97 (m, 2H, pyrrolidine-NCH_2), 3.47 (dd, J = 13.2, 3.8 Hz, 1H, ArCHCH_2), 2.95 (m, 2H, pyrrolidine-NCH_2), 2.87 (s, 3H, NMe), 2.09 (m, 4H, pyrrolidine-CCH_2); FABMS [MH$^+$] 301.

***N*-Methyl-*N*-[(1*S*)-1-(2-nitrophenyl)-2-(1-pyrrolidinyl)-ethyl]trifluoroacetamide (26) and *N*-Methyl-*N*-[(1*S*)-1-(4-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]trifluoroacetamide (27).** To the amide **28** (1.0 g, 3.33 mmol) was added a mixture of concentrated sulfuric acid (10 mL, 187.7 mmol) and sodium nitrate (3.00 g, 35.3 mmol). The mixture was heated at 60 °C for 12 h under argon. The solution was then cooled in an ice bath and basified with solid sodium bicarbonate added in portions. The mixture was extracted with methylene chloride (2 × 50 mL), dried (Na_2SO_4), and evaporated to give 0.53 g (46%) of a mixture of **26** and **27** as an oil: ^{1}H NMR ($CDCl_3$) δ 8.26 (m, 2H, Ar), 7.72–7.54 (m, 2H, Ar), 5.97 (m, 1H, ArCH), 3.20 (m, 1H, ArCHCH_2), 3.00 (m, 1H, ArCHCH_2), 2.95 (s, 3H, NMe), 2.72 (m, 2H, pyrrolidine-NCH_2), 2.62 (m, 2H, pyrrolidine-NCH_2), 1.82 (m, 4H, pyrrolidine-CCH_2); IR (neat) 1685, 1526, 1350 cm^{-1}.

***N*-Methyl-*N*-[(1*S*)-1-(2-nitrophenyl)-2-(1-pyrrolidinyl)-ethyl]-3,4-dichlorophenylacetamide (29) and *N*-Methyl-*N*-[(1*S*)-1-(4-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]-3,4-dichlorophenylacetamide (30).** A solution of the mixture **25** and **26** (0.50 g, 1.45 mmol) in 2 mL of water and 8 mL of methanol was stirred at ambient temperature for 7 h. The mixture was evaporated to remove methanol and extracted with methylene chloride (2 × 25 mL). The solution was dried (Na_2SO_4) and evaporated to give a mixture (0.35 g, 96%) of the *o*- and *p*-nitrophenyl diamines **26** and **27** as an oil. This mixture was used in the next reaction.

To a solution of 3,4-dichlorophenylacetyl chloride (0.29 g, 1.30 mmol) in methylene chloride (10 mL) were added pyridine (0.1 g, 1.30 mmol) and the mixture of amines **26** and **27** (0.25 g, 1.00 mmol). The mixture was stirred at ambient temperature for 12 h. The mixture was then basified and washed with aqueous sodium bicarbonate solution, dried (Na_2SO_4), and evaporated. Flash column chromatography on silica gel using ethyl acetate:methanol as eluent first gave 5 mg of **30** followed by a large number of mixed fractions and then 4 mg of **29**. The total yield for the mixture was 0.36 g (75%). The CD spectrum of **30** gave the identical Cotton effects, although of diminished intensity.

Biological Testing. Hartley-VAF Plus guinea pigs (300–350 g) were obtained from Charles River for preparation of the brain homogenate. A Brandel Harvestor and FP-100 Whatman GF/B fired filter paper were used for protein filtration. The filter paper in the κ-opioid receptor-binding assay was pretreated with aqueous 0.1% poly(ethyleneimine) to coat the glass fibers.[48] All glassware used in the binding assays was silanized with Prosil-28.

