# 3-(α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-alkyl-*N*-arylbenzamides: Potent, Non-Peptidic Agonists of Both the *μ* and *δ* Opioid Receptors

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Opioid analgesics with both *μ* and *δ* opioid receptor activation represent a new approach to the treatment of severe pain with an improved safety profile. Compounds with this profile may exhibit strong analgesic properties due to *μ* agonism, with a reduced side effect profile resulting from *δ* agonism. Replacing the *p*-diethylamide of the known potent *δ* opioid receptor selective agonist BW373U86 with a *m*-diethylamide resulted in a compound with agonist activity at both the *μ* and *δ* opioid receptors. Modifying the amide to an *N*-methyl-*N*-phenylamide increased agonist potency at both receptors. A series of 3-(α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-alkyl-*N*-arylbenzamides have been made to explore the structure−activity relationship (SAR) around the *N*-methyl-*N*-phenylamide. Several potent agonists of both the *μ* and *δ* opioid receptors have been identified, including (+)-3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-(4-fluorophenyl)-*N*-methylbenzamide (**23**), which has $EC_{50}$ values of 0.67 and 1.1 nM at the *μ* (guinea pig ileum assay) and *δ* (mouse vas deferens assay) opioid receptors, respectively.

## Introduction

The clinical treatment of moderate to severe pain relies on traditional opioid analgesics, such as morphine (**1**) and fentanyl (**2**) (Figure 1).[1] These powerful analgesics relieve pain primarily through agonism of *μ* opioid receptors. While *μ* opioid agonists produce profound analgesia, their use is also associated with some deleterious physiological effects, such as respiratory depression, muscle rigidity, emesis, constipation, and physical dependence.[2] The search for potent analgesics with reduced side effects continues because of the suboptimal pharmacological profile of current *μ* opioid analgesics.

The existence of at least two other opioid receptors (*μ*, *δ*, and *κ* opioid receptors have been cloned, expressed, and sequenced),[3] and evidence for various subtypes[4] have led to new avenues of opioid research. Agonism, partial agonism, or even antagonism at one of these receptors or subtypes could lead to a therapeutically useful agent for pain, drug addiction, and urological or gastrointestinal disorders possibly lacking the side effects associated with *μ* opioid receptor agonism. Early research in these labs and many others focused on exploring the therapeutic potential of *δ* opioid receptor specific agonists.

To evaluate the physiological effects of *δ* opioid receptor activation, selective agonists and antagonists have been explored.[5] Small peptides provided early examples of *δ* opioid receptor selective ligands.[6] An important breakthrough in the field was Portoghese's discovery of the *δ* opioid receptor antagonist naltrindole, the first reported *δ* selective non-peptide opioid ligand.[7] Over the past decade, non-peptidic *δ* opioid receptor selective agonists have also been discovered. Selective *δ* opioid receptor agonists have been disclosed in several structural classes, including morphinans,[8] octahydroisoquinolines,[9] phenoxyethylpiperidines,[10] and benzhydrylpiperazines.[11] These small-molecule agonists have been valuable tools in evaluating the role of the *δ* opioid receptor in nociception and other physiological events.

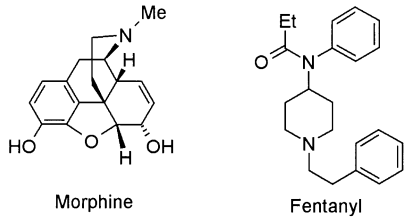


**Figure 1.**

While there are *δ* opioid receptor agonists in preclinical development, there are no current marketed opioid analgesics that interact primarily with the *δ* opioid receptor. The proposed therapeutic application for *δ* agonists in development is typically treatment of hyperalgesia, not operative or postoperative analgesia. In our evaluation of BW373U86 (**3**) (Figure 2), a potent, selective *δ* opioid receptor agonist in the benzhydrylpiperazine series, the analgesic efficacy and potency of this compound did not meet our expectations for treatment of severe pain, and proconvulsant activity precluded further development.[12] However, BW373U86 did not cause respiratory depression in laboratory animals and may in fact reverse or block typical *μ* opioid agonist induced respiratory depression.[13]

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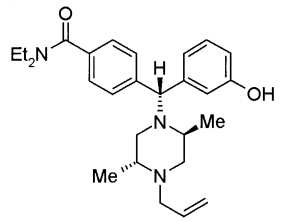

BW373U86, **3**

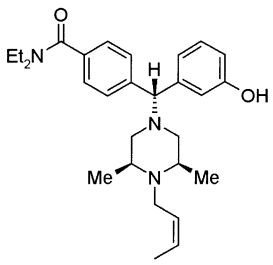

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**Figure 2.**

This exciting result added to the evidence that $\delta$ opioid receptor agonists modulate and/or potentiate $\mu$ opioid effects.[14] Recent work in rats has shown that hypercapnia induced by the highly $\mu$ selective opioid agonist alfentanil can be reversed by a number of $\delta$ selective agents in addition to BW373U86, including naltrindole, cyclic [D-Pen2,5]enkephalin, deltorphin II, and H-Tyr-Tic($\psi$)[$CH_2NH$]Phe-Phe-OH.[15] However, the $\delta$ selective agents did not lessen the analgesic effect of the $\mu$ selective agonist. In this study, both traditional $\delta$ receptor agonists and antagonists reversed the respiratory effects of alfentanil. However, a new $\delta$ antagonist, DPI-2505 (Figure 2), blocked the effects of all of these agents on alfentanil-induced hypercapnia. This suggests that in this study, $\delta$ antagonists naltrindole and H-Tyr-Tic($\psi$)[$CH_2NH$]Phe-Phe-OH behave like $\delta$ agonists with low but sufficient intrinsic activities to reverse alfentanil-induced hypercapnia in rats. In another study,[13] when BW373U86 and fentanyl were coadministered to mice, BW373U86 convulsive activity was attenuated by fentanyl in a dose-dependent manner and the fentanyl-induced Straub tail effect (indicative of muscle rigidity) was also attenuated by BW373U86, again in a dose-dependent manner. However, hot-plate analgesic activity was additive between the two compounds.

Our recent goal has been to exploit the exciting intermodulatory effects of $\mu$ and $\delta$ opioid receptor activation to develop useful therapeutic agents. Research efforts in the benzhydrylpiperazine series have shifted from the development of $\delta$ selective compounds to identifying non-peptidic mixed $\delta/\mu$ agonists that will show strong analgesic properties due to $\mu$ agonism, with a reduced side effect profile resulting from $\delta$ agonism.[16]

If one wishes to extend the message−address concept that Portoghese developed for $\delta$ opioids to benzhydrylpiperazines, the phenol/piperazine region of BW373U86 could correspond to the tyrosine residue found in enkephalins, the putative opioid "message" domain essential for receptor activation.[17] The diethylamide is appropriately positioned as the $\delta$ opioid "address" region, the part of the molecule that confers opioid receptor-type selectivity. Dondio and co-workers have previously stated this hypothesis and have published an elegant application of the diethylamide as a nonaromatic $\delta$ opioid address (Figure 3).[18] Our results support this hypothesis, since the location of the amide on BW373U86 and related structures has a profound influence on $\delta/\mu$ opioid receptor selectivity (Figure 4). Movement of the diethylamide from the para position of BW373U86 to the meta position of the phenyl ring (**4**) produced a 30-fold increase in $\mu$ activity and a 30-fold decrease in $\delta$ activity. Changing the *m*-diethylamide

