# Probes for Narcotic Receptor Mediated Phenomena. 23.[1] Synthesis, Opioid Receptor Binding, and Bioassay of the Highly Selective δ Agonist (+)-4-[(α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (SNC 80) and Related Novel Nonpeptide δ Opioid Receptor Ligands

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The highly selective delta (δ) opioid receptor agonist SNC 80 [(+)-4-[(α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide, **(+)-21**] and novel optically pure derivatives were synthesized from the enantiomers of 1-allyl-*trans*-2,5-dimethylpiperazine (**2**). The piperazine **(±)-2** was synthesized, and its enantiomers were obtained on a multigram scale in >99% optical purity by optical resolution of the racemate with the camphoric acids. The absolute configuration of **(+)-2** was determined to be 2*S*,5*R* by X-ray analysis of the salt with (+)-camphoric acid. Since the chirality of the starting material was known, and the relative configuration of compounds **(−)-21**, **(−)-22**, and **(+)-23** were obtained by single-crystal X-ray analysis, the assignment of the absolute stereochemistry of the entire series could be made. Radioreceptor binding studies in rat brain preparations showed that methyl ethers **(+)-21** (SNC 80) and **(−)-25** exhibited strong selectivity for rat δ receptors with low nanomolar affinity to δ receptors and only micromolar affinity for rat mu (μ) opioid receptors. Compounds **(−)-21**, **(−)-22**, and **(−)-23** showed micromolar affinities for δ opioid receptors. The unsubstituted derivative **(+)-22** and the fluorinated derivative **(−)-27** showed >2659- and >2105-fold δ/μ binding selectivity, respectively. The latter derivatives are the most selective ligands described in the new series. Studies with some of the compounds described in the isolated mouse vas deferens and guinea pig ileum bioassays revealed that all were agonists with different degrees of selectivity for the δ opioid receptor. These data show that **(+)-21** and **(+)-22** are potent δ receptor agonists and suggest that these compounds will be valuable tools for further study of the δ opioid receptor at the molecular level, including its function and role in analgesia and drug abuse.

## Introduction

Intensive research for the last two decades has led to the identification of three types of opioid receptors, referred to as mu (μ), delta (δ), and kappa (κ), and to the description of subtypes for each.[2] It has become clear that each receptor mediates unique pharmacological responses and is differentially distributed in the central nervous system.[3] Recent advances in the understanding of the δ opioid receptor pharmacology have highlighted the important role of this receptor in the modulation of pain[4] and in the release of mesolimbic dopamine.[5] It is known that agonists acting at the δ opioid receptor produce analgesia in animal models of pain while appearing to show a limited ability to produce the undesirable effects associated with prototypic analgesic drugs such as morphine.[6] Recently, it has been recognized that opposing tonically active endogenous opioid systems modulate the mesolimbic dopaminergic pathways and control reinforcing behavior by mediation of dopamine release in reward circuits of the brain and that this system can be altered by exogenous opioids.[5a,b] Studies in human brain autopsy tissue,[7] positron emission tomography (PET) studies in humans,[8a] and *ex vivo* autoradiographic studies in rats[8b] have revealed that cocaine alters the opioid receptor endorphin system. In addition, the δ opioid agonist DPLPE produces a cocaine-like discriminative stimulus[9] and the δ opioid receptor antagonist, naltrindole, blocks the cocaine-induced facilitation of responding for rewarding brain stimulation.[10] These and other studies[11] indicate a linkage between the opioid system and those involved in the mediation of the reinforcing effects of cocaine. Thus, the δ opioid receptor system has become an attractive candidate for the development of analgesics and for the study of novel approaches in the treatment of drug addiction and perhaps other reinforcing behaviors. Progress in the study of the δ opioid pharmacology

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is dependent on the development of highly selective and potent δ opioid ligands with good central bioavailability. We have thus undertaken the design and synthesis of such compounds.

The discovery and identification of BW373U86 [**(±)-1**] (Scheme 2) as a highly selective nonpeptide δ receptor agonist with a novel carbon−nitrogen skeleton is a major advance in this area.[12] Subsequent studies *in vivo* confirmed that **(±)-1** was a δ receptor agonist which produced some of its effects through μ receptors.[13]

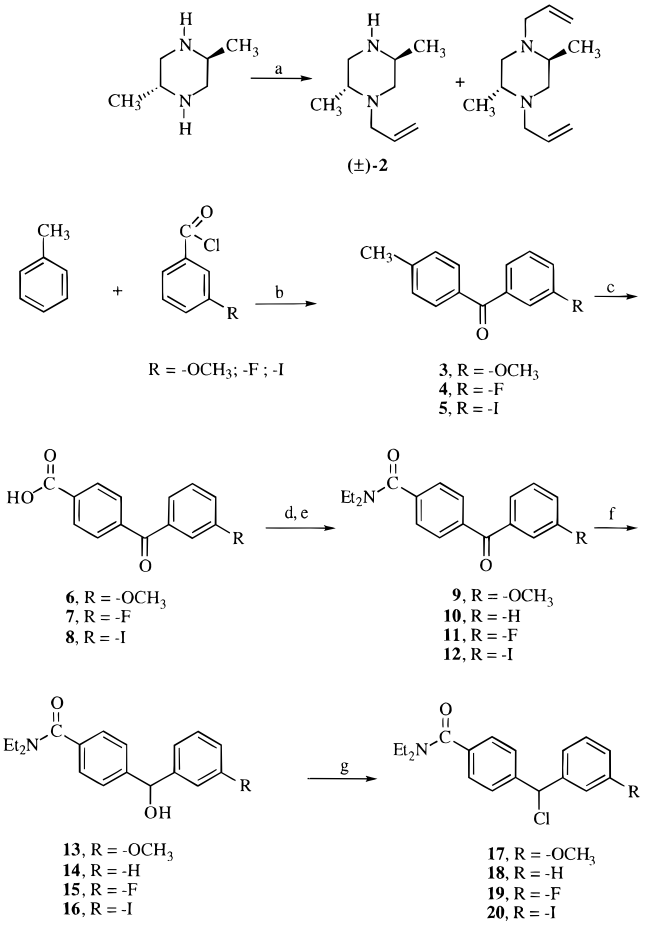
Recently, we reported the synthesis and absolute configuration of the optically pure enantiomers of the nonpeptide δ opioid agonist, **(±)-1**, its benzylic epimers, and their methyl ethers.[14] This work was designed to begin a detailed study of stereochemistry in relation to δ receptor pharmacology in this series and to avoid the well-known problems inherent in the study of racemates.[15] From this first series of compounds, **(+)-21** (SNC 80) exhibited a remarkable μ/δ selectivity in both receptor binding and bioassays. This compound was shown to be a systemically active opioid agonist in the mouse; this compound exerts its effects through both δ1 and δ2 (but not μ) receptors.[16]

On the basis of our previous results, and in an effort to further characterize the structural requirements for agonist and antagonist activity at the δ opioid receptor, we now report the synthesis of a novel series of **(+)-21** related compounds. It is well-known that small changes in the aromatic substituents of opioids can have dramatic effects on biological activity as in the benzimidazole series of which etonitazene is the prototype.[17] The effect of the replacement of the methoxy group present in **(+)-21** by a hydroxyl function, hydrogen, fluorine, or iodine was analyzed. The latter substitution was studied in the context of development of a δ receptor ligand for SPECT imaging studies. Herein, we described the synthesis of these enantiomerically pure derivatives of **(+)-21**, their benzylic epimers, and the optical resolution of the piperazine intermediate **(±)-2**.

## Chemistry

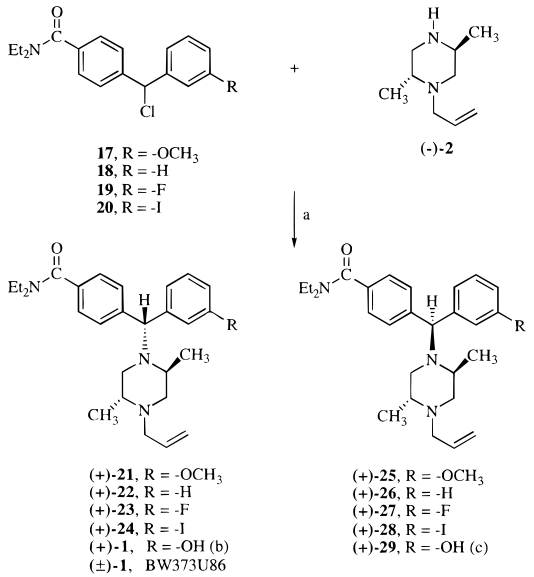
The novel SNC 80 analogs were synthesized according to the procedure[14] outlined in Schemes 1 and 2. Repetition of Scheme 2 with piperazine **(+)-2** gave the corresponding **(−)**-enantiomers of these compounds. Our synthetic route involved the assembly of these molecules from two components: (a) the appropriate benzhydryl chloride and (b) the *trans*-1-allyl-2,5-dimethylpiperazine enantiomers. This approach offers the dual advantage that only one optical resolution is required, that of the *trans*-1-allyl-2,5-dimethylpiperazine [**(±)-2**],[18] and that both optically pure, readily separable, benzylic epimers were obtained in a single step which facilitated our study of the effect of stereochemistry on receptor selectivity. The disclosure describing **(±)-1**, its enantiomers, and related compounds prepared by a similar route has appeared.[19a] More recently, a stereoselective synthesis of **(+)-21** from the piperazine **(−)-2** has been described which affords 60% of **(+)-1** and **(+)-29** in a ratio of approximately 93:7, in favor of the desired **(+)-1**.[19b] The optical resolution[14] of **(±)-2** was achieved using (+)- and **(−)**-camphoric acids which provided **(+)-(2*S*,5*R*)-** and **(−)-(2*R*,5*S*)-2** of >99% optical purity as determined by HPLC of the ureas formed with 1-naphthyl isocyanate on a Chiracel OD chiral column. Due to difficulties in the availability and cost of the unnatural **(−)**-camphoric acid and our need of a large amount of **(−)-2**, we explored the possibility of obtaining the desired piperazine through an enantiospecific

**Scheme 1**[a]



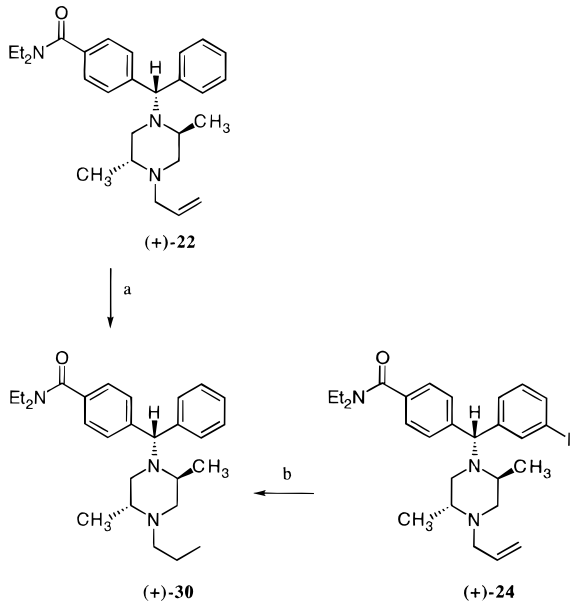

[a] (a) Allyl bromide/ethanol;[18] (b) $AlCl_3$/nitromethane; (c) $KMnO_4$/*tert*-butyl alcohol/$H_2O$; (d) $SOCl_2$; (e) 44% $Et_2NH$; (f) $NaBH_4$; (g) 36% HCl.