Opioid Receptor Binding. The binding assay was carried out essentially as described by Lin and Simon,[35] with slight modifications. Hartley-VAF Plus guinea pigs were killed by decapitation and the brains removed. The brains, less cerebellum, were homogenized in six volumes of 0.05 M Trizma buffer (pH 7.4) with a Virtrishear homogenizer at a control setting of 70 for three 5 s intervals. The homogenate was centrifuged at 25000*g* at 4 °C for 20 min. The pellet was resuspended in six volumes of aqueous 0.32 M sucrose and stored at −70 °C until needed. Frozen homogenate was thawed at room temperature and diluted with 0.05 M Trizma buffer (pH 7.4) to give a final dilution ratio of 1:60 (initial brain weight to total solution volume). Radioligands used were [^{3}H]bremazocine (0.5 nM) for total ligand binding, [^{3}H]DAMGO (1.0 nM) for μ-receptor binding, [^{3}H]DPDPE (1.0 nM) for δ-receptor binding, and [^{3}]U-69,593 (1.0 nM) for κ-receptor binding.[36–38] Synthetic ligands were tested in duplicate at nine concentrations between 1.0 and 1000 nM, except for **8** which was tested against [^{3}H]U-69,593 in triplicate at five concentrations between 0.22 and 4.7 nM. Nonspecific binding was measured in the presence of 10 μM naloxone. The samples were incubated for 60 min at 25 °C. Samples were filtered, rinsed with ice cold buffer (3 × 2 mL), eluted with 10 mL aliquots of liquid scintillation cocktail, and counted.

Irreversibility and Protection Studies. Guinea pig brain homogenate was diluted as described in the ligand displacement assay. It was then incubated with each synthetic ligand for 60 min at 25 °C. For protection studies and recovery samples, the homogenate was preincubated with 1 μM naloxone for 15 min at 37 °C. After incubation, the samples were diluted 3-fold with ice cold 0.05 M Trizma buffer (pH 7.4) and centrifuged at 10000*g* for 15 min at 4 °C. The membrane preparation was then washed by decanting the supernatant, resuspending the pellet in 3 times the original volume of ice cold buffer, incubating for 15 min at 37 °C, and then centrifugating again. This wash process was repeated, the supernatant was decanted, and the pellet was resuspended in 1.9 mL of buffer. A binding assay using [^{3}H]U-69,593 (1.0 nM) was performed as described above.

Acknowledgment. We acknowledge the support of this work by the National Institute on Drug Abuse through research grant DA 06675 and by the National Institute of General Medical Sciences through National Research Service Award GM-07750.