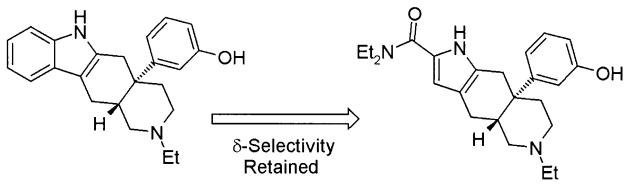


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**Figure 3.**

**Table 1.** $\delta$ and $\mu$ Opioid Activity[a]

| | $EC_{50}$ (nM) | | $K_i$ (nM) | |
|---|---|---|---|---|
| compd | $\delta$ agonism (MVD) | $\mu$ agonism (GPI) | $\delta$ binding (RBM) | $\mu$ binding (RBM) |
| morphine | 19700 ± 170 | 51 ± 4 | 90 | 1 |
| fentanyl | 490 ± 15 | 4.5 ± 1.4 | 400 | 1.5 |
| BW373U86 | 0.2 ± 0.21 | 150 ± 7 | 1.8 | 15 |
| **4** | 5.85 ± 0.40 | 4.35 ± 0.71 | 2.1 | 3.2 |
| **5** | 0.47 ± 0.30 | 1.22 ± 0.15 | 1.06 ± 0.04 | 1.55 ± 0.09 |
| **14** | 1.70 ± 0.25 | 59.5 ± 8.81 | 1.37 ± 0.28 | 1.06 ± 0.47 |
| **15** | 0.96 ± 0.06 | 0.94 ± 0.14 | 2.17 ± 0.30 | 3.39 ± 0.03 |
| **16** | 2.40 ± 0.07 | 18 | 1.26 ± 0.20 | 1.82 ± 0.10 |
| **17** | 1.42 ± 0.13 | 1.23 ± 0.24 | 1.92 ± 0.14 | 2.37 ± 0.50 |
| **18** | 1.70 ± 0.2 | 41 | 9.20 ± 0.03 | 8.88 ± 0.57 |
| **19** | 1.05 ± 0.15 | 11.5 ± 1.85 | 1.18 ± 0.06 | 2.55 ± 0.49 |
| **20** | 5.60 ± 0.3 | 6.07 ± 0.54 | 1.88 ± 0.27 | 2.16 ± 0.08 |
| **21** | 0.34 ± 0.07 | 6.6 ± 1.25 | 1.75 ± 0.23 | 2.19 ± 0.5 |
| **23** | 1.10 ± 0.2 | 0.67 | 1.40 ± 0.06 | 1.49 ± 0.03 |
| **24** | 0.79 ± 0.54 | 3.4 ± 1.6 | 0.18 ± 0.03 | 0.46 ± 0.08 |
| **25** | 0.69 ± 0.1 | 4.1 ± 0.52 | 1.69 ± 0.17 | 1.58 ± 0.32 |
| **26** | 2.60 ± 0.6 | 4.9 | 2.73 ± 0.92 | 3.46 ± 0.41 |
| **27** | 0.95 ± 0.15 | 5.6 ± 1.14 | 2.31 ± 0.15 | 2.74 ± 0.46 |
| **28** | 0.36 ± 0.04 | 1.1 ± 0.10 | 2.01 ± 0.33 | 2.35 ± 0.17 |
| **29** | 2.30 ± 0.32 | 4.1 ± 0.52 | 2.41 ± 0.48 | 2.78 ± 1.06 |
| **30** | 1.40 ± 0.1 | 4 | 6.95 ± 1.27 | 7.08 ± 1.32 |
| **31** | 0.68 ± 0.09 | 1053 | 2.75 ± 0.58 | 7.06 ± 0.49 |
| **32** | 25.3 ± 3.2 | 1800 | 11.39 ± 0.10 | 7.56 ± 1.17 |

[a] Each value is an average of at least three runs ± SEM. MVD = mouse vas deferens; GPI = guinea pig ileum; RBM = rat brain membranes. [$^3$H]Deltorphin II and [$^3$H]DAMGO were used for the $\delta$ and $\mu$ receptor binding studies, respectively. See Experimental Section for full descriptions of the assays.

to a *m*-*N*-methylanilide (**5**) resulted in both a 12-fold increase in $\delta$ agonism and a 3-fold increase in $\mu$ agonist activity (see Table 1).[19]

The biological activity of **5** represented a breakthrough in the search for potent mixed $\delta/\mu$ opioid agonists. Changes to the *m*-*N*-methylanilide were made to probe the structural limitations of this phenomenon. A series of 3-(α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-alkyl-*N*-arylbenzamides have been synthesized and show potent $\mu$ and $\delta$ opioid receptor agonism in vitro.

## Chemistry

Convergent, stereoselective synthetic approaches to BW373U86 have been reported.[20] However, because the main focus of this research effort was to establish the specific structure−activity relationship surrounding the amide portion of the 3-(α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-alkyl-*N*-arylbenzamides, a divergent approach was taken, with the amides synthesized from a common late intermediate, acid chloride **6** (Scheme 1). The general strategy for formation of the benzhydrylpiperazine opioids was to first assemble the benzhydryl portion from the two separate aromatic fragments and then to attach the functionalized piperazine ring.

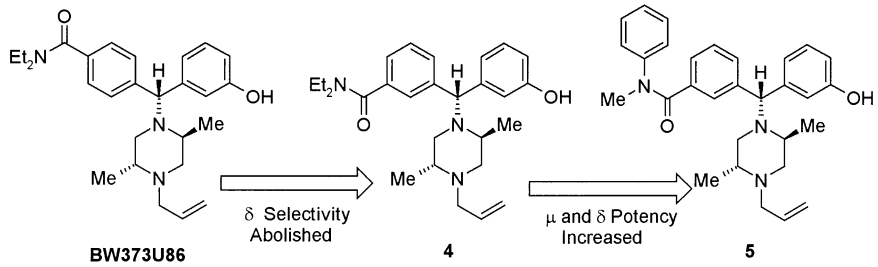
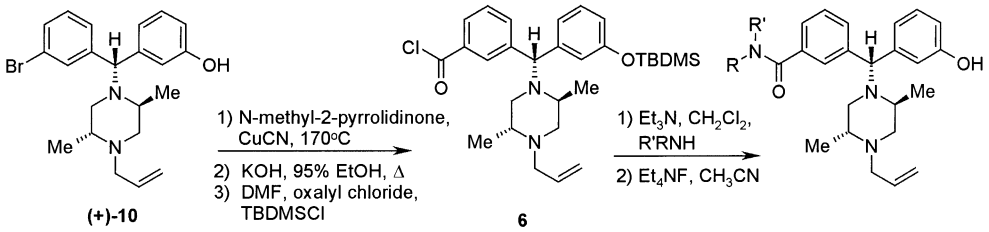
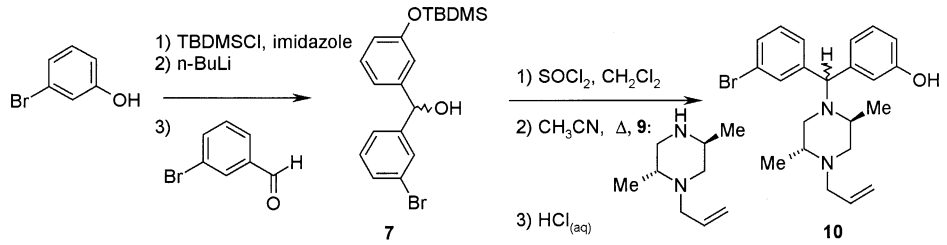