**Scheme 2**[a]




[a] (a) $K_2CO_3$/acetonitrile, reflux for 72 h; (b) from **(+)-21** using $BBr_3$; (c) from **(+)-25** using $BBr_3$.

**Scheme 3**[a]




[a] (a) $H_2$/10% Pd−C/ethanol; (b) $H_2$/10% Pd−C/20% acetic acid/sodium acetate.

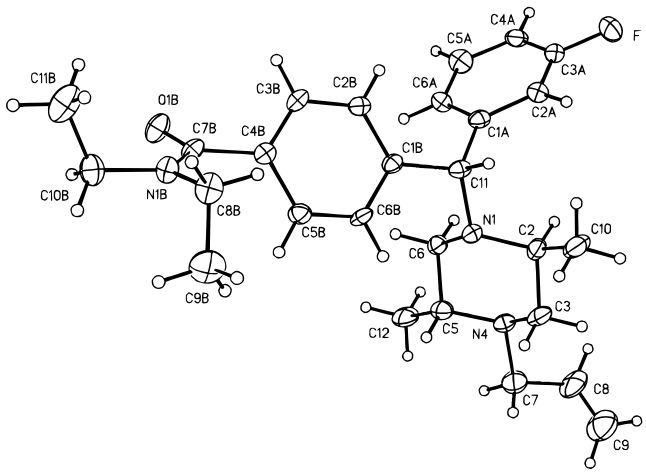



**Figure 1.** Results of the X-ray studies for compound **(+)-23**. The figure is drawn using the experimentally determined coordinates with thermal parameters at the 20% probability level.

synthesis.[19a] Boc-*N*-allyl-D-alanine was obtained by treatment of the commercially available Boc-D-alanine with allyl bromide using sodium hydride as base[20] in tetrahydrofuran or by modification of the procedure described by Hansen and Pilipauskas[21] that required the use of *tert*-butyllithium. Dicyclohexylcarbodiimide (DCC) or 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) promoted coupling with L-alaninemethyl ester,[20,22] and subsequent deprotection and cyclization of the boc dipeptide using 98% formic acid[23] gave the *trans*-dimethyldiketopiperazine. Reduction of the diketopiperazine using lithium aluminum hydride gave the piperazine **(−)-2**. Racemization throughout this route was not observed. and the optical purity of the piperazine obtained in this way was assessed by measurement of the optical rotation and by HPLC under the conditions mentioned above. Although this approach provided **(−)-2,** it proved to be less practical for our purposes than the shorter, two-step alkylation−optical resolution sequence of **(±)-2**. The absolute configuration of **(+)-2** was determined as 2*S*,5*R* by single-crystal X-ray analysis of the salt with (+)-camphoric acid.[14] These data and the X-ray determination of the relative configuration of compounds **(−)-21**,[14] **(−)-22**, **(+)-23**, and **(+)-30** allowed the assignment of the absolute configuration of the compounds shown in Scheme 2, their enantiomers, and other compounds described herein. The results of the X-ray studies on compound **(+)-23** are illustrated in Figure 1. Compounds **(+)-24** and **(+)-28** did not give crystals suitable for X-ray analysis. The absolute configuration of **(+)-24** and **(+)-28** was assigned as α*R*,2*S*,5*R* and α*S*,2*S*,5*R* by interchemical correlation and unequivocally by X-ray analysis of compound **(+)-30**. As outlined in Scheme 3, compound **(+)-30** was obtained by reduction of the allylic double bond and hydrogenolysis of the aromatic iodine of **(+)-24** under catalytic conditions. The same compound, **(+)-30**, was obtained by catalytic hydrogenation of **(+)-22** of previously determined absolute configuration.

## Results and Discussion

The affinities of the compounds described for $\mu$ and $\delta$ receptors (Table 1) were determined by inhibition of binding of [$^3$H]DAMGO[24] and [$^3$H]DADLE[25] to rat brain membranes using 100 nM DAMGO to block $\mu$ receptors. The enantiomers of **1** and their benzylic epimers **29** showed high affinity for $\delta$ receptors and retained varying affinity for $\mu$ receptors. In this phenolic series, **(+)-1** and **(−)-29** showed highest affinity for $\delta$ opioid receptors, in the binding assays. However, these compounds retained significant $\mu$ binding affinity which limited their selectivity to 6.5 and 95.9, respectively, as measured by the $\mu/\delta$ $IC_{50}$ ratio.

The most selective compounds in these new series are **(+)-21** (SNC 80), **(+)-22**, **(+)-23**, **(+)-24**, **(−)-25, (−)-26**, and **(−)-27**. These compounds have the same spatial orientation of the substituents at the benzhydryl α position, and this orientation seems to be the preferred one for binding at the $\delta$ opioid receptor. It should be noted that the spatial orientation at the α position of **(+)-22** and **(−)-26** is the same as in **(+)-21** and **(−)-25**,

**Table 1.** Inhibition of Radioligand Binding to Rat Brain $\mu$ and $\delta$ Receptors

| | $IC_{50}$, nM ± SD | | |
|---|---|---|---|
| compound | $\mu$ binding[a] | $\delta$ binding[b] | $\mu/\delta$ ratio |
| **(+)-1** | 9.71 ± 0.37 | 1.49 ± 0.33 | 6.5 |
| **(−)-1** | 2322 ± 199 | 58.3 ± 6.56 | 39.8 |
| **(+)-21** | 2467 ± 200 | 2.88 ± 0.35 | 856.6 |
| **(−)-21** | 9366 ± 798 | 430.0 ± 41.2 | 21.8 |
| **(+)-22** | >2500 | 0.94 ± 0.09 | >2659.6 |
| **(−)-22** | >10000 | 852 ± 106 | >11.7 |
| **(+)-23** | 1977 ± 260 | 2.92 ± 0.36 | 677.1 |
| **(−)-23** | >10000 | 1375 ± 110 | >7.3 |
| **(+)-24** | 1227 ± 171 | 3.91 ± 0.33 | 313.8 |
| **(+)-25** | 5712 ± 457 | 63.3 ± 13.2 | 90.2 |
| **(−)-25** | 9138 ± 823 | 4.88 ± 0.52 | 1872.5 |
| **(+)-26** | >10000 | 60.0 ± 5.62 | >166.7 |
| **(−)-26** | 8446 ± 447 | 9.22 ± 2.16 | 916.1 |
| **(+)-27** | >10000 | 62.5 ± 25.7 | >160.0 |
| **(−)-27** | >10000 | 4.75 ± 0.31 | >2105.3 |
| **(+)-28** | 3378 ± 618 | 41.1 ± 5.25 | 82.2 |
| **(+)-29** | 426 ± 53 | 11.4 ± 0.97 | 37.4 |
| **(−)-29** | 167 ± 42 | 1.74 ± 0.10 | 95.9 |

[a] Binding against [$^3$H]DAMGO. [b] Binding against [$^3$H]DADLE.

**Table 2.** Agonist Activity in the Mouse Vas Deferens (MVD) and Guinea Pig Ileum (GPI) Bioassays

| compound | $IC_{50} \pm SEM$, nM GPI ($\mu$ receptors) | $IC_{50} \pm SEM$, nM MVD ($\delta$ receptors) | $IC_{50}$ ratio: GPI ($\mu$)/MVD ($\delta$) |
|---|---|---|---|
| DPDPE | 7300 ± 1700 | 5.1 ± 0.5 | 1800 |
| [D-Ala$^2$,Glu$^4$]deltorphin | 15000 ± 1000 | 0.85 ± 0.07 | 17647 |
| **(+)-21** | 5457.00 ± 2052.00 | 2.73 ± 0.48 | 1998.90 |
| **(+)-22** | 8583.00 ± 1304.00 | 10.56 ± 0.38 | 812.78 |
| **(+)-23** | 2596.00 ± 740.00 | 9.77 ± 1.28 | 264.90 |
| **(+)-24** | >3000[a] | 44.21 ± 9.27 | ND |
| **(−)-25** | 1517.00 ± 214.00 | 30.89 ± 4.05 | 49.11 |
| **(−)-26** | 1778 ± 330[a] | 126.2 ± 10.7 | ND |
| **(+)-21** + ICI174864 (SR)[b] | | 646.8 ± 269.3 (236.9) | |
| **(+)-21** + CTAP (SR) | | 5.34 ± 1.6 (1.9) | |
| **(+)-22** + ICI174864 (SR) | | 182.4 ± 21.4 (17.3) | |
| **(+)-22** + CTAP (SR) | | 14.07 ± 0.9 (1.3) | |
| **(+)-23** + ICI174864 (SR) | | 199.54 ± 75.46 (20.4) | |
| **(+)-23** + CTAP (SR) | | 10.25 ± 2.44 (1.04) | |

[a] The $IC_{50}$ was not shifted by naloxone. [b] Shift ratio (SR), $IC_{50}$ in the presence of the antagonist/$IC_{50}$ in the absence of the antagonist.

and the designation of α*R*-[**(+)-21** and **(−)-25**] and α*S*-[**(+)-22** and **(−)-26**] is arbitrary and results from the application of the Cahn, Ingold, and Prelog nomenclature rules.[26] Other studies have shown that replacement of the N-4 nitrogen with its allyl group by oxygen or a methylene group abolishes opioid binding affinity.[27]

A remarkable $\delta$ receptor enantioselectivity was observed with compounds **21**, **22**, and **23**. Whereas the dextro enantiomers showed nanomolar affinity for $\delta$ opioid receptors, their levo antipodes showed affinity for the same receptors in the micromolar range.