References

(1) Martin, W. R.; Eades, C. G.; Thompson, J. A.; Huppler, R. E.; Gilbert, P. E. The Effects of Morphine and Nalorphine-like Drugs in the Nondependent and Morphine-Dependent Chronic Spinal Dog. *J. Pharmacol. Exp. Ther.* **1976**, *197*, 517–532.
(2) Gilbert, P. E.; Martin, W. R. The Effects of Morphine and Nalorphine-like Drugs in the Nondependent, Morphine-Dependent and Cyclazocine-Dependent Chronic Spinal Dog. *J. Pharmacol. Exp. Ther.* **1976**, *198*, 66–82.
(3) Lord, J. A. H.; Waterfield, A. A.; Hughes, J.; Kosterlitz, H. W. Endogenous Opioid Peptides: Multiple Agonists and Receptors. *Nature* **1977**, *267*, 495–499.
(4) Martin, W. R. Pharmacology of Opioids. *Pharmacol. Rev.* **1983**, *35*, 283–323.
(5) Paterson, S. J.; Robson, L. E.; Kosterlitz, H. W. Classification of Opioid Receptors. *Br. Med. Bull.* **1983**, *39*, 31–36.
(6) Zukin, R. S.; Zukin, S. R. The Case for Multiple Opiate Receptors. *Trends Neurosci.* **1984**, *7*, 160–164.
(7) Cowan, A.; Gmerek, D. E. In vivo Studies on Kappa Opioid Receptors. *Trends Pharmacol. Sci.* **1986**, *7*, 69–72.
(8) Millan, M. J. κ-Opioid Receptors and Analgesia. *Trends Pharmacol. Sci.* **1990**, *11*, 70–76.
(9) Rees, D. C. Chemical Structure and Biological Activities of Non-Peptide Selective Kappa Opioid Ligands. *Prog. Med. Chem.* **1992**, *29*, 109–139.
(10) Costello, G. F.; Main, B. G.; Barlow, J. J.; Carroll, J. A.; Shaw, J. S. A Novel Series of Potent and Selective Agonists at the Opioid κ-Receptor. *Eur. J. Pharmacol.* **1988**, *151*, 475–478.
(11) Halfpenny, P. R.; Horwell, D. C.; Hughes, J.; Humblet, C.; Hunter, J. C.; Neuhaus, D.; Rees, D. C. Highly Selective κ-Opioid Analgesics. 4. Synthesis of Some Conformationally Restricted Naphthalene Derivatives with High Receptor Affinity and Selectivity. *J. Med. Chem.* **1991**, *34*, 190–194.
(12) Vecchietti, V.; Giordani, A.; Giardina, G.; Colle, R.; Clark, G. D. (2S)-1-(Arylacetyl)-2-(aminomethyl)piperidine Derivatives: Novel, Highly Selective κ-Opioid Analgesics. *J. Med. Chem.* **1991**, *34*, 397–403.
(13) Scopes, D. I. C.; Hayes, N. F.; Bays, D. E.; Belton, D.; Brain, J.; Brown, D. S.; Judd, D. B.; McElroy, A. B.; Meerholtz, C. A.; Naylor, A.; Hayes, A. G.; Sheehan, M. J.; Birch, P. J.; Tyers, M. B. New κ-Receptor Agonist Based upon a 2-[(Alkylamino)methyl]-piperidine Nucleus. *J. Med. Chem.* **1992**, *35*, 490–501.
(14) Rice, K. C.; Jacobson, A. E.; Burke, T. R.; Bajwa, B. S.; Streaty, R. A.; Klee, W. A. Irreversible Ligands with High Selectivity Toward δ or μ Opiate Receptors. *Science* **1983**, *220*, 314–316.
(15) Simonds, W. F.; Burke, T. R., Jr.; Rice, K. C.; Jacobson, A. E.; Klee, W. A. Purification of the Opiate Receptor of NG108-15 Neuroblastoma-Glioma Hybrid Cells. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 4974–4978.

(16) de Costa, B. R.; Rothman, R. B.; Bykov, V.; Band, L.; Pert, A.; Jacobson, A. E.; Rice, K. C. Probes for Narcotic Receptor Mediated Phenomena. 17. Synthesis and Evaluation of a Series of *trans*-3,4-Dichloro-N-Methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-benzeneacetamide (U50,488) Related Isothiocyanate Derivatives as Opioid Receptor Affinity Labels. *J. Med. Chem.* **1990**, *33*, 1171–1176.

(17) Barlow, J. J.; Blackburn, T. P.; Costello, G. F.; James, R.; Le Count, D. J.; Main, B. G.; Pearce, R. J.; Russell, K.; Shaw, J. S. Structure/Activity Studies Related to 2-(3,4-Dichlorophenyl)-N-methylN-[2-(1-pyrrolidinyl)-1-substituted-ethyl]acetamides: A Novel Series of Potent and Selective κ-Opioid Agonists. *J. Med. Chem.* **1991**, *34*, 3149–3158.

(18) Kim, S.; Yi, K. Y. Di-2-Pyridyl Thionocarbonate. A New Reagent for the Preparation of Isothiocyanates and Carbodiimides. *Tetrahedron Lett.* **1985**, *26*, 1661–1664.

(19) Feuer, H.; Braunstein, D. M. The Reduction of Oximes, Oxime Ethers and Oxime Esters with Diborane. A Novel Synthesis of Amines. *J. Org. Chem.* **1969**, *34*, 1817–1821.