**Figure 4.**

**Scheme 1**




**Scheme 2**




The aromatic ring that will eventually bear the amide group was introduced into the synthesis via 3-bromobenzaldehyde. The benzhydryl portion of the molecular framework was formed by treating the *tert*-butyldimethylsilyl ether of 3-bromophenol with *n*-butyllithium at −78 °C and then adding the solution to 3-bromobenzaldehyde (Scheme 2). This produced a 50:50 mixture of enantiomeric benzhydryl alcohols (**7**). The racemic benzhydryl alcohol was converted to the benzhydryl chloride **8** using thionyl chloride in dichloromethane at room temperature. Without purification, the benzhydryl chloride was treated with (−)-(2*R*,5*S*)-1-allyl-2,5-dimethylpiperazine **9** and deprotected to give benzhydrylpiperazine **10** as a mixture of epimers at the benzhydryl position. The silyl protecting group was removed to improve the efficiency of the silica gel column chromatography, which yielded the two enantiopure isomers. The absolute stereochemistry was proven by transforming a single stereoisomer of **10** into a crystalline analogue and determining the structure by X-ray crystallography (for example, the X-ray structure of the 3-fluorophenyl-*N*-methyl analogue **24** was determined).[21]

(−)-(2*R*,5*S*)-1-Allyl-2,5-dimethylpiperazine **9** has been prepared by direct enantiospecific synthesis[19,22] and via classical resolution of the racemic piperazine.[23] Kiloscale batches of (−)-(2*R*,5*S*)-1-allyl-2,5-dimethylpiperazine **9** have been prepared from nonchiral *trans*-2,5-dimethylpiperazine by a three-step monoallylation, followed by a resolution using di-*p*-toluoyl-D-tartaric acid.

The acid chloride was prepared via displacement of the bromide of bromobenzhydrylpiperazine (+)-**10** with cyanide using cuprous cyanide in *N*-methylpyrrolidinone (Scheme 1).[24] The nitrile was hydrolyzed using aqueous potassium hydroxide, and the resulting carboxylic acid was converted to the acid chloride via the *tert*-butyldimethylsilyl ester, using oxalyl chloride and catalytic DMF (this transformation also reprotected the phenol as the TBDMS ether).[25]

All of the substituted anilines used to make anilides have been previously reported. However, some of these were not commercially available and were prepared by various literature procedures. *N*-Methyl compounds were prepared by N-formylation of the appropriate aniline using the mixed anhydride method (acetic/formic anhydride), followed by borane/dimethyl sulfide reduction to the *N*-methylaniline.[26] Similarly, *N*-ethyl, *N*-propyl, and *N*-butyl compounds were prepared by acylation of the aniline followed by borane reduction of the amide.[27] *N*-Cyclopropylaniline was prepared from cyclopropylamine via adaptation of Barton's phenylation procedure using triphenylbismuth and copper acetate.[28] All of these anilines reacted readily with acid chloride **6** in the presence of triethylamine to produce, after deprotection of the phenol using tetraethylammonium fluoride, the desired targets. The descarbonyl compound **32** was prepared via allane reduction of compound **24** using a literature procedure.[29]

## Results and Discussion

The $\delta$ and $\mu$ opioid agonist activities of the 3-($\alpha R$)-$\alpha$-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-alkyl-*N*-arylbenzamides were evaluated using the mouse vas deferens (MVD) and guinea pig ileum

(GPI) preparations, respectively (see Table 1).[30] All new compounds in this series described in this manuscript were effective in inhibiting the electrically stimulated twitch in both the MVD and GPI tissues, indicating that they profiled as full agonists in this assay within the limits of differentiation. $\delta$ and $\mu$ opioid agonist binding affinities for these compounds are also found in Table 1. These were determined by measuring the displacement of ligand from rat brain membranes, as described in the Experimental Section. For most compounds in this series, the binding affinity and agonist potency (and thus the receptor selectivity) tracked reasonably well. There are a few instances where compounds were significantly less potent in the GPI tissue preparations than in the $\mu$ receptor binding assay, and these discrepancies will be highlighted in the discussion below. This phenomenon has been observed for 7TM receptor agonists, and potency discrepancies between opioid receptor in vitro binding and functional assays have been previously discussed.[31]

To investigate the SAR of the *m*-*N*-alkyl-*N*-arylbenzamide portion of this series, the following structural modifications were made: (1) variation of the *N*-alkyl chain; (2) placement of an alkyl linker between the amide nitrogen and the *N*-aryl ring; (3) substitution on the *N*-aryl ring; and (4) replacement of the amide carbonyl with a methylene.

Synthesis of the des-*N*-methyl analogue of **5** resulted in a compound (**14**) with significantly reduced $\mu$ agonist activity (however, this compound retained its ability to bind to $\mu$ receptors on rat brain membranes, since the $\mu$ RBM $K_i$ values for **14** and **5** are indistinguishable). Lengthening the alkyl chain to *N*-ethyl (**15**) was well-tolerated, but an order of magnitude drop in $\mu$ activity was observed upon lengthening the chain from *N*-ethyl to *N*-*n*-propyl (**16**). *N*-Cyclopropyl (**17**) was tolerated and was roughly equipotent at the $\delta$ and $\mu$ receptors. *N*-*n*-butyl (**18**) resulted in a further 2-fold decline in $\mu$ activity beyond the *N*-*n*-propyl analogue **16**.

It is interesting that both removing the *N*-alkyl chain and lengthening the chain (to *n*-propyl and *n*-butyl) resulted in increases in $\delta$ vs $\mu$ activity selectivity. In this series, when increased selectivity is observed, the selectivity is due to a decrease in the ligand's agonist potency at the $\mu$ receptor, not to an increase in potency at the $\delta$ receptor. Constraining the *N*-propylanilide as the tetrahydroquinoline amide (**19**) resulted in a compound that was slightly more potent at both $\delta$ and $\mu$ receptors. It appears that the area of the $\mu$ receptor where these molecules interact does not readily accommodate anything larger than a propyl group on the amide for activation, but it is important to have a small alkyl group there for potent $\mu$ receptor activation.

Insertion of a spacer between the anilide nitrogen and the aromatic ring was explored. The *N*-benzyl-*N*-methylamide (**20**) was an order of magnitude less potent than compound **5** at the $\delta$ receptor and roughly 5-fold less potent at the $\mu$ receptor. Curiously, the *N*-methyl-*N*-phenethylamide (**21**) regained the $\delta$ receptor potency without picking up $\mu$ activity.

From exploration of the effect of substitution on the anilide phenyl ring, it was discovered that most small substituents were reasonably well-tolerated. Small halogens were very good at all positions on the aromatic ring. The *p*-fluoro (**23**), *m*-fluoro (**24**), and *o*-fluoro (**25**) analogues of **5** were potent agonists at both the $\delta$ and $\mu$ receptors. While there were small differences in potency between the analogues with substituents on the phenyl ring, no small substituent caused a significant loss of either $\mu$ or $\delta$ opioid activity. Further examples include the *o*-trifluoromethyl (**27**), *p*-methoxy (**28**), and *p*-nitroaniline (**29**) analogues, all of which were tolerated by both receptors, with compound **28** slightly more potent at $\delta$ and $\mu$ than **27** and **29**.