The opioid like activity of the most selective compounds was evaluated in mouse vas deferens (MVD) and guinea pig ileum (GPI) preparations (Table 2).[28] All of the compounds showed agonist activity with differing degrees of selectivity. These studies also revealed that the high pharmacologic $\delta$ selectivity observed for compounds **(+)-21**, **(+)-22**, and **(+)-23** paralleled their high $\delta$ receptor affinity and these compounds are the most selective and potent ones *in vitro* binding and in bioassays. Compounds **(+)-24** and **(−)-25** are more selective in the binding assays than in functional assays. The $\delta$ activity of compounds **(+)-21**, **(+)-22,** and **(+)-23** was confirmed by determination of the $IC_{50}$ in the presence of 1 $\mu$M of the $\delta$ antagonist ICI 174,684[29] and separately in the presence of 1 $\mu$M of the $\mu$ antagonist CTAP.[30] In these assays, ICI 174,684 produced an $IC_{50}$ shift of 270, 17.3, and 20.4, respectively, whereas CTAP only shifted the $IC_{50}$ of these two compounds 1.9-, 1.3-, and 1.04-fold, respectively.

In conclusion, we have developed a practical synthesis of **(+)-21** and related derivatives. Some of the novel analogs of **(+)-21** showed high selectivity for $\delta$ opioid receptors in binding assays and in bioassays (MVD and GPI). The data previously presented confirm that **(+)-21** and **(+)-22** are extremely selective $\delta$ opioid agonists. Thus, these ligands together with the novel heterocycle-condensed derivatives of octahydroisoquinolines[31] (TAN-67 and related analogs) are among the most selective nonpeptide $\delta$ opioid agonists described. Further studies are required to determine $\delta$ receptor subtype selectivity in this series. Additional structure−activity relationship studies using **(+)-21** and **(+)-22** as a template are in progress to develop highly selective affinity labels and other research tools.

## Experimental Section

**General Instrumentation and Methods.** Proton NMR were recorded for the free bases of all compounds on a Varian Gemini-300 spectrometer, and the data is reported in the following format: chemical shift (all relative to $Me_4Si$), multiplicity (s = singlet, d =doublet, t = triplet, m = multiplet, br = broad), coupling constants, and integration. Chemical ionization mass spectra (CIMS, $NH_3$) were recorded on a Finnigan 4600, and high-resolution mass spectra were recorded on a VG-70E spectrometer. Infrared spectra (IR) were recorded on a Bio-Rad FTS-45 spectrophotometer. Polarimetric measurements were taken using a Perkin-Elmer 241 MC polarimeter. Thin layer chromatography (TLC) was performed on Analtech silica gel GHLF 0.25 mm plates. Flash column chromatography was performed with Fluka silica gel 60 (mesh 220−440). Drying refers to the use of $Na_2SO_4$. High-pressure liquid chromatography (HPLC) was performed on a Shimadzu LC-6A equipped with a SPD-SAV detector, a CR-601 plotter, and a Daicel Chiracel OD column. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA, and were within 0.4% of the theoretical values. Melting points were recorded on a Thomas-Hoover capillary apparatus and are uncorrected. All compounds exhibited NMR, IR, and mass spectral data consistent with those of the structures assigned. The yields reported are not optimized.

**(+)-4-[(α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]-*N*,*N*-diethylbenzamide [(+)-1, (+)-BW373U86].** A solution of $BBr_3$ (0.44 mL, 4.64 mmol) in 13 mL of pentene-stabilized (ps) $CHCl_3$ was added dropwise to a solution of **(+)-21**[14] (0.52 g, 1.16 mmol) in 14 mL of ps $CHCl_3$ at −30 °C. After the addition was completed, the reaction mixture was allowed to warm to 20 °C and quenched with 15 mL of MeOH. The volatiles were removed under reduced pressure. This procedure was repeated twice. The residue was dissolved in a solution of 15% $NH_4OH$, and the pH of the solution was adjusted to 9 by addition of 1 M HCl. The desired compound was extracted with $CHCl_3$ (3 × 10 mL). The volatiles were removed under reduced pressure, and the residue was purified by flash chromatography ($CHCl_3$/MeOH, 10:0.8) to give 0.21g (42%) of **(+)-1** as a glass: $^1$H NMR ($CDCl_3$) $\delta$ 0.95 (d, $J$ = 6.0 Hz, 3H), 1.15−1.28 (m, 9H), 1.91 (br t, 1H), 2.15 (br t, 1H), 2.53−2.90 (m, 5H), 3.25−3.60 (m, 5H), 5.11−5.25 (m, 3H), 5.78−5.93 (m, 1H), 6.65−6.70 (m, 1H), 6.88−6.91 (m, 2H), 7.07−7.15 (m, 1H), 7.20 (d, $J$ = 8.2 Hz, 2H), 7.35 (d, $J$ = 8.2 Hz, 2H); CIMS $m/z$ 436 ($MH^+$); $[\alpha]^{20}_D$ = +18.6° (*c* 1.0, MeOH). **(+)-1·*p*-Di-toluyl-L-tartrate,** mp 152−153 °C. This salt was recrystallized from ethanol/water, $[\alpha]^{22}_D$ = −55.1° (*c* 1.0, MeOH). Anal. ($C_{47}H_{55}N_3O_{10}\cdot 1.5H_2O$) C, H, N.

**(−)-4-[(α*S*)-α-((2*R*,5*S*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]-*N*,*N*-diethylbenzamide [(−)-1, (−)-BW373U86].** Compound **(−)-1** was obtained as a glass from **(−)-21** (48%) according to the procedure described for the synthesis and purification of compound **(+)-1**: $^1$H NMR

(DMSO-$d_6$) $\delta$ 0.95 (d, $J$ = 6.1 Hz, 3H), 1.12 (br d, 9H), 1.80−1.90 (br t, 1H), 2.11 (br t, 1H), 2.65−2.90 (m, 5H), 3.13−3.58 (m, 5H), 5.08−5.25 (m, 3H), 5.74−5.91 (m, 1H), 6.73−6.85 (m, 3H), 7.12−7.18 (m, 1H), 7.31 (d, $J$ = 8.1 Hz, 2H), 7.45 (d, $J$ = 8.1 Hz, 2H); CIMS $m/z$ 436 ($MH^+$); $[\alpha]^{20}_D$ = −18.4° (*c* 1.0, MeOH). **(−)-1·Di-*p*-toluyl-D-tartrate:** recrystallized from ethanol/water; mp 147−149 °C; $[\alpha]^{22}_D$ = +54.8° (*c* 1.0, MeOH). Anal. ($C_{47}H_{55}N_3O_{10}\cdot H_2O$) C, H, N.

**(±)-*trans*-1-Allyl-2,5-dimethylpiperazine [(±)-2].** A modification of the procedure described by Ikeda et al.[18] was used. A solution of allyl bromide (60.6 mL, 700.6 mmol) in 200 mL of anhydrous EtOH was added dropwise to a solution of *trans*-2,5-dimethylpiperazine (American Tokyo Kasei, 100 g, 875.7 mmol) in 300 mL of anhydrous EtOH. The reaction was allowed to stir at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was taken up in 600 mL of 15% KOH. Several extractions were made with ether (10 × 100 mL). The combined organic layers were dried, and the volatiles were evaporated under reduced pressure to give 84.43 g of a mixture of monoallyl- and diallyl-*trans*-2,5-dimethylpiperazine. The unreacted starting material was extracted with $CHCl_3$ (5 × 100 mL) from the alkaline solution, and after evaporation of the volatiles under reduced pressure, 18.21 g (159.47 mmol, 18.2%) of starting material was recovered. Compound **(±)-2** was purified by fractional crystallization of the salt formed with oxalic acid. A solution of the monoallyl- and diallyl-*trans*-2,5-dimethylpiperazine (84.43 g) in 450 mL of acetone was added to a solution of oxalic acid (49.28 g, 547 mmol) in 400 mL of acetone. The salt was filtered, and the filter cake was washed several times with acetone. This procedure was followed by recrystallization of the salt from water/methanol. The salt was dissolved in 15% NaOH, and the free base (39.65 g) was extracted with $CHCl_3$: bp 60−61 °C/5 mmHg (lit.[16] bp 175−176 °C, bp 109−112 °C/55 mmHg); $^1$H NMR ($CDCl_3$) $\delta$ 1.01 (d, $J$ = 6.0 Hz, 3H), 1.05 (d, $J$ = 6.0 Hz, 3H), 1.77 (t, $J$ = 11.1 Hz, 1H), 2.21−2.29 (m, 1H), 2.58 (t, $J$ = 11.2 Hz, 1H), 2.81−2.90 (m, 4H), 3.43−3.50 (m, 1H), 5.14−5.20 (m, 2H), 5.82−5.95 (m, 1H); CIMS $m/z$ 155 ($MH^+$).

**(+)-(2*S*,5*R*)-1-Allyl-2,5-dimethylpiperazine [(+)-2]**. A solution of **(±)-2** (30.58 g, 198.3 mmol) in 250 mL of acetone was added to a solution of (+)-camphoric acid (19.85 g, 99.14 mmol) in 100 mL of acetone. The salt was filtered and recrystallized from a solution of 300 mL of MeOH and 700 mL of acetone. The precipitate was recrystallized twice from a mixture of methanol/acetone. **(+)-2·(+)-Camphoric acid:** mp 179−181 °C; yield 24.48 g (70%); $[\alpha]^{20}_D$ = +46.8° (*c* 1.0, MeOH). Anal. ($C_{19}H_{34}N_2O_4$) C, H, N. The salt was dissolved in 15% NaOH and the free base was extracted with $CHCl_3$. The organic layer was dried, and the volatiles were evaporated under reduced pressure to give of **(+)-2**, $[\alpha]^{20}_D$ = +55.5° (*c* 1.4, EtOH). Optical purity was shown to be >99% by HPLC (Chiracel OD, 1.0 mL/min, 1:1 hexanes/2-PrOH/0.1% $Et_2NH$) of the ureas formed with 1-naphthyl isocyanate. A solution of 21.4 mg of the free base in 0.2 mL of ps $CHCl_3$ was added dropwise to a solution of 20 $\mu$L of 1-naphthyl isocyanate in 0.2 mL of ps $CHCl_3$, and the reaction mixture was allowed to stay at room temperature for 10 min. The absence of starting material was checked by TLC ($CHCl_3$/MeOH/$NH_4OH$, 90:10:0.5). The solvent was evaporated, and the residue was dissolved in 2-PrOH. The approximate retention time was 6.26 min, observing at 254 nm.