(20) Brown, H. C.; Choi, Y. M.; Narashimhan, S. Selective Reductions. 29. A Simple Technique to Achieve an Enhanced Rate of Reduction of Representative Organic Compounds by Borane-Dimethyl Sulfide. *J. Org. Chem.* **1982**, *47*, 3153–3163.

(21) Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Nakahama, S. Catalytic Behaviour of Optically Active Amino Alcohol-Borane Complex in the Enantioselective Reduction of Acetophenone Oxime O-Alkyl Ethers. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395–396.

(22) Sakito, Y.; Yoneyoshi, Y.; Suzukamo, G. Asymmetric Reduction of Oxime Ethers. Distinction of Anti and Syn Isomers Leading to Enantiomeric Amines. *Tetrahedron Lett.* **1988**, *29*, 223–224.

(23) Didier, E.; Lubinoux, B.; Ramos Tombo, G. M.; Rihs, G. Chemo-Enzymatic Synthesis of 1,2- and 1,3-Amino-Alcohols and Their Use in the Enantioselective Reduction of Acetophenone and Anti-Acetophenone Oxime Methyl Ether with Borane. *Tetrahedron* **1991**, *47*, 4941–4958.

(24) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. Asymmetric Synthesis Using Chirally Modified Borohydrides. Part 3. Enantioselective Reduction of Ketones and Oxime Ethers with Reagents Prepared from Borane and Amino Alcohols. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039–2044.

(25) Helmchen, G.; Nill, G.; Flockerzi, D.; Schuhle, W.; Youssef, M. S. K. Extreme Liquid Chromatographic Separation Effects in the Case of Diastereomeric Amides Containing Polar Substituents. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 62–63.

(26) Helmchen, G.; Nill, G.; Flockerzi, D.; Youssef, M. S. K. Preparative Scale Directed Resolution of Enantiomeric Carboxylic Acids and Lactones *via* Liquid Chromatography and Neighbouring-Group Assisted Hydrolysis of Diastereomeric Amides. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 63–65.

(27) Helmchen, G.; Nill, G. Preparative Scale Directed Resolution of Enantiomeric Amines *via* Liquid Chromatography of Diastereomeric 4-Hydroxybutyramides. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 65–66.

(28) Pfister, J. R. Synthesis of the Enantiomers of 7,8-Dimethoxy-2-phenyl-1,2,4,5-tetrahydro-3-benzazepine. *Heterocycles* **1986**, *24*, 2099–2103.

(29) Breitholle, E. G.; Stammer, C. H. Stereoselective Formation of Pseudo Oxazolone. *J. Org. Chem.* **1974**, *39*, 1311–1312.

(30) Berlingozzi, S.; Adembri, G.; Bucci, G. Optically Active Amino Acids. XVI. Resolution of DL Forms by Asymmetric Acylation. *Gazz. Chim. Ital.* **1954**, *84*, 383–392.

(31) Pracejus, G. Optiche Activierung von N-Phthalyl-α-Aminosaure Derivaten Durch Tert-Basen-Katalyse. *Liebigs Ann. Chem.* **1959**, *622*, 10–22.

(32) Parker, D.; Taylor, R. J. Direct ^{1}H NMR Assay of the Enantiomeric Composition of Amines and β-Amino Alcohols Using O-Acetyl Mandelic Acid as a Chiral Solvating Agent. *Tetrahedron* **1987**, *43*, 5451–5456.

(33) Bose, A. K.; Lal, B.; Dayal, B.; Manhas, M. S. A Stereoselective Synthesis of α-Alkoxy-β-Lactams. *Tetrahedron Lett.* **1974**, 2633–2636.

(34) Cossio, F. P.; Palomo, C. Stereoselective Annelation of Trimethylsiloxyacetic Acids and Imines into 3-Hydroxy-β-lactams. *Tetrahedron Lett.* **1985**, *26*, 4239–4242.