Combining the *p*-fluoro feature that brought good potency at both the $\delta$ and $\mu$ receptors in compound **23** with the acceptable alkyl chains ethyl (**15**) or propyl (**16**) gave interesting results. The *N*-ethyl-*p*-fluorophenyl compound (**30**) showed potency close to that of **23** and **15**, with a slight (~5-fold) drop in $\mu$ activity. However, The *N*-propyl-*p*-fluorophenyl compound (**31**) showed $\delta$ receptor potency close to that of **16** but lost a significant amount of $\mu$ activity, dropping to an $EC_{50}$ greater than 1000 nM. This makes it a $\delta$ receptor-selective agonist, with receptor agonism selectivity similar to BW373U86. Like BW373U86, the binding affinity selectivity is not as great as the functional agonism selectivity because of an apparent difference in the ability of compound **31** to activate $\mu$ receptors in guinea pig ileum smooth muscle and its ability to bind to and displace [$^3$H]-DAMGO from rat CNS $\mu$ receptors. Several reasons for these differences are possible, including possible species or tissue differences in the pharmacology.[31a]

An analogue of the potent *m*-fluoro compound **24** was also prepared that lacked the amide carbonyl (**32**). While this molecule was still an agonist at both receptors, it lost >30-fold potency at the $\delta$ receptor and >500-fold in $\mu$ activity (this resulted in a tissue selectivity that was not mirrored in the binding affinities). The presence of the carbonyl is likely important in orienting the amide *N*-alkyl and *N*-aryl substituents into a favorable conformation for receptor activation.

## Conclusions

To exploit the exciting intermodulatory effects of $\delta$ and $\mu$ receptor ligands, our research efforts in the benzhydrylpiperazine series have shifted from the development of $\delta$ selective compounds to identifying nonpeptidic mixed $\delta/\mu$ agonists that will show strong analgesic properties due to $\mu$ agonism, with a reduced side effect profile resulting from $\delta$ agonism. Mixed $\delta/\mu$ agonists were discovered in the benzhydrylpiperazine series by moving the *p*-diethylamide $\delta$ address portion of the molecule to the meta position of the phenyl where it no longer conferred $\delta$ selectivity. Changing the *m*-diethylamide to a *m*-*N*-methylanilide resulted in a potency increase at both the $\delta$ and $\mu$ receptors, and a series of 3-(α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-alkyl-*N*-arylbenzamides have been synthesized to explore the $\mu$ and $\delta$ opioid receptor agonism SAR. A number of various 3-(α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-alkyl-*N*-arylbenzamides have been identified that show significant opioid activity at the $\mu$ and $\delta$ receptors. Many small functional groups are tolerated on the aryl ring. Additionally, *N*-methyl through *N*-propyl substituents can be placed on the amide nitrogen and retain activity. Increasing the size of the substituents (and increasing

flexibility by removing the carbonyl) resulted in compounds with increasing $\delta$ selectivity by reducing $\mu$ agonist activity. These compounds may be putting a lipophilic group back into part of the $\delta$ address region that was occupied by the *p*-diethylamide.

The identification of several compounds that have in vitro potencies in the 1−5 nM range at both the $\mu$ and $\delta$ receptors, such as compounds **5**, **15**, **17**, **23**−**26**, and **28**−**30**, has provided useful tools to test the pharmacological effects of mixed $\delta/\mu$ opioid agonists. In vivo work demonstrating that these opioid agonists exhibit a promising therapeutic profile will be reported in due course.

## Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. All chemical reagents were purchased from Aldrich Chemical Co., Milwaukee, WI, unless otherwise specified. Commercial solvents were used without further purification except tetrahydrofuran, which was distilled from potassium. Nuclear magnetic resonance (NMR) spectra were obtained with Varian XL-200 and XL-300 spectrometers. HPLC analyses were performed with a Waters liquid chromatography system equipped with a 700 satellite WISP, 600E system controller, and a 991 photodiode array detector, with a 4.6 mm × 250 mm Cyclobond I column (Advanced Separations Technologies, Whippany, NJ) at a flow rate of 1 mL/min. Optical rotations were obtained with a Perkin-Elmer 241 polarimeter. Mass spectra were performed by Oneida Research Services, Whitesboro, NY. X-ray crystallography and structural determination of compound **24** were performed by Dr. Steven J. Geib at the University of Pittsburgh Chemistry X-Ray Diffraction Facility on a Siemens P3 single-crystal diffractometer. Analytical thin-layer chromatography was performed on Analtech glass plates precoated with silica gel GF (250 microns). Elemental analyses were performed by Atlantic Microlab, Norcross, GA.

**In Vitro Bioassays.** The $\delta$ and $\mu$ opioid agonist activities of the 3-(α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-alkyl-*N*-arylbenzamides were evaluated using the mouse vas deferens (MVD) and guinea pig ileum (GPI) preparations, respectively.[30]

Vas deferens were isolated from mice weighing 20−25 g following cervical dislocation. Muscles were dissected and suspended in individual organ baths containing Mg-free Krebs−Henseleit solution (37 °C, aerated with $O_2/CO_2$, 95:5) of the following composition (millimolar): NaCl, 117.5; KCl, 4.75; $CaCl_2$, 2.6; $KH_2PO_4$, 1.2; $NaHCO_3$, 24.5; glucose, 11.

The vas deferens segments were positioned between platinum electrodes and connected to a Grass FTO3 isometric force transducer. Muscles were stimulated to contract by administering 400 ms pulse trains (1 ms duration, supramaximal voltage, 10 Hz) with a Grass S88 stimulator; resting tension was 0.5 g.

Intact ileums (about 3 cm in length) were removed from guinea pig and suspended with 1 g of tension in a bath chamber as described for the vasa deferentia. The modified Krebs's buffer also contained $MgSO_4$ (1.20 mM). The ileums were stimulated with electrical square-wave pulses of 0.1 Hz, 0.5 ms pulse duration at supramaximal voltage.

To establish cumulative concentration−response relationships, the compound was added to organ baths and allowed to produce maximal response before addition of the next higher concentration. The percentage inhibition of the electrically induced muscle contractions was determined for the compounds at varying cumulative concentrations. The $EC_{50}$ values were extrapolated from curves showing the dose−concentration plotted against the response.[32] Each reported value is the average of at least three experiments, with average standard error of the mean (SEM) values of ±22% and ±17% for the MVD and GPI assay results, respectively.

**Membrane Preparation and Opioid Radioligand Binding Assays.** The $\delta$ and $\mu$ opioid receptor binding affinities of the 3-(α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-alkyl-*N*-arylbenzamides were evaluated using rat brain membranes obtained from brain tissue of Sprague−Dawley rats. The brain tissue was rinsed with ice-cold 50 mM Tris-HCl buffer (pH 7.4, 25 °C) containing the following protease inhibitors: 50 $\mu$g/mL soybean trypsin inhibitor, 0.1 mM phenylmethylsulfonyl fluoride (PMSF), 1 mM (ethylenedinitrilo)tetraacetic acid (EDTA), 10 $\mu$g/mL leupeptin, 200 $\mu$g/mL bacitracin, and 0.5 $\mu$g/mL aprotinin. Brains were homogenized in 5−10 volumes per gram wet weight in ice-cold 50 mM Tris buffer containing protease inhibitors. The homogenate was prepared using a glass/Teflon homogenizer and centrifuged at 6000*g* for 15 min at 4 °C. The resulting supernatant was centrifuged at 41000*g* for 30 min at 4 °C. The pellet was suspended in 10 volumes per gram wet weight of 10 mM Tris-sucrose buffer and sonicated with a Polytron tissue grinder (10 s, low speed). The homogenate was then centrifuged at 41000*g* for 30 min at 4 °C. The resulting membrane pellet was resuspended in 50 mM Tris buffer with protease inhibitors at a final protein concentration that ranged from 40 to 50 $\mu$g/mL. The membrane preparation was frozen under liquid $N_2$ and stored at −80 °C prior to use in receptor binding studies. Protein determination was determined by the method described by Bradford.[33] Membrane fractions were incubated with 0.1 nM [$^3$H]deltorphin II or 0.1 nM [$^3$H]-DAMGO in 2 mL of 10 mM Tris-HCl buffer containing 5 mM $MgCl_2$ and protease inhibitors in the presence or absence of DPI-125. Incubation was carried out for 90 min at 25 °C. These conditions permitted the complete equilibration of the radioligand with opioid receptors. The reaction was terminated by rapid filtration through Whatman GF/C glass fiber filters using a cell harvester (model M-48R, Brandel Instruments, Gaithersburg, MD) followed by three 3 mL rinses with ice-cold 50 mM Tris buffer. Nonspecific binding was defined as that radioligand bound in the presence of $1 \times 10^{-6}$ M naloxone. Filters were counted by liquid scintillation spectrometry at an efficiency determined by external standards of 50−65%.