**(−)-(2*R*,5*S*)-1-Allyl-2,5-dimethylpiperazine [(−)-2].** All of the filtrates from the above resolution were evaporated to dryness under reduced pressure, and the residue was treated with 100 mL of 15% NaOH. This aqueous solution was extracted with $CHCl_3$ (4 × 100 mL). The organic layers were dried, and evaporation gave a yellow oil. A 15.26 g portion of this oil was dissolved in 50 mL of warm acetone and added to a solution of 19.81 g of **(−)**-camphoric acid (Aldrich) in 125 mL of acetone. The isolated crystals were recrystallized from a solution of 85 mL of MeOH and 100 mL of acetone. The precipitate was recrystallized twice from a mixture of methanol/acetone. **(−)-2·(−)-Camphoric acid salt:** mp 178−180 °C; yield 26.11 g (74%); $[\alpha]^{20}_D$ = −46.7° (*c* 1.0, MeOH). Anal. ($C_{19}H_{34}N_2O_4$) C, H, N. The salt was dissolved in 15% NaOH, and the free base was extracted with $CHCl_3$. The organic layer was dried, and the volatiles were evaporated under reduced pressure to give of **(−)-2**, $[\alpha]^{20}_D$ = −52.3° (*c* 2.5, EtOH). Optical purity was shown to be >99% by HPLC (1.0 mL/min, 1:1 hexanes/2-PrOH/0.1% $Et_2NH$) of the ureas formed with 1-naphthyl isocyanate. A solution of 53.6 mg of the free base in 0.5 mL of ps $CHCl_3$ was added dropwise to a solution of 50 mL of 1-naphthylisocyanate in 0.5 mL of ps $CHCl_3$. After 10 min the absence of starting material was verified by TLC ($CHCl_3$/MeOH/$NH_4OH$, 90:10:0.5). The solvent was evaporated, and the residue was dissolved in 2-PrOH. The approximate retention time was 13.86 min, observing at 254 nm.

**3-Methoxy-4′-methylbenzophenone (3)**. A solution of $AlCl_3$ (86.02 g, 64.52 mmol) in 600 mL of nitromethane was cooled to 20 °C, and *m*-anisoyl chloride (Aldrich, 100 g, 586.5 mmol) was added dropwise within 1 min. After the solution was stirred at 20 °C for 20 min, anhydrous toluene (156 mL) was added dropwise. After the addition was completed, the reaction mixture was allowed to stir at room temperature for 45 min. The reaction mixture was poured over a mixture of 3 kg of ice and 150 mL of 37% HCl. The mixture was transferred to a separatory funnel and washed with $CHCl_3$ (3 × 500 mL). The organic layers were combined and washed with water (3 × 250 mL). The solvent was evaporated under reduced pressure, and the remaining nitromethane was azeotropically distilled with toluene (3 × 100 mL). The residue was taken in 600 mL of ether and washed with 15% NaOH (4 × 200 mL) and water (2 × 150 mL). The solution was dried and the solvent evaporated under reduced pressure. The residue was distilled, and the main fraction (111.0 g, 84%) was collected at 147−151 °C/0.3 mmHg: mp 40−42 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.45 (s, 3H), 3.85 (s, 3H), 7.10−7.14 (m, 1H), 7.30−7.35 (m, 5H), 7.73 (d, $J$ = 7.8 Hz, 2H); CIMS $m/z$ 227 ($MH^+$), 244 ($MH^+$ + 17); IR 1651 $cm^{-1}$. Anal. ($C_{15}H_{14}O_2$) C, H.

**3-Fluoro-4′-methylbenzophenone (4).** Compound **4** was obtained according to the procedure described for the synthesis and purification of compound **3**. A solution of $AlCl_3$ (23.12 g, 173.4 mmol) in 150 mL of nitromethane was cooled to 20 °C. Neat 3-fluorobenzoyl chloride (Aldrich, 25.0 g, 157.7 mmol) was added dropwise within 1 min to the above solution. After the solution was stirred at 20 °C for 20 min, anhydrous toluene (41.9 mL) was added dropwise. After the addition was completed, the reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was poured over a mixture of 200 g of ice and 100 mL of 37% HCl. The mixture was transferred to a separatory funnel and washed with $CHCl_3$ (3 × 100 mL). The organic layers were combined and washed with water (2 × 50 mL). The solvent was evaporated under reduced pressure. The residue was dissolved in 50 mL of $CHCl_3$ and washed with 15% NaOH (4 × 25 mL) and water (2 × 25 mL). The solution was dried and the solvent evaporated under reduced pressure to give 30.09 g (88%) of **4**. This crystalline residue was homogeneous by TLC (hexane/ethyl acetate, 5:1), and it was recrystallized from hexane: mp 48−50 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.44 (s, 3H), 7.26−7.31 (m, 1H), 7.41−7.58 (m, 3H), 7.72 (d, $J$ = 7.9 Hz, 2H); CIMS $m/z$ 215 ($MH^+$), 232 ($MH^+$ + 17). Anal. ($C_{14}H_{11}OF$) C, H.

**3-Iodo-4′-methylbenzophenone (5).** A mixture of 3-iodobenzoic acid (10.4 g, 42.1 mmol), thionyl chloride (105 mL), and catalytic amounts of anhydrous DMF was heated at reflux for 2 h. The reaction mixture was evaporated under reduced pressure to give 3-iodobenzoyl chloride as a colorless oil. The residue was dissolved in anhydrous dichloromethane (105 mL), and aluminum chloride (14.0 g, 105.0 mmol) was added under ice−water cooling. Anhydrous toluene (22 mL, 207.0 mmol) was added slowly to this mixture in an ice−water bath, and the reaction mixture was stirred for 2.5 h at room temperature. To this mixture was added slowly 105 mL of 1 N hydrochloric acid under ice−water cooling, and the mixture was stirred for 30 min at room temperature. The organic layer was separated, washed with water and with a saturated solution of $NaHCO_3$, and dried, and the volatiles were evaporated under reduced pressure. Flash chromatography (silica gel, eluted with hexanes/dichloromethane, 9:1, and hexanes/dichloromethane, 1:1) followed by recrystallization from isopropyl ether gave compound **5** (10.25 g, 75.6%): $^1$H NMR ($CDCl_3$) $\delta$ 2.46 (s, 3H), 7.23

(t, $J$ = 8.0 Hz, 1H), 7.30 (d, $J$ = 8.0 Hz, 2H), 7.71 (d, $J$ = 8.0 Hz, 2H), 7.73 (d, $J$ = 8.0 Hz, 1H), 7.92 (d, $J$ = 8.0 Hz, 1H), 8.12 (s, 1H); CIMS $m/z$ 323 ($MH^+$).

**4-(3-Methoxybenzoyl)benzoic Acid (6).** $KMnO_4$ (32.16 g, 203.50 mmol) was added to a rapidly mechanically stirred solution of **3** (40.00 g, 177.0 mmol) in a mixture of 200 mL of *tert*-butyl alcohol and 75 mL of water. The reaction mixture was heated at reflux for 2.5 h. An additional 16.10 g (101.9 mmol) of $KMnO_4$ was added together with 50 mL of a 1:1 mixture of *tert*-butyl alcohol/water. The reaction mixture was refluxed until the permanganate color disappeared (about 2 h). Finally, an additional 16.10 g (101.9 mmol) of $KMnO_4$ and 100 mL of a 1:1 mixture of *tert*-butyl alcohol/water were added, and the reaction mixture was refluxed until the permanganate color disappeared (about 3 h). The reaction mixture was filtered through Celite, and the volatiles were removed under reduced pressure. The residue was dissolved in 600 mL of 5% NaOH, and the solution was washed with ether (4 × 150 mL) and carefully acidified with 37% HCl. Compound **6** (22.4 g, 53%) was filtered and recrystallized from MeOH/water: mp 160−162 °C; IR 1692, 1657 $cm^{-1}$; CIMS $m/z$ 274 ($MH^+$ + 17), 291 ($MH^+$ + 34). Anal. ($C_{15}H_{12}O_4 \cdot 0.25H_2O$) C, H.

**4-(3-Fluorobenzoyl)benzoic Acid (7).** Compound **7** was obtained (9.9 g, 35%) from **4** (24.5 g, 114.5 mmol) as described for the synthesis of compound **6**. After the reaction was complete and the volatiles were evaporated, the residue was dissolved in a mixture of 300 mL of 15% NaOH and 700 mL of 1 M $NH_4OH$. The solution was washed with ether (4 × 100 mL) and carefully acidified with 37% HCl. Compound **7** was separated by filtration and dried, and 0.50 g were recrystallized from 25 mL of MeOH: mp 212−213 °C; CIMS $m/z$ 262 ($MH^+$ + 17), 279 ($M^+$ + 34). Anal. ($C_{14}H_9O_3F$) C, H.

**4-(3-Iodobenzoyl)benzoic Acid (8).** $KMnO_4$ (5.77 g, 36.51 mmol) was added to a rapidly mechanically stirred solution of **6** (9.80 g, 30.40 mmol) in a mixture of 90 mL of *tert*-butyl alcohol and 30 mL of water. The reaction mixture was heated at reflux for 3 h. An additional 5.77 g (36.51 mmol) of $KMnO_4$ was added together with 50 mL of a 1:1 mixture of *tert*-butyl alcohol/water. The reaction mixture was refluxed until the permanganate color disappeared (about 12 h). Finally, an additional 5.77 g (36.51 mmol) of $KMnO_4$ and 100 mL of a 1:1 mixture of *tert*-butyl alcohol/water were added, and the reaction mixture was refluxed for 24 h. The reaction mixture was cooled to room temperature and poured into 200 mL of a 1:1 solution of ethyl acetate/1 N hydrochloric acid. The reaction mixture was filtered through Celite, and the organic layer was separated. The aqueous layer was further extracted with ethyl acetate (4 × 100 mL). The filter cake was washed with hot ethyl acetate (2 × 200 mL). The combined organic layers were washed with brine and dried, and the volatiles were evaporated under reduced pressure to give 5.73 g of compound **8** (53.5%): $^1$H-NMR ($CDCl_3/CD_3OD$) $\delta$ 7.16 (t, $J$ = 8.0 Hz, 1H), 7.64 (d, $J$ = 8.0 Hz, 1H), 7.72 (d, $J$ = 8.0 Hz, 2H), 7.86 (d, $J$ = 8.0 Hz, 1H), 8.03 (s, 1H), 8.08 (d, $J$ = 8.0 Hz, 2H); CIMS $m/z$ 353 ($MH^+$).