(35) Lin, H.-K.; Simon, E. J. Phospholipase A Inhibition of Opiate Receptor Binding Can Be Reversed by Albumin *Nature (London)* **1978**, *271*, 383–384.

(36) Bhargava, H. N. Multiple Opiate Receptors of Brain and Spinal Cord in Opiate Addiction. *Gen. Pharmacol.* **1991**, *22*, 767–772.

(37) Leslie, F. M. Methods Used for the Study of Opioid Receptors. *Pharmacol. Rev.* **1987**, *39*, 197–249.

(38) Golstein, A.; Naidu, A. Multiple Opioid Receptors: Ligand Selectivity Profiles and Binding Site Signatures. *Mol. Pharmacol.* **1989**, *36*, 265–272.

(39) Cheng, C.-Y.; Wu, S.-C.; Hsin, L.-W.; Tam, S. W. Selective Reversible and Irreversible Ligands for the κ Opioid Receptor. *J. Med. Chem.* **1992**, *35*, 2243–2247.

(40) deCosta, B. R.; Rothman, R. B.; Bykov, V.; Jacobson, A. E.; Rice, K. C. Selective and Enantionspecific Acylation of κ Opioid Receptors by (1S,2S)-*trans*-2-Isothiocyanato-N-methyl[2-(1-pyrrolidinyl)cyclohexyl]benzacetamide. Demonstration of κ Receptor Heterogeneity. *J. Med. Chem.* **1989**, *32*, 281–283.

(41) deCosta, B. R.; Band, L.; Rothman, R. B.; Jacobson, A. E.; Bykov, V.; Pert, A.; Rice, K. C. Synthesis of an Affinity Ligand ('UPHIT') for In Vivo Acylation of the κ-Opioid Receptor. *FEBS Lett.* **1989**, *249*, 178–192.

(42) Chen, Y.; Mestek, A.; Lin, J.; Yu, L. Molecular Cloning of a Rat Kappa Opioid Receptor Reveals Sequence Similarities to the Mu and Delta Opioid Receptors. *Biochem. J.* **1993**, *295*, 625–628.

(43) Lin, S.; Zhu, J.; Chen, C.; Chen, Y.; Deriel, J.; Ashby, B.; Liu-Chen, L. Molecular Cloning and Expression of a Rat Kappa Opioid Receptor. *Biochem. J.* **1993**, *295*, 629–633.

(44) Yasuda, K.; Raynor, K.; Kong, H.; Breder, D.; Takeda, J.; Reisine, T.; Bell, G. I. Cloning and Functional Comparison of Kappa and Delta Opioid Receptors from Mouse Brain. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6736–6740.

(45) Chang, A.-C.; Takemori, A. E.; Portoghese, P. S. 2-(3,4-Dichlorophenyl)-N-methyl-N-[(1S)-1-(3-isothiocyanatophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide: An Opioid Receptor Label That Produced Selective and Long-Lasting κ-Antagonism in Mice. *J. Med. Chem.* **1994**, *37*, 1547–1549.

(46) Masaki, M.; Fukui, K.; Ohta, M. The Reaction of α-Halo Oxime and Triphenylphosphine. Formation of Imidoyl Bromide and of Oximinophosphonium Salts by a Novel Catalytic Effect of Bases. *J. Org. Chem.* **1967**, *32*, 3564–3568.

(47) Fischer, H. P.; Grob, C. A. Herstellung und Konfigurationsbestimmung von *syn* und *anti* α-Aminoketoxim-Derivaten. *Helv. Chim. Acta* **1962**, *45*, 2528–2538.

(48) Houghten, R. A.; Johnson, N.; Pasternak, G. W. [^{3}H]-Beta-Endorphine Binding in Rat Brain. *J. Neurosci.* **1984**, *4*, 2460–2465.