Receptor binding data were analyzed by a nonlinear regression of the one-site competition model to determine the $IC_{50}$ and $K_i$ values using a computer program, Prism (GraphPad Software Inc., San Diego, CA). The apparent dissociation constants, $K_i$ values, were determined by the method of Cheng and Prusoff.[34]

**3-Bromophenyl *tert*-Butyldimethylsilyl Ether.** A mixture of 3-bromophenol (1400 g, 8.1 mol), *tert*-butylchlorodimethylsilane (1218 g, 8.1 mol), and imidazole (1376 g, 20.2 mol) in DMF was stirred at room temperature under nitrogen for 18 h. The reaction mixture was poured into pH 8 aqueous buffer and extracted with $Et_2O$. The ether extracts were washed with water and brine and dried over sodium sulfate, and the solvent was evaporated under vacuum to give 2314 g of crude 3-bromophenyl *tert*-butyldimethylsilyl ether as an orange oil. NMR ($CDCl_3$, 200 MHz): $\delta$ 0.2 (s, 6H), 0.95 (s, 9H), 6.8 (m, 1H), 7.0−7.1 (m, 3H).

**α-(3-Bromophenyl)-3-(*tert*-butyldimethylsilyloxy)benzyl Alcohol (7).** 3-Bromophenyl *tert*-butyldimethylsilyl ether (1771 g, 6.17 mol) was dissolved in dry THF (4 L) under nitrogen and cooled to −78 °C. *n*-Butyllithium (3.85 L of a 1.6 M solution in hexane) was added at a rate to keep the temperature below −70 °C. Stirring was continued at −78 °C for 2 h. A solution of 3-bromobenzaldehyde (1119 g, 6.05 mol) in dry THF (600 mL) was added at a rate to keep the reaction temperature below −70 °C. After the mixture was stirred for 2 h at −78 °C, the reaction was quenched with saturated aqueous $NH_4Cl$ (1.4 L) and the mixture was warmed to room temperature. The mixture was filtered to remove solids. The organic phase was washed with brine, dried over sodium sulfate, and evaporated to give 2.5 kg of crude α-(3-bromophenyl)-3-(*tert*-butyldimethylsilyloxy)benzyl alcohol as a yellow oil. Chromatography on silica gel of 1 kg of the crude product with hexane/dichloromethane (gradient from 90:10 to 75:25, followed by dichloromethane/ethyl acetate at a ratio of 90:10)

gave 692.3 g of α-(3-bromophenyl)-3-(*tert*-butyldimethylsilyloxy)benzyl alcohol as a yellow oil. NMR ($CDCl_3$, 200 MHz): $\delta$ 0.2 (s, 6H), 0.95 (s, 9H), 2.3 (br s, 1H), 5.7 (s, 1H), 6.75 (d, $J$ = 8 Hz, 1H), 6.8 (s, 1H), 6.9 (d, $J$ = 8 Hz, 1H), 7.2 (m, 2H), 7.3 (d, $J$ = 8 Hz, 1H), 7.4 (d, $J$ = 8 Hz, 1H), 7.5 (s, 1H).

**α-(3-Bromophenyl)-3-(*tert*-butyldimethylsilyloxy)benzyl Chloride (8).** Thionyl chloride (38 mL, 0.51 mol) was added dropwise to a solution of benzhydryl alcohol **7** (160 g, 0.41 mol) in 1 L of $CH_2Cl_2$, and the mixture was stirred overnight at room temperature. The solvent was removed under vacuum, the residue was dissolved in toluene, and the solvent was again removed under vacuum to give crude α-(3-bromophenyl)-3-(*tert*-butyldimethylsilyloxy)benzyl chloride as a brown oil. The benzhydryl chloride was used without further purification. NMR ($CDCl_3$, 200 MHz): $\delta$ 0.2 (s, 6H), 0.95 (s, 9H), 6.0 (s, 1H), 6.8−7.0 (m, 3H), 7.2−7.6 (m, 5H).

**(−)-(2*R*,5*S*)-1-Allyl-2,5-dimethylpiperazine (9).** A 12 L, three-necked round-bottom flask was charged with *trans*-2,5-dimethylpiperazine (767 g, 6.72 mol). The flask was cooled in an ice bath, and a solution of methanesulfonic acid (1290 g, 13.4 mol) in 600 mL of water was added slowly, maintaining the temperature below 40 °C. The solution was cooled to 20 °C, and 800 mL of ethanol was added. The pH was adjusted to 4.0 with 60% aqueous potassium acetate, then ethyl chloroformate (642 mL, 6.71 mol in 360 mL of THF) and potassium acetate solutions were simultaneously added dropwise with adjustment of rate to maintain the reaction solution at pH 4.0 ± 0.1, with cooling to maintain temperature at 25 °C. After the mixture was stirred an additional hour, the organic solvents were removed and the remaining aqueous solution was washed with ethyl acetate. The ethyl acetate wash was extracted with two 500 mL portions of 1 M HCl to recover the desired product. The acid extracts were combined with the original aqueous solution, and the pH was adjusted to 11 by addition of 10 M NaOH, with cooling to maintain temperature below 40 °C. The aqueous solution was extracted with ethyl acetate, the combined extracts were dried over magnesium sulfate, and the solvent was removed to give 927 g (74%) of ethyl *trans*-2,5-dimethyl-1-piperazinecarboxylate as a yellow oil.

A mixture of ethyl *trans*-2,5-dimethyl-1-piperazinecarboxylate (643 g, 3.45 mol), allyl bromide (328 mL, 3.80 mol), and sodium carbonate (440 g, 4.15 mol) in 2.5 L of $CH_3CN$ was heated at reflux for 1.5 h. The reaction mixture was cooled to room temperature and filtered, and the solvent was removed under vacuum. The residue was dissolved in 4 L of $CH_2Cl_2$, washed with 1 M NaOH, and dried over magnesium sulfate, and the solvent was removed to give 630 g (81%) of ethyl *trans*-4-allyl-2,5-dimethyl-1-piperazinecarboxylate as an oil.