**4-(3-Methoxybenzoyl)-*N*,*N*-diethylbenzamide (9).** A solution of **6** (22.38 g, 87.42 mmol) in 44 mL of $SOCl_2$ and 50 mL of benzene was allowed to stir at reflux for 3 h under Ar. The volatiles were removed under reduced pressure. The remaining $SOCl_2$ was coevaporated with toluene (3 × 50 mL). The acid chloride was dissolved in 100 mL of ps $CHCl_3$, and the resulting solution was added dropwise to a stirred solution (240 mL) of 44% diethylamine. The biphasic reaction mixture was allowed to stir at room temperature for 4 h. The organic layer was separated, washed with water (2 × 25 mL), and dried. The solvent was evaporated under reduced pressure, and the residue was triturated with a mixture of ethyl acetate/hexane. The precipitate was separated by filtration and recrystallized from ethyl acetate/hexane to give 24.5 g (90%) of **9**: mp 88−89 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.15 (br s, 3H), 1.28 (br s, 3H), 3.25 (s, 2H), 3.58 (s, 2H), 3.85 (s, 3H), 7.11−7.42 (m, 4H), 7.48 (d, $J$ = 8.0 Hz, 2H), 7.83 (d, $J$ = 8.0 Hz, 2H); CIMS $m/z$ 312 ($MH^+$); IR 1620, 1660 $cm^{-1}$. Anal. ($C_{19}H_{21}NO_3$) C, H, N.

**4-Benzoyl-*N*,*N*-diethylbenzamide (10)**. Compound **10** was obtained (8.83 g, 71%) from 4-benzoylbenzoic acid (Aldrich, 10.00 g, 44.20 mmol) according to the procedure described for the synthesis and purification of **9**. Compound **10** was recrystallized from ethyl acetate/hexane: mp 72−73 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.12(br t, 3H), 1.29 (br t, 3H), 3.25 (br d, 2H), 3.58 (br d, 2H), 7.42−7.54 (m, 4H), 7.58 7.65 (m, 1H), 7.79−7.86 (m, 4H); CIMS $m/z$ 281 ($MH^+$). Anal. ($C_{18}H_{19}NO_2$) C, H, N.

**4-(3-Fluorobenzoyl)-*N*,*N*-diethylbenzamide (11).** Compound **11** was obtained (9.10 g, 79%) from compound **7** (9.38 g, 38.44 mmol) according to the procedure described for the synthesis and purification of **9**. Compound **11** was recrystallized from ethyl acetate/hexane: mp 71−72 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.14 (br t, 3H), 1.28 (br t, 3H), 3.26 (br d, 2H), 3.28 (br d, 2H), 7.28−7.32 (m, 1H), 7.47−7.59 (m, 5H), 7.82 (d, $J$ = 8.01, 2H); CIMS $m/z$ 300 ($MH^+$). Anal. ($C_{18}H_{18}NO_2F$) C, H, N.

**4-(3-Iodobenzoyl)-*N*,*N*-diethylbenzamide (12).** Compound **12** was obtained (5.72 g, 94%) from **8** (5.23 g, 14.9 mmol) according to the procedure described for the synthesis of **9**. Compound **12** was purified by flash chromatography (hexane/ethyl acetate, 1:1) and recrystallized from ether: mp 117−118 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.14 (br s, 3H), 1.28 (br s, 3H), 3.26 (br s, 2H), 3.59 (br s, 2H), 7.24 (t, $J$ = 8.0 Hz, 1H), 7.50 (d, $J$ = 8.0 Hz, 2H), 7.74 (d, $J$ = 8.0 Hz, 1H), 7.81 (d, $J$ = 8.0 Hz, 2H), 7.94 (d, $J$ = 8.0 Hz, 1H), 8.14 (s, 1H); CIMS $m/z$ 408 ($MH^+$). Anal. ($C_{18}H_{18}INO_2$) C, H, N.

**4-(3-Methoxy-α-hydroxybenzyl)-*N*,*N*-diethylbenzamide (13).** To a solution of **9** (18.10 g, 58.2 mmol) in 240 mL of 3:1 ethanol/water mixture was added portionwise 13.21 g (349.20 mmol) of $NaBH_4$. The reaction mixture was allowed to stir at room temperature for 2 h. The volatiles were evaporated under reduced pressure, and the pH of the solution was adjusted to 9 by dropwise addition of 1 M HCl solution. Extraction with $CHCl_3$ (3 × 100 mL) was followed by washing of the combined organic fractions with 25 mL of water, drying, and evaporation of the solvent in vacuo to give 12.7 g (70%) of **13**. This compound was homogeneous by TLC ($CHCl_3$/MeOH/$NH_4OH$, 95:5:1). The solid residue was recrystallized from ethyl acetate/hexane: mp 89−90 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.20 (br d, 6H), 2.37 (s, 1H), 3.24 (br s, 2H), 3.52 (br s, 2H), 3.79 (s, 3H), 5.82 (s, 1H), 6.80−6.84 (m, 1H), 6.92−6.95 (m, 2H), 7.23−7.28 (m, 1H), 7.34 (d, $J$ = 8.2 Hz, 2H), 7.41 (d, $J$ = 8.2 Hz, 2H); CIMS $m/z$ 314 ($MH^+$). Anal. ($C_{19}H_{23}NO_3$) C, H, N.

**4-(α-Hydroxybenzyl)-*N*,*N*-diethylbenzamide (14).** Compound **14** was obtained (6.50 g, 81%) from **10** (8.00 g, 28.47 mmol) according to the procedure described for the synthesis and purification of **13**. Compound **14** was recrystallized from ethyl acetate/hexane: mp 59−62 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.10 (br s, 3H), 1.22 (br s, 3H), 1.29 (s, 1H), 3.25 (br s, 2H), 3.53 (br s, 2H), 5.86 (s, 1H), 7.32−7.42 (m, 9H); CIMS $m/z$ 283 ($MH^+$). Anal. ($C_{18}H_{21}NO_2$) C, H, N.

**4-(3-Fluoro-α-hydroxybenzyl)-*N*,*N*-diethylbenzamide (15).** Compound **15** was obtained (7.74 g, 89%) from **11** (8.58 g, 28.70 mmol) according to the procedure described for the synthesis and purification of **13**. Compound **15** was recrystallized from ethyl acetate/hexane: mp 75−77 °C; $^1$H ($CDCl_3$) $\delta$ 1.11 (br s, 3H), 1.23 (br s, 3H), 3.25 (s, 2H), 3.52 (s, 2H), 6.94−7.00 (m, 1H), 7.09−7.14 (m, 2H), 7.28−7.40 (m, 5H); CIMS $m/z$ 302 ($MH^+$), 319 ($MH^+$ + 17). Anal. ($C_{18}H_{20}NO_2F$) C, H, N.

**4-(3-Iodo-α-hydroxybenzyl)-*N*,*N*-diethylbenzamide (16).** To a solution of **12** (4.48 g, 11.0 mmol) in 45 mL of MeOH was added portionwise 0.62 g (16.5 mmol) of $NaBH_4$. The reaction mixture was allowed to stir at room temperature for 0.5 h. The reaction mixture was diluted with 125 mL of 1 M HCl solution. Extraction with $CH_2Cl_2$ (3 × 50 mL) was followed by washing of the combined organic fractions with 25 mL of brine, drying, and evaporation of the solvent under reduced pressure to give 4.50 g (100%) of **16**. This compound was homogeneous by TLC ($CHCl_3$/MeOH/$NH_4OH$, 95:5:1) and was used in the next step without further purification. An analytical sample was prepared by recrystallization from ether: mp 245−246 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.12 (br s, 3H), 1.22 (br s, 3H), 2.56 (d, $J$ = 2.0 Hz, 1H), 3.24 (br s, 2H), 3.53 (br s, 2H), 5.87 (d, $J$ = 2.0 Hz, 1H), 7.07 (t, $J$ = 8.0 Hz, 1H), 7.31 (d, $J$ = 8.0 Hz, 1H), 7.34 (d, $J$ = 8.0 Hz, 2H), 7.38 (d, $J$ = 8.0 Hz, 2H),

7.61 (d, $J$ = 8.0 Hz, 1H), 7.76 (s, 1H); CIMS $m/z$ 410 ($MH^+$). Anal. ($C_{18}H_{20}INO_2$) C, H, N.

**4-(3-Methoxy-α-chlorobenzyl)-*N,N*-diethylbenzamide (17).** A solution of **13** (11.7 g, 37.38 mmol) in 50 mL of ps $CHCl_3$ was added dropwise to 150 mL of 37% HCl. The biphasic reaction mixture was allowed to stir at room temperature overnight. The organic layer was separated, washed with (2 × 25 mL) water, dried, and evaporated under reduced pressure. This compound was homogeneous by TLC ($CHCl_3$/MeOH/$NH_4OH$, 90:10:1). The residue was recrystallized from ethyl acetate/hexane to give 11.16 g of **17**: mp 61−63 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.19 (br d, 6H), 3.26 (br s, 2H), 3.54 (br s, 2H), 3.80 (s, 3H), 6.08 (s, 1H), 6.82−6.86 (m, 1H), 6.95−6.97 (m, 2H), 7.23−7.29 (m, 1H), 7.34 (d, $J$ = 7.8 Hz, 2H), 7.44 (d, $J$ = 7.8 Hz, 2H); CIMS $m/z$ 332 ($MH^+$), 334 ($MH^+$ + 2), 349 ($MH^+$ + 17). Anal. ($C_{19}H_{22}NO_2Cl$) C, H, N, Cl.

**4-(α-Chlorobenzyl)-*N,N*-diethylbenzamide (18).** Compound **18** was obtained (6.5 g, 94%) from compound **14** by the method analogous to the synthesis of **17** above. Compound **18** was recrystallized from ethyl acetate/hexane: mp 54−56 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.18 (br s, 6H), 3.30−3.49 (br d, 4H), 6.13 (s, 1H), 7.34−7.46 (m, 9H); CIMS $m/z$ 302 ($MH^+$). Anal. ($C_{18}H_{20}NOCl$) C, H, N.

**4-(3-Fluoro-α-chlorobenzyl)-*N,N*-diethylbenzamide (19).** Compound **19** was obtained (6.67 g, 92%) from **15** (6.84 g, 22.71 mmol) according to the procedure described for the synthesis and purification of **17**. It was recrystallized from ethyl acetate/hexane: mp 75−76 °C; $^1$H NMR $\delta$ 1.27 (br s, 3H), 1.24 (br s, 3H), 3.26 (br s, 2H), 3.54 (br s, 2H), 6.09 (s, 1H), 7.12−7.16 (m, 2H), 7.28−7.44 (m, 5H); CIMS $m/z$ 320 (M), 321 ($MH^+$), 338 ($MH^+$ + 17). Anal. ($C_{18}H_{19}NOClF$) C, H, N.

**4-(3-Iodo-α-chlorobenzyl)-*N,N*-diethylbenzamide (20).** Compound **20** (2.95 g, 78%) was obtained from **16** (4.26 g, 10.4 mmol) according to the procedure described for the synthesis of **17**. Compound **20** was recrystallized from isopropyl ether: mp 74−75 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.12 (br s, 3H), 1.22 (br s, 3H), 3.26 (br s, 2H), 3.53 (br s, 2H), 6.03 (s, 1H), 7.08 (t, $J$ = 8.0 Hz, 1H), 7.31−7.47 (m, 5H), 7.64 (d, $J$ = 8.0 Hz, 1H), 7.76 (s, 1H); CIMS $m/z$ 428 ($MH^+$). Anal. ($C_{18}H_{19}NOClI$) C, H, N.

**(+)-4-[(α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N,N*-diethylbenzamide [(+)-21, SNC 80].** A mixture of compound **17** (9.44 g, 28.53 mmol), **(−)-2** (5.5 g, 35.65 mmol), and anhydrous $K_2CO_3$ (1.48 g, 107.0 mmol) in 75 mL of anhydrous acetonitrile was allowed to stir at reflux for 72 h, under Ar. The solution was filtered, and the volatiles were evaporated under reduced pressure. The residue was dissolved in 150 mL of 0.5 M citric acid and extracted with ether (15 × 50 mL), which was discarded. The desired diastereomeric mixture was extracted with $CHCl_3$ (5 × 50 mL). The chloroform layers were combined, washed with water (2 × 50 mL), and dried. The solvent was evaporated under reduced pressure to give 8.35 g (65%) of a mixture of **(+)-21** and **(+)-25** as a yellow oil, TLC (ethyl acetate). Somewhat better yields of about 80% were obtained when 2 mmol of the resolved piperazine per 1 mmol of chloride were used, but utilization of a 1:1 molar ratio was the most economical in terms of the available **(−)-2**. The oily residue was triturated with a mixture of ethyl acetate/hexane to give a solid which was separated by filtration. The volatiles were removed under reduced pressure, and trituration of the residue with ethyl acetate/hexane was repeated. The solid was filtered and combined with the previously obtained solid. The filtrate was highly enriched in **(+)-25**, which was purified as described below. The combined solid was recrystallized from a 6:1 mixture of acetonitrile/water to give 3.8 g (29%) of **(+)-21**: mp 122−123 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.04 (d, $J$ = 6.4 Hz, 3 H), 1.10−1.28 (br d, 9 H), 1.89 (t, $J$ = 9.0 Hz, 1 H), 2.15 (t, $J$ = 9.0 Hz, 1 H), 2.40−2.55 (m, 1 H), 2.57−2.69 (m, 2 H), 2.80−2.95 (m, 2 H), 3.23−3.39 (m, 3 H), 3.52 (br s, 2 H), 3.80 (s, 3 H), 5.12−5.25 (m, 3 H), 5.78−5.93 (m, 1 H), 6.72−6.93 (m, 3 H), 7.21−7.35 (m, 3 H), 7.47 (d, $J$ = 7.8 Hz, 2 H); CIMS $m/z$ 450 ($MH^+$); $[\alpha]^{22}_D$ = +23.7° (*c* 1.0, MeOH). Anal. ($C_{28}H_{39}N_3O_2$) C, H, N.

**(−)-4-[(α*S*)-α-((2*R*,5*S*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N,N*-diethylbenzamide [(−)-21].** Reaction of **17** (4.69 g, 14.17 mmol), **(+)-2** (2.73 g, 17.71 mmol) in 40 mL of anhydrous acetonitrile, and 5.87 g (42.50 mmol) of anhydrous $K_2CO_3$, according to the procedure described for the synthesis of the desired mixture of **(+)-21** and **(+)-25**, gave a mixture of **(−)-21** and **(−)-25**. Compound **(−)-21** (1.83 g, 29%) was purified in a manner analogous to that for **(+)-21,** and the filtrates were reserved for isolation of **(−)-25**: mp 122−124 °C; $^1$H NMR ($CDCl_3$) $\delta$ 0.98 (d, $J$ = 6.3 Hz, 3 H), 1.17−1.19 (br d, 9 H), 1.89 (t, $J$ = 9.0 Hz, 1 H), 2.13 (t, $J$ = 9.0 Hz, 1 H), 2.45 (br s, 1 H), 2.57−2.62 (m, 2 H), 2.78−2.88 (m, 2 H), 3.28−3.38 (m, 3 H), 3.53 (br s, 2 H), 3.78 (s, 3 H), 5.12−5.21 (m, 3 H), 5.80−5.94 (m, 1 H), 6.68−6.85 (m, 3 H), 7.26−7.31 (m, 3 H), 7.47 (d, $J$ = 8.3 Hz, 2 H); CIMS $m/z$ 450 ($MH^+$); $[\alpha]^{22}_D$ = −23.3° (*c* 1.0, MeOH). Anal. ($C_{28}H_{39}N_3O_2$) C, H, N.

**(+)-4-[(α*S*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-benzyl]-*N,N*-diethylbenzamide [(+)-22].** Reaction of **18** (2.00 g, 6.64 mmol), **(−)-2** (1.25 g, 8.10 mmol) in 40 mL of anhydrous acetonitrile, and 2.75 g (19.93 mmol) of anhydrous $K_2CO_3$, according to the procedure described for the synthesis of **(+)-21** and **(+)-25**, gave a mixture of **(+)-22** and **(+)-26**. The filtrate from trituration of crude **(+)-22** was retained for isolation of **(+)-26**. Compound **(+)-22** (0.61 g, 22%) was recrystallized from acetonitrile/water: mp 148−149 °C; $^1$H NMR ($CDCl_3$) $\delta$ 0.98 (d, $J$ = 6.4 Hz, 3H), 1.13−1.20 (br d, 9H), 1.81−1.88 (m, 1H), 2.09−2.16 (m, 1H), 2.44−2.48 (m, 1H), 2.54−2.61 (m, 2H), 2.77−2.87 (m, 2H), 3.29−3.39 (m, 3H), 3.53 (br s, 2H), 5.12−5.27 (m, 3H), 5.78−5.92 (m, 1H), 7.15−7.17 (m, 2H), 7.28−7.32 (m, 5H), 7.46 (d, $J$ = 8.1 Hz, 2H); $[\alpha]^{20}_D$ = +27.5° (*c* 0.2, MeOH). Anal. ($C_{27}H_{37}N_3O$) C, H, N.

**(−)-4-[(α*R*)-α-((2*R*,5*S*)-4-Allyl-2,5-dimethyl-1-piperazinyl)benzyl]-*N,N*-diethylbenzamide [(−)-22].** Reaction of **18** (3.83 g, 12.71 mmol), **(+)-2** (2.45 g, 15.89 mmol) in 40 mL of anhydrous acetonitrile, and 5.27 g (38.13 mmol) of anhydrous $K_2CO_3$, according to the procedure described for the synthesis and purification of **(+)-21** and **(+)-25**, gave a mixture of **(−)-22** and **(−)-26.** The filtrate from trituration of **(−)-22** was retained for isolation of **(−)-26**. Compound **(−)-22** (1.36 g, 25%) was recrystallized from acetonitrile/water: mp 146−147 °C; $^1$H NMR ($CDCl_3$) $\delta$ 0.99 (d, $J$ = 6.3 Hz, 3H), 1.12−1.19 (br d, 9H), 1.86−1.92 (m, 1H), 2.04−2.18 (m, 1H), 2.49−2.69 (m, 3H), 2.78−2.98 (m, 2H), 3.31−3.38 (m, 3H), 3.54−3.55 (m, 2H), 5.13−5.26 (m, 3H), 5.78−5.92 (m, 1H), 7.5 (d, $J$ = 8.3 Hz, 2H), 7.25−7.35 (m, 5H), 7.48 (d, $J$ = 8.3 Hz); CIMS $m/z$ 420 ($MH^+$); $[\alpha]^{22}_D$ = −28.6° (*c* 0.7, MeOH). Anal. ($C_{27}H_{37}N_3O$) C, H, N.

**(+)-4-[(α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-fluorobenzyl]-*N,N*-diethylbenzamide [(+)-23].** Reaction of **19** (2.00 g, 6.25 mmol), **(−)-2** (1.20 g, 7.81 mmol), and anhydrous $K_2CO_3$ (2.60 g, 18.75 mmol) according to the procedure described for the synthesis of the diastereomeric mixture of **(+)-21** and **(+)-25** gave a mixture of **(+)-23** and **(+)-27**. After evaporation of the volatiles under reduced pressure, the oily residue was dissolved in 50 mL of 0.5 M citric acid solution. Several extractions were performed with ether until a higher $R_f$ impurity detected by TLC (ethyl acetate, UV 254 nm) was removed. The pH of the aqueous solution was adjusted to 9 with 40% NaOH, and the diastereomeric mixture of **(+)-23** and **(+)-27** was extracted in $CHCl_3$. The combined organic layers were dried and the volatiles evaporated under reduced pressure. Compounds **(+)-23** and **(+)-27** (see below) were purified by flash chromatography and eluted with ethyl acetate. Recrystallization from acetonitrile/water gave 0.60 g of **(+)-23** (23%): mp 102−103 °C; $^1$H NMR $\delta$ 0.98 (d, $J$ = 6.1 Hz, 3H), 1.18 (br d, 9H), 1.80−1.81 (m, 1H), 2.06−2.16 (m, 1H), 2.45−2.48 (m, 1H), 2.56−2.60 (m, 2H), 2.78−2.80 (m, 2H), 3.29−3.38 (m, 3H), 3.54 (br s, 2H), 5.12−5.25 (m, 3H), 5.78−5.92 (m, 1H), 6.86−6.97 (m, 3H), 7.28−7.32 (m, 3H), 7.43 (d, $J$ = 8.2 Hz, 2H); CIMS $m/z$ 438 ($MH^+$); $[\alpha]^{20}_D$ = +30.1° (*c* 0.7, MeOH). Anal. ($C_{27}H_{36}N_3OF$) C, H, N.