Ethyl *trans*-4-allyl-2,5-dimethyl-1-piperazinecarboxylate (630 g, 2.78 mol) was added to a solution of 87% potassium hydroxide pellets (2970 g, 46 mol) in 4300 mL of 95% ethanol, and the mixture was heated at reflux for 1.5 h. The reaction mixture was cooled below reflux temperature, and 2 L of toluene was carefully added. Ethanol was removed by azeotropic distillation at 105 °C while adding an additional 4 L of toluene to the reaction flask during the course of the distillation. After collection of 9 L of distillate, the reaction mixture was cooled to 100 °C and 1 L of toluene was added. The solution was slowly cooled to 5 °C and maintained at 5 °C for 30 min. The solution was filtered, and the filter cake was washed with an additional 1.5 L of toluene. The filtrate was washed with 1 L of water and dried over magnesium sulfate, and the solvent was removed to give 296 g (69%) of *trans*-1-allyl-2,5-dimethylpiperazine as a dark liquid. NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.87 (d, $J$ = 6.3 Hz, 3H), 0.92 (d, $J$ = 6.3 Hz, 3H), 1.63 (t, $J$ = 11 Hz, 1H), 2.05 (m, 1H), 2.30 (t, $J$ = 11 Hz, 1H), 2.6−2.8 (m, 4H), 3.33 (dd, $J_1$ = 5 Hz, $J_2$ = 14 Hz, 1H), 5.09 (d, $J$ = 8.7 Hz, 1H), 5.13 (d, $J$ = 14 Hz, 1H), 5.8 (m, 1H).

Di-*p*-toluoyl-D-tartaric acid (1.25 kg, 3.2 mol) was dissolved in hot 95% EtOH (16 L), and racemic *trans*-1-allyl-2,5-dimethylpiperazine (500 g, 3.2 mol) was added in several portions (caution: exothermic). The hot solution was seeded with crystals of the stereoisomerically pure salt (obtained from a previous small-scale resolution) and cooled to room temperature over 2−3 h. The solution was slowly stirred for 2 days at room temperature. The resulting salt was collected by filtration, washed twice with 95% EtOH, and dried under vacuum to give 826.5 g of a white solid (47%). The process was repeated with a second batch of the di-*p*-toluoyl-D-tartaric acid and racemic *trans*-1-allyl-2,5-dimethylpiperazine to give 869 g (50%).

The total of 1695 g of salt was divided into three batches, and each batch was recrystallized twice from 95% ethanol. The total amount recovered was 1151 g. The salt was dissolved in 3 L of 2 M aqueous NaOH, and the aqueous solution was extracted with four 1 L portions of $CH_2Cl_2$. The organic extracts were combined and dried over sodium sulfate, and the solvent was removed by rotary evaporation (temperature less than 20 °C) to give 293 g (29% based on racemic weight) of (2*R*,5*S*)-1-allyl-2,5-dimethylpiperazine as a clear oil. $[\alpha]^{20}_D$ −55.1° (*c* 1.2, absolute ethanol). The trifluoroacetamide of the product was prepared with trifluoroacetic anhydride and analyzed by chiral capillary gas chromatography (Chiraldex B-PH column, 20 m × 0.32 mm, Advanced Separation Technologies Inc., Whippany, NJ, 120 °C) indicating an enantiopurity of >99% ee (retention time of desired enantiomer, 11.7 min; other enantiomer, 10.7 min).

**3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-bromobenzyl)phenol (10).** A mixture of benzhydryl chloride **8** and (−)-(2*R*,5*S*)-1-allyl-2,5-dimethylpiperazine **9** (137.6 g, 0.89 mol) in 1500 mL of acetonitrile was heated at reflux for 48 h and concentrated in vacuo, and the residue was dissolved in ethyl acetate. The mixture was washed with 0.25 M aqueous NaOH, dried over sodium sulfate, and concentrated in vacuo to give 202.6 g of dark oil, which was dissolved in acetonitrile (1 L) and treated with tetraethylammonium fluoride dihydrate (88.9 g, 0.48 mol). After the mixture was stirred at room temperature overnight, the solvent was removed under vacuum. The residue was dissolved in $CH_2Cl_2$ (2 L), washed with pH 8 aqueous buffer solution, dried over sodium sulfate, and concentrated to give 163 g of a dark solid. A portion (11 g) of this solid was purified by chromatography on silica gel with ethanol (0−2.5%) in $CH_2Cl_2$. An amount of 2.2 g of (+)-3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-bromobenzyl)phenol, the second spot to elute, was obtained as a white solid. NMR (DMSO-$d_6$, 200 MHz): $\delta$ 0.95 (d, $J$ = 6 Hz, 3H), 1.03 (d, $J$ = 6 Hz, 3H), 1.8 (dd, $J_1$ = 6 Hz, $J_2$ = 10 Hz, 1H), 2.1 (dd, $J_1$ = 6 Hz, $J_2$ = 10 Hz, 1H), 2.4−2.6 (m, 3H), 2.7 (d, $J$ = 11 Hz, 1H), 2.8 (dd, $J_1$ = 7 Hz, $J_2$ = 14 Hz, 1H), 3.2 (dd, $J_1$ = 6 Hz, $J_2$ = 13 Hz, 1H), 4.9 (s, 1H), 5.1 (d, $J$ = 10 Hz, 1H), 5.2 (d, $J$ = 18 Hz, 1H), 5.7−5.9 (m, 1H), 6.6−6.8 (m, 3H), 7.0−7.4 (m, 4H), 7.55 (s, 1H), 9.35 (s, 1H).

**Acid Chloride (6) Preparation. (+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzonitrile.** Compound (+)-**10** (147.3 g, 0.355 mol) was dissolved in 1 L of *N*-methyl-2-pyrrolidinone with cuprous cyanide (63.6 g, 0.71 mol), and the reaction mixture was heated at 170 °C for 30 h.[24] The reaction mixture was cooled to room temperature and poured into 7 L of aqueous 14% sodium cyanide. The mixture was stirred overnight and extracted with ethyl acetate. The ethyl acetate extracts were combined, washed with water, dried over sodium sulfate, and concentrated in vacuo to give 133.3 g of a brown solid. Chromatography on silica gel with ethanol (2−7%) in $CH_2Cl_2$ gave 97.8 g of crude (+)-3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl) benzonitrile. Recrystallization from acetonitrile gave 74.2 g (58%) of (+)-3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzonitrile as a white solid.

**(+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzoic Acid.** (+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzonitrile (78.8 g, 0.22 mol) was combined with 60 g of NaOH pellets in 1 L of 95% EtOH and heated at reflux for 72 h. The mixture was concentrated in vacuo and dissolved in water, and the resulting solution was adjusted to pH 5 with concentrated HCl. The solvent was removed in vacuo to give 138.8 g of the 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hy-

droxybenzyl)benzoic acid as a mixture with sodium chloride. A portion (5.0 g) of the crude acid was stirred with 50 mL of water. The resulting slurry was filtered and the solid in the filter was washed three times with water and then dried under vacuum for 3 h to give 2.02 g of (+)-3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzoic acid as a light-beige solid. NMR (DMSO-$d_6$, 200 MHz): $\delta$ 0.95 (d, $J = 6$ Hz, 3H), 1.1 (d, $J = 6$ Hz, 3H), 1.9 (ddd, $J_1 = 3$ Hz, $J_2 = 7$ Hz, $J_3 = 10$ Hz, 1H), 2.1 (dd, $J_1 = 8$ Hz, $J_2 = 10$ Hz, 1H), 2.5 (m, 2H), 2.7−2.9 (m, 2H), 3.2 (m, 2H), 5.05 (d, $J = 12$ Hz, 1H), 5.2 (d, $J = 18$ Hz, 1H), 5.8 (m, 1H), 6.7 (m, 3H), 7.1 (t, $J = 8$ Hz, 1H), 7.4 (t, $J = 8$ Hz, 1H), 7.65 (d, $J = 8$ Hz, 1H), 7.8 (d, $J = 8$ Hz, 1H), 8.0 (s, 1H), 9.4 (s, 1H). $[\alpha]^{20}_D$ +4.1° (*c* 1.09, 0.1 M aqueous sodium hydroxide). Mass spectrum (CI − $CH_4$) *m/e*: 381 (M + 1, 35%), 380 (M, 2%), 227 (28%), 155 (100%), 153 (83%). Anal. ($C_{23}H_{28}N_2O_3 \cdot 0.75H_2O$) C, H, N.

**3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyloxy)benzyl)benzoyl Chloride (6).** 3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzoic acid (25.9 g of a 50 wt % mixture with sodium chloride, 34.0 mmol) was dissolved in 40 mL of DMF with 12.8 g (84.9 mmol) of *tert*-butylchlorodimethylsilane and 11.5 g (169.1 mmol) of imidazole, and the mixture was stirred overnight at room temperature. The reaction solution was poured into 500 mL of ice/water and extracted with 500 mL of $Et_2O$. The extract was washed twice with 250 mL of water and then with 125 mL of brine. The ether solution was dried over sodium sulfate, and the solvent was removed to give 20.8 g of crude *tert*-butyldimethylsilyl 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyloxy)benzyl)-benzoate.

The crude silyl ether/silyl ester (20.7 g, ≤33.9 mmol based on the previous reaction) was dissolved in 60 mL of dichloromethane and cooled to 0 °C under nitrogen. Oxalyl chloride (3.7 mL, 42.4 mmol) was added dropwise. While the bath temperature was maintained at 0 °C, catalytic DMF (10 drops) was added slowly. The bath temperature was maintained at 0 °C for 30 min and then allowed to warm to room temperature. The solution was stirred at room temperature for 24 h. All of the volatiles were removed by evaporation under reduced pressure to give 29.76 g of crude 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyloxy)benzyl)benzoyl chloride as a yellow-brown solid. The crude acid chloride was used without purification.

**General Benzamide Formation Method. (+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-(hydroxybenzyl)-*N*-methyl-*N*-phenylbenzamide (5).** 3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyloxy)benzyl)benzoyl chloride (2.33 g of crude, approximately 1.44 g of actual compound, 2.81 mmol based on 3-((α*R*)-α-((2*S*, 5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzoic acid) was dissolved in 12 mL of dichloromethane at room temperature under nitrogen. Triethylamine (0.5 mL) was added to the solution. *N*-Methylaniline (0.46 mL, 4.3 mmol) was added dropwise to the solution, and the reaction mixture was stirred overnight at room temperature. All volatiles were removed by evaporation under reduced pressure to provide a gummy brown solid. This crude solid was dissolved in acetonitrile (8 mL) under nitrogen at room temperature. Tetraethylammonium fluoride dihydrate (1.19 g, 6.42 mmol) was added, and the solution was stirred for 1 h at room temperature. After removal of solvent, the residue was purified by chromatography on silica gel with 0.5−2% ethanol in dichloromethane to give 0.368 g (28% over four steps from 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzoic acid) of (+)-3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(hydroxybenzyl)-*N*-methyl-*N*-phenylbenzamide as a light-yellow solid. NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.89 (d, $J = 6.0$ Hz, 3H), 0.96 (d, $J = 6.0$ Hz, 3H), 1.66 (dd, $J_1 = 7.3$ Hz, $J_2 = 11.4$ Hz, 1H), 2.01 (dd, $J_1 = 7.8$ Hz, $J_2 = 10.6$ Hz, 1H), 2.26 (br d, $J = 10.6$ Hz, 1H), 2.37−2.54 (m, 2H), 2.66 (br d, $J = 11.0$ Hz, 1H), 2.82 (dd, $J_1 = 7.0$ Hz, $J_2 = 13.9$ Hz, 1H), 3.17 (dd, $J_1 = 4.8$ Hz, $J_2 = 13.9$ Hz, 1H), 3.34 (s, 3H), 4.77 (s, 1H), 5.10 (d, $J = 10.1$ Hz, 1H), 5.16 (d, $J = 17.3$ Hz, 1H), 5.70−5.82 (m, 1H), 6.41 (d, $J = 7.4$ Hz, 1H), 6.54 (s, 1H), 6.64 (d, $J = 8.0$ Hz, 1H), 7.05−7.26 (m, 10H), 9.31 (s, 1H). Mass spectrum (CI − $CH_4$) *m/e*: 470 (M + 1, 100%), 376 (81%), 316 (45%), 153 (97%). $[\alpha]^{20}_D$ +12.3° (*c* 1.2, ethanol). The free amine (0.339 g) was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 3.0 followed by precipitation with diethyl ether from dichloromethane to give 0.321 g (88% recovery) of the monohydrochloride salt as a hygroscopic light-yellow powder. Anal. ($C_{30}H_{35}N_3O_2 \cdot HCl \cdot H_2O$) C, H, N, Cl.

**General *N*-Methylaniline Formation Method. *N*-Methyl-4-fluoroaniline (22).** Following a general literature procedure for reductive alkylation, acetic-formic anhydride was prepared by slowly adding formic acid (7.5 mL) to acetic anhydride at 0 °C.[26] After being stirred for 5 min at 0 °C, the mixture was heated at 55 °C for 1.75 h. The mixture was cooled to 0 °C and used without purification. 4-Fluoroaniline (3.1 mL, 32.8 mmol) in THF (10 mL) was added to acetic-formic anhydride (12.5 mL, 88 mmol) at 0 °C. The reaction mixture was stirred for 25 min, and the volatiles were removed under vacuum to provide the formamide as a brown solid. A portion of the crude solid (2.39 g, 17.2 mmol) was dissolved in THF (8 mL) and cooled to 0 °C. Borane in THF (40 mL of a 1.0 M solution) was added dropwise. After the addition, the solution was heated to reflux and maintained for 3 h. The solution was cooled to 0 °C, and methanol (10 mL) was added carefully. After the mixture was stirred for 10 min, ethanolic HCl (7 mL of a 7.1 M solution) was added and the reaction was stirred overnight. After removal of all volatiles in vacuo, crude *N*-methyl-4-fluoroaniline was obtained as a light-purple solid. NMR (200 MHz, DMSO-$d_6$): $\delta$ 2.65 (s, 3H), 5.54 (s, 1H), 6.51 (dd, $J_1 = 4.7$ Hz, $J_2 = 8.8$ Hz, 2H), 6.93 (dd, $J_1 = 8.9$ Hz, $J_2 = 8.8$ Hz, 2H).