**(−)-4-[(α*S*)-α-((2*R*,5*S*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-fluorobenzyl]-*N,N*-diethylbenzamide [(−)-23].** Reaction of **19** (1.95 g, 6.10 mmol), **(+)-2** (1.88 g, 12.20 mmol), and anhydrous $K_2CO_3$ (2.53 g, 18.30 mmol) according to the procedure described for the synthesis compound **(+)-23** gave a mixture of **(−)-23** and **(−)-27**. After isolation of the diastereomeric mixture of **(−)-23** and **(−)-27** by extraction with $CHCl_3$, compounds **(−)-23** (0.60 g, 22.5%) and **(−)-27** (see

below) were purified by flash column chromatography and recrystallized as for its enantiomer: mp 101−102 °C; $^1$H NMR $\delta$ 0.99 (d, $J$ = 6.1 Hz, 3H), 1.11−1.26 (br d, 9H), 1.80−1.87 (m, 1H), 2.09−2.16 (m, 1H), 2.42−2.49 (br t, 1H), 2.56−2.60 (m, 2H), 2.78−2.88 (m, 2H), 3.29−3.38 (m, 3H), 3.50−3.58 (br s, 2H), 5.13−5.25 (m, 3H), 5.78−5.92 (m, 1H), 6.85−6.97 (m, 2H), 7.28−7.32 (m, 4H), 7.44 (d, $J$ = 8.0 Hz, 2H); CIMS $m/z$ 438 (MH$^+$); $[\alpha]^{22}_D$ = −27.2° ($c$ 0.7, MeOH). Anal. ($C_{27}H_{36}N_3OF$) C, H, N.

**(+)-4-[(α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-iodobenzyl]-*N*,*N*-diethylbenzamide [(+)-24].** A mixture of **20** (3.25 g, 7.60 mmol), **(−)-2** (1.17 g, 7.58 mmol), anhydrous $K_2CO_3$ (3.15 g, 22.8 mmol), and tetrabutylammonium iodide (0.28 g, 0.76 mmol) in 90 mL of anhydrous acetonitrile was allowed to stir at reflux for 84 h under nitrogen. The solution was filtered, and the volatiles were evaporated under reduced pressure. The residue was dissolved in 100 mL of a 1:1 mixture of ethyl acetate/water. The organic layer was separated, washed with water (1 × 25 mL), and dried. The volatiles were removed under reduced pressure to give a mixture of **(+)-24** and **(+)-28** (4.06 g, crude). The crude oil was purified by flash chromatography (silica gel, ethyl acetate) to give 1.66 g of **(+)-24** as an oil (40.2%) and **(+)-28** (see below): $^1$H NMR ($CDCl_3$) $\delta$ 0.98 (d, $J$ = 6.0 Hz, 3H), 1.16 (d, $J$ = 6.0 Hz, 3H), 1.05−1.30 (br s, 6H), 1.82 (dd, $J$ =10.0 Hz, $J$ = 9.0 Hz, 1H), 2.12 (dd, $J$ = 10.0 Hz, $J$ =9.0 Hz, 1H), 2.40−2.63 (br m, 3H), 2.76−2.89 (m, 2H), 3.29 (br s, 2H), 3.36 (dd, $J$ = 15.0 Hz, $J$ = 6 Hz, 1H), 3.53 (br s, 2H), 5.22−5.10 (m, 3H), 5.80−5.95 (m, 1H), 7.05 (d, $J$ = 8.0 Hz, 1H), 7.12 (t, $J$ = 8.0 Hz, 1H), 7.32 (d, $J$ = 8.0 Hz, 2H), 7.43 (d, $J$ = 8.0 Hz, 2H), 7.53 (s, 1H), 7.62 (d, $J$ = 8.0 Hz, 1H); CIMS $m/z$ 545 (MH$^+$); HRMS ($C_{27}H_{36}N_3OI$) requires 545.1903 (MH$^+$), found 545.1910. Compound **(+)-24**·HCl lyophilizate, $[\alpha]^{22}_D$ = +6.6° ($c$ 0.84, MeOH). Anal. ($C_{27}H_{36}N_3OI$·HCl·2H$_2$O) C, H, N.

**(+)-4-[(α*S*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide [(+)-25].** After separation of **(+)-21** from the trituration mixture by filtration, the volatiles were evaporated under reduced pressure. The residue was purified by flash column chromatography eluted with ethyl acetate to give 3.5 g (25%) of **(+)-25** as a glass: $^1$H NMR ($CDCl_3$) $\delta$ 0.95 (d, $J$ = 6.1 Hz, 3H), 1.12−1.28 (br d, 9H), 1.85 (t, $J$ = 9.1 Hz, 1H), 2.15 (t, $J$ = 9.1 Hz, 1H), 2.45−2.70 (m, 3H), 2.75−2.90 (m, 2H), 3.22−3.39 (m, 3H), 3.55 (br s, 2H), 3.80 (s, 3H), 5.11−5.25 (m, 3H), 5.75−5.89 (m, 1H), 6.70−6.80 (m, 1H), 6.90−6.95 (m, 1H), 7.15−7.28 (m, 4H), 7.35 (d, $J$ = 8.1 Hz, 2H); CIMS $m/z$ 450 (MH$^+$); $[\alpha]^{20}_D$ = +25.2° ($c$ 1.0, MeOH). **(+)-25**·HCl lyophilizate, $[\alpha]^{22}_D$ = +6.4° ($c$ 0.5, MeOH). Anal. ($C_{28}H_{39}N_3O_2$·2HCl·1.25H$_2$O) C, H, N.

**(−)-4-[(α*R*)-α-((2*R*,5*S*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide [(−)-25].** Compound **(−)-25** was obtained as a glass (1.56 g, 24%) according to the procedure described for the purification of compound **(+)-25**: $^1$H NMR ($CDCl_3$) $\delta$ 0.99 (d, $J$ = 6.3 Hz, 3 H), 1.16−1.28 (br d, 9 H), 1.85−1.90 (m, 1 H), 2.11−2.19 (m, 1 H), 2.45−2.65 (m, 3 H), 2.75−2.94 (m, 2 H), 3.28−3.39 (m, 3 H), 3.55 (br s, 2 H), 3.80 (s, 3 H), 5.12−5.25 (m, 3 H), 5.78−5.93 (m, 1 H), 6.75−6.95 (m, 3 H), 7.08−7.35 (m, 3 H), 7.45 (d, $J$ = 8.0 Hz, 2 H); CIMS $m/z$ 450 (MH$^+$); $[\alpha]^{20}_D$ = −24.1° ($c$ 1.8, MeOH). **(−)-25**·HCl lyophilizate, $[\alpha]^{22}_D$ = −6.4° ($c$ 0.5, MeOH). Anal. ($C_{28}H_{39}N_3O_2$·2HCl·0.5H$_2$O) C, H, N.

**(+)-4-[(α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)benzyl]-*N*,*N*-diethylbenzamide [(+)-26].** After separation of **(+)-22** by filtration from the trituration mixture as described above, the volatiles were evaporated under reduced pressure and **(+)-26** was purified by flash column chromatography (ethyl acetate) to give 0.58 g of **(+)-26** (21%) as an oil: $^1$H NMR ($CDCl_3$) $\delta$ 0.99 (d, $J$ = 6.2 Hz, 3H), 1.17−1.19 (br d, 9H), 1.86−1.93 (m, 1H), 2.12−2.19 (m, 1H), 2.49−2.68 (m, 3H), 2.77−2.91 (m, 2H), 3.32−3.38 (m, 3H), 3.54 (br s, 2H), 5.13−5.26 (m, 3H), 5.80−5.91 (m, 1H), 7.21−7.36 (m, 7H), 7.41 (d, $J$ = 7.6 Hz, 2H); $[\alpha]^{22}_D$ = +23.5° ($c$ 0.2, MeOH). Anal. **(+)-26**·HCl lyophilizate ($C_{27}H_{37}N_3O$·2HCl·2H$_2$O) C, H, N.

**(−)-4-[(α*S*)-α-((2*R*,5*S*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-benzyl]-*N*,*N*-diethylbenzamide [(−)-26].** Compound **(−)-26** was obtained as an oil (1.17g, 22%) according to the procedure described for the synthesis and purification of **(+)-26**: $^1$H NMR ($CDCl_3$) $\delta$ 0.99 (d, $J$ = 6.2 Hz, 3H), 1.15−1.23 (br d, 9H), 1.86−1.93 (m, 1H), 2.12−2.18 (m, 1H), 2.49−2.68 (m, 3H), 2.77−2.91 (m, 2H), 3.19−3.38 (m, 3H), 3.54 (br s, 2H), 5.13−5.26 (m, 3H), 5.80−5.93 (m, 1H), 7.21−7.42 (m, 9H); $[\alpha]^{22}_D$ = −23.9° ($c$ 0.9, MeOH). Anal. **(−)-26**·HCl lyophilizate ($C_{27}H_{37}N_3O$·2HCl·1.5H$_2$O) C, H, N.

**(+)-4-[(α*S*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-fluorobenzyl]-*N*,*N*-diethylbenzamide [(+)-27].** Compound **(+)-27** was obtained as a glass (0.58 g, 22%) during the chromatography of **(+)-23** with ethyl acetate: $^1$H NMR $\delta$ 0.99 (d, $J$ = 6.2 Hz, 3H), 1.18 (br d, 9H), 1.83−1.90 (m, 1H), 2.11−2.17 (m, 1H), 2.48−2.63 (m, 4H), 2.77−2.90 (m, 2H), 3.30−3.39 (m, 3H), 3.52 (br s, 2H), 5.14−5.25 (m, 3H), 5.69−5.93 (m, 1H), 6.89−6.95 (m, 1H), 7.07−7.10 (m, 1H), 7.18−7.26 (m, 4H), 7.36 (d, $J$ = 8.0 Hz, 2H); CIMS $m/z$ 438 (MH$^+$); $[\alpha]^{20}_D$ = +24.2° ($c$ 0.3, MeOH). Anal. **(+)-27**·HCl lyophilizate ($C_{27}H_{36}N_3OF$·2HCl·2H$_2$O) C, H, N.

**(−)-4-[(α*R*)-α-((2*R*,5*S*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-fluorobenzyl]-*N*,*N*-diethylbenzamide [(−)-27].** Compound **(−)-27** (0.45 g, 17%) was obtained as an oil during the chromatography of **(−)-23** with ethyl acetate: $^1$H NMR $\delta$ 0.99 (d, $J$ = 6.5 Hz, 3H), 1.19 (br d, 9H), 1.83−1.90 (m, 1H), 2.11−2.17 (m, 1H), 2.50−2.63 (m, 3H), 2.77−2.90 (m, 2H), 3.32−3.39 (m, 3H), 3.54 (br s, 2H), 5.13−5.25 (m, 3H), 5.79−5.92 (m, 1H), 6.90−6.94 (m, 1H), 7.07−7.10 (br d, 1H), 7.18−7.24 (m, 4H), 7.36 (d, $J$ = 7.9 Hz, 1H); CIMS $m/z$ 438 (MH$^+$); $[\alpha]^{20}_D$ = +24.0° ($c$ 0.7, MeOH). Anal. **(−)-27**·HCl lyophilizate ($C_{27}H_{36}N_3OF$·2HCl·3H$_2$O) C, H, N.

**(+)-4-[(α*S*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-iodobenzyl]-*N*,*N*-diethylbenzamide [(+)-28].** Compound **(+)-28** (1.50 g, 36.3%) was obtained as an oil described in the synthesis and chromatographic purification of compound **(+)-24**: $^1$H NMR ($CDCl_3$) $\delta$ 1.00 (d, $J$ = 6.0 Hz, 3H), 1.18 (d, $J$ = 6.0 Hz, 3H), 1.05−1.32 (br s, 6H), 1.87 (dd, $J$ =10.0 Hz, $J$ = 9.0 Hz, 1H), 2.14 (dd, $J$ = 10.0 Hz, $J$ =9.0 Hz, 1H), 2.42−2.64 (br m, 3H), 2.75−2.92 (m, 2H), 3.20−3.40 (m, 3H), 3.53 (br s, 2H), 5.10−5.23 (m, 3H), 5.80−5.95 (m, 1H), 7.00 (t, $J$ = 8.0 Hz, 1H), 7.12−7.22 (m, 3H), 7.34 (d, $J$ = 8.0 Hz, 2H), 7.57 (d, $J$ = 8.0 Hz, 1H), 7.80 (s, 1H); CIMS $m/z$ 545 (MH$^+$); HRMS ($C_{27}H_{36}N_3OI$) requires 545.1903 (MH$^+$), found 545.1915. Compound **(+)-28**·HCl lyophilizate, $[\alpha]^{22}_D$ = +8.34° ($c$ 0.73, MeOH). Anal. **(+)-28**·HCl lyophilizate ($C_{27}H_{36}N_3OI$·HCl·2H$_2$O) C, H, N.

**(+)-4-[(α*S*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]-*N*,*N*-diethylbenzamide [(+)-29].** Compound **(+)-29** was obtained as a glass (0.87 g, 50%) from **(+)-25**, according to the procedure described for the synthesis and purification of compound **(+)-1**. $^1$H NMR ($CDCl_3$) $\delta$ 1.02 (d, $J$ = 6.1 Hz, 3H), 1.15−1.25 (m, 9H), 1.95 (br t, 1H), 2.18 (br t, 1H), 2.48−2.95 (m, 5H), 3.28−3.65 (m, 5H), 5.12−5.25 (m, 3H), 5.81−5.98 (m, 1H), 6.60−6.70 (m, 1H), 6.90−6.98 (m, 2H), 7.10−7.18 (m, 1H), 7.23 (d, $J$ = 8.1 Hz, 2H), 7.35 (d, $J$ = 8.1 Hz, 2H); CIMS $m/z$ 436 (MH$^+$); $[\alpha]^{20}_D$ = +19.3° ($c$ 0.6, MeOH).

**(+)-29·Di-*p*-toluyl-L-tartrate:** mp 145−147 °C; recrystallized from ethanol/water; $[\alpha]^{22}_D$ = −61.3° ($c$ 1.0, MeOH). Anal. ($C_{47}H_{55}N_3O_{10}$·0.75H$_2$O) C, H, N.

**(−)-4-[(α*R*)-α-((2*R*,5*S*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]-*N*,*N*-diethylbenzamide [(−)-29].** Compound **(−)-29** was obtained as a glass (0.42, 44%) from **(−)-25** according to the procedure described for the synthesis and purification of **(−)-1**: $^1$H NMR ($CDCl_3$) $\delta$ 0.98 (d, $J$ = 6.2 Hz, 3H), 1.16−1.27 (br d, 9H), 1.88 (dd, $J$ = 11.1 Hz, $J$ = 8.8 Hz, 1H), 2.14 (dd, $J$ = 11.1 Hz, $J$ = 8.8 Hz, 1H), 2.48−2.93 (m, 5H), 3.27−3.63 (m, 5H), 5.11−5.28 (m, 3H), 5.78−5.93 (m, 1H), 6.68−6.71 (m, 1H), 6.89−6.98 (m, 2H), 7.11−7.18 (m, 1H), 7.22 (d, $J$ = 8.2 Hz, 2H), 7.35 (d, $J$ = 8.2 Hz, 2H); CIMS $m/z$ 436 (MH$^+$); $[\alpha]^{20}_D$ = −17.9° ($c$ 0.5, MeOH).

**(−)-29·Di-*p*-toluyl-D-tartrate:** recrystallized from ethanol/water; mp 135−138 °C; $[\alpha]^{22}_D$ = +63.1° ($c$ 0.5, MeOH). Anal. ($C_{47}H_{55}N_3O_{10}$·1.5H$_2$O) C, H, N.

**(+)-4-[(α*R*)-α-((2*S*,5*R*)-4-Propyl-2,5-dimethyl-1-piperazinyl)benzyl]-*N*,*N*-diethylbenzamide [(+)-30].** A solution of **(+)-22** (0.07 mg, 0.17 mmol) in ethanol (10 mL) containing 10% Pd/C (0.025 g) was shaken for 1 h at room temperature under 25 psig of $H_2$. The solution was filtered, and the volatiles were evaporated under reduced pressure to give 0.06

g (84%) of **(+)-30** as a white crystalline residue, homogeneous by TLC (solvent: ethyl acetate and $CHCl_3$/MeOH/$NH_4OH$, 95:5:0.5). This compound was recrystallized from acetonitrile/water: mp 146−147 °C; $^1$H NMR ($CDCl_3$) $\delta$ 0.85 (t, $J$ = 7.3 Hz, 3H), 0.95 (d, $J$ = 6.2 Hz, 3H), 1.11−1.25 (m, 9H), 1.38−1.50 (m, 2H), 1.80−1.87 (m, 1H), 2.11−2.20 (m, 2H), 2.42−2.48 (m, 1H), 2.55−2.62 (m, 3H), 2.79−2.84 (m, 1H), 3.29 (br s, 2H), 3.53 (br s, 2H), 5.28 (s, 1H), 7.15−7.18 (m, 3H), 7.28−7.30 (m, 3H), 7.47 (d, $J$ = 8.1 Hz, 2H); CIMS $m/z$ 422 ($MH^+$); $[\alpha]^{22}_D$ = +18.0° ($c$ 0.5, methanol).

Compound **(+)-30** was also obtained from compound **(+)-24**. A solution of **(+)-24** (0.19 g, 0.35 mmol) in 10 mL of 20% aqueous acetic acid and 0.10 g of sodium acetate (0.70 mmol) containing 0.10 g of 10% Pd/C was shaken for 3 h at room temperature under 25 psig of $H_2$. The solution was filtered, and the volatiles were evaporated under reduced pressure to give a crystalline residue which was further purified by flash chromatography ($CHCl_3$/MeOH/$NH_4OH$, 90:10:0.5) to give 0.13 g (87%) of a compound which its mp, $^1$H NMR, and CIMS matched those of **(+)-30**: $[\alpha]^{22}_D$ = +18.2° ($c$ 1.2, methanol).

**Single-Crystal X-ray Analysis of Compounds (−)-22, (+)-23, and (+)-30.** Crystals of compounds **(−)-22**, **(+)-23**, and **(+)-30** were grown from acetonitrile/water. Data were collected on a computer-controlled automatic Siemens R3/m diffractometer and corrected for Lorentz and polarization effects. No absorption corrections were applied. The structures were solved by direct methods with the aid of program SHELXTL[32] and refined by full-matrix least-squares on $F^2$ values using program SHELXL.[33] The parameters refined included the coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were included using a riding model in which the coordinate shifts of their covalently bonded atoms were applied to the attached hydrogens with C−H = 0.96 Å. H angles were idealized and $\mathbf{U}_{iso}$ (H) set at fixed ratios of $\mathbf{U}_{iso}$ values of bonded atoms. Tables of crystal coordinates, bond distances, bond angles, and hydrogen bonds are available as Supporting Information as well as from the Cambridge Crystallographic Database.[34]

## Biological Assays

**[$^3$H]DAMGO and [$^3$H]DADLE Radioligand Binding Assays.** $\mu$ binding sites were labeled using [$^3$H]DAMGO (1−3 nM) and rat brain membranes as previously described.[24] Briefly, incubations proceeded for 4 h at 25 °C in 50 mM Tris-HCl, pH 7.4, along with a protease inhibitor cocktail (PIC). The nonspecific binding was determined using 20 $\mu$M levallorphan. $\delta$ binding sites were labeled using [$^3$H]DADLE (1.7−2.5 nM) and rat brain membranes as previously described.[35] Incubations proceeded for 3−4 h at 25 °C in 10 nM Tris-HCl, pH 7.4, containing 100 mM choline chloride, 3 mM $MnCl_2$, and 100 nM DAMGO to block binding to $\mu$ sites and PIC. Nonspecific binding was determined using 20 $\mu$M levallorphan. Each $^3$H ligand was displaced by 8−10 concentrations of test drug, two times. All drug dilutions were done in 10 mM Tris-HCl, pH 7.4, containing 1 mg/mL bovine serum albumin. The $IC_{50}$ and slope factor ($n$) were obtained by using the program MLAB.

**GPI and MVD Bioassays.** Electrically induced smooth muscle contraction of mouse vas deferens and strips of guinea pig ileum longitudinal muscle myenteric plexus were used. Tissues came from male ICR mice weighing 25−40 g and male Hartley guinea pigs weighing 250−500 g. The tissues were tied to gold chain with suture silk, suspended in 20 mL baths containing 37 °C oxygenated (95% $O_2$, 5% $CO_2$) Krebs bicarbonated solution (magnesium free for the MVD), and allowed to equilibrate for 15 min. The tissues were then stretched to optimal length previously determined to be 1 g tension (0.5 g for MVD) and allowed to equilibrate for 15 min. The tissues were stimulated transmurally between platinum wire electrodes at 0.1 Hz, 0.4-ms pulses (2-ms pulses for MVD), and supramaximal voltage. Drugs were added to the baths in 14−60 $\mu$M volumes. The agonists remained in contact with the tissue until maximum inhibition was reached before the addition of the next cumulative dose. Percent inhibition was calculated by using the average contraction height for 1 min preceding the addition of the agonist divided by the contraction height at maximal inhibition after exposure to the dose of agonist. $IC_{50}$ values represent the mean of two to four tissues. $IC_{50}$ estimates and their associated standard errors were determined by using a computerized nonlinear least-squares method.[36]

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**Supporting Information Available:** ORTEP drawings of **(−)-22** and **(+)-30**, crystal data and refinement parameters, and tables of crystallographic data including bond lengths, bond angles, and atomic coordinates for **(−)-22**, **(+)-23**, and **(+)-30** (18 pages). Ordering information is given on any current masthead page. Atomic coordinates may also be obtained from the Cambridge Crystallographic Data Centre (Cambridge University Chemical Laboratory, Cambridge CB2 1EW, U.K.).

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