**(+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-(4-fluorophenyl)-*N*-methylbenzamide (23). 23** was prepared from 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyloxy)benzyl)benzoyl chloride and 4-fluoro-*N*-methylaniline as described above. (+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-(hydroxybenzyl)-*N*-(4-fluorophenyl)-*N*-methylbenzamide was obtained as a yellow powder. NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.88 (d, $J = 6.0$ Hz,3H), 0.96 (d, $J = 6.0$ Hz, 3H), 1.68 (dd, $J_1 = 7.7$ Hz, $J_2 = 10.8$ Hz, 1H), 2.02 (dd, $J_1 = 7.1$ Hz, $J_2 = 10.7$ Hz, 1H), 2.28 (br d, $J = 10.7$ Hz, 1H), 2.35−2.52 (m, 2H), 2.66 (br d, $J = 10.6$ Hz, 1H), 2.82 (dd, $J_1 = 7.4$ Hz, $J_2 = 13.9$ Hz, 1H), 3.16 (dd, $J_1 = 4.6$ Hz, $J_2 = 14.0$ Hz, 1H), 3.32 (s, 3H), 4.77 (s, 1H), 5.10 (d, $J = 10.3$ Hz, 1H), 5.16 (d, $J = 17.3$ Hz, 1H), 5.70−5.84 (m, 1H), 6.43 (d, $J = 7.4$ Hz, 1H), 6.56 (s, 1H), 6.64 (d, $J = 8.0$ Hz, 1H), 7.02−7.22 (m, 9H), 9.31 (s, 1H). Mass spectrum (CI − $CH_4$) *m/e*: 488 (M + 1,-100%), 334 (11%), 153 (68%). $[\alpha]^{20}_D$ +6.9° (*c* 1.6, ethanol). The monohydrochloride salt was formed as described above to give a hygroscopic light-yellow powder. Anal. ($C_{30}H_{34}N_3O_2F \cdot HCl \cdot H_2O$) C, H, N, F, Cl.

**(−)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-phenylbenzamide (14).** This compound was obtained as a light-yellow powder from aniline and 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyl-dimethylsilyloxy)benzyl)benzoyl chloride as described above. NMR (200 MHz, DMSO-$d_6$): $\delta$ 0.99 (d, $J = 5.7$ Hz, 3H), 1.10 (d, $J = 5.8$ Hz, 3H), 1.91 (dd, $J_1 = 7.0$ Hz, $J_2 = 10.5$ Hz, 1H), 2.14 (dd, $J_1 = 6.0$ Hz, $J_2 = 10.4$ Hz, 1H), 2.51−2.81 (m, 4H), 2.88 (dd, $J_1 = 6.8$ Hz, $J_2 = 13.9$ Hz, 1H), 3.18 (dd, $J_1 = 5.4$ Hz, $J_2 = 13.8$ Hz, 1H), 5.06 (d, $J = 15.6$ Hz, 1H), 5.14 (s, 1H), 5.19 (d, $J = 18.1$ Hz, 1H), 5.75 (m, 1H), 6.73 (m, 3H), 7.10 (d, $J = 7.8$ Hz, 1H), 7.17 (d, $J = 8.0$ Hz, 1H), 7.30−7.59 (m, 3H), 7.65 (d, $J = 7.6$ Hz, 1H), 7.71−7.83 (m, 3H), 7.93 (s, 1H), 9.37 (s, 1H), 10.21 (s, 1H). Mass spectrum (CI − $CH_4$) *m/e*: 456 (M + 1,100%), 302 (41%), 153 (77%). $[\alpha]^{20}_D$ −4.44° (*c* 1.4, ethanol). The monohydrochloride salt was prepared to give a hygroscopic light-yellow powder. Anal. ($C_{29}H_{33}N_3O_2 \cdot HCl \cdot 0.75H_2O$) C, H, N, Cl.

**(+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-ethyl-*N*-phenylbenzamide (15).**

**15** was prepared from 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyloxy)benzyl)benzoyl chloride and *N*-ethylaniline as described above. (+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-ethyl-*N*-phenylbenzamide was obtained as a white solid. NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.89 (d, $J$ = 6.1 Hz, 3H), 0.96 (d, $J$ = 6.1 Hz, 3H), 1.07 (t, $J$ = 7.0 Hz, 3H), 1.67 (dd, $J_1$ = 7.4 Hz, $J_2$ = 10.4 Hz, 1H), 2.02 (dd, $J_1$ = 7.4 Hz, $J_2$ = 10.6 Hz, 1H), 2.27 (dd, $J_1$ = 1.4 Hz, $J_2$ = 10.6 Hz, 1H), 2.36−2.52 (m, 2H), 2.66 (br d, $J$ = 10.4 Hz, 1H), 2.82 (dd, $J_1$ = 7.8 Hz, $J_2$ = 13.5 Hz, 1H), 3.16 (dd, $J_1$ = 4.0 Hz, $J_2$ = 13.9 Hz, 1H), 3.83 (q, $J$ = 7.0 Hz, 2H), 4.75 (s, 1H), 5.09 (d, $J$ = 9.9 Hz, 1H), 5.16 (d, $J$ = 17.2 Hz, 1H), 5.70−5.84 (m, 1H), 6.41 (d, $J$ = 7.6 Hz, 1H), 6.54 (s, 1H), 6.63 (d, $J$ = 8.2 Hz, 1H), 7.03−7.29 (m, 10H), 9.30 (s, 1H). Mass spectrum (CI − $CH_4$) *m*/*e*: 484 (M + 1,-100%), 330 (57%), 153 (66%). $[\alpha]^{20}_D$ +10.4° (*c* 1.2, ethanol). The monohydrochloride salt was prepared to give a hygroscopic white powder. Anal. ($C_{27}H_{37}N_3O_2$·HCl·$H_2O$): C, H, N, Cl.

**(+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-phenyl-*N*-propylbenzamide (16).** *N*-Propylaniline (Pfaltz & Bauer, Inc., 172 E. Aurora Street, Waterbury, CT 06708) was coupled with 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyloxy)-benzyl)benzoyl chloride, deprotected, and purified by the methods described above to give (+)-3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(hydroxybenzyl)-*N*-phenyl-*N*-propylbenzamide as a light-yellow solid. NMR (200 MHz, DMSO-$d_6$): $\delta$ 0.87 (t, $J$ = 7.4 Hz, 3H), 0.91 (d, $J$ = 5.9 Hz, 3H), 0.98 (d, $J$ = 6.0 Hz, 3H), 1.51 (m, 2H), 1.69 (dd, $J_1$ = 7.2 Hz, $J_2$ = 10.9 Hz, 1H), 2.06 (dd, $J_1$ = 7.0 Hz, $J_2$ = 10.5 Hz, 1H), 2.30 (d, $J$ = 10.3 Hz, 1H), 2.39−2.54 (m, 2H), 2.65 (br d, $J$ = 10.3 Hz, 1H), 2.85 (dd, $J_1$ = 7.4 Hz, $J_2$ = 14.5 Hz, 1H), 3.16 (dd, $J_1$ = 5.1 Hz, $J_2$ = 14.2 Hz, 1H), 3.79 (t, $J$ = 7.6 Hz, 2H), 4.77 (s, 1H), 5.12 (d, $J$ = 10.2 Hz, 1H), 5.18 (d, $J$ = 16.0 Hz, 1H), 5.71−5.84 (m, 1H), 6.43 (d, $J$ = 7.6 Hz, 1H), 6.57 (s, 1H), 6.64 (d, $J$ = 8.0 Hz, 1H), 7.02−7.33 (m, 10H), 9.32 (s, 1H). Mass spectrum (CI − $CH_4$) *m*/*e*: 498 (M + 1, 100%), 344 (23%), 153 (80%). $[\alpha]^{20}_D$ +8.9° (*c* 1.1, ethanol). The free amine (0.585 g) was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 4.0 followed by precipitation with diethyl ether from dichloromethane to give 0.479 g of the monohydrochloride salt as a hygroscopic off-white powder. Anal. ($C_{32}H_{39}N_3O_2$·HCl·0.75$H_2O$) C, H, N, Cl.

**(+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-cyclopropyl-*N*-phenylbenzamide (17).** *N*-Cyclopropylaniline was prepared via the Barton approach for arylation of amines.[28] Cyclopropylamine (1.0 g, 17.5 mmol) was added to triphenylbismuth (9.25 g, 21.0 mmol) and cupric acetate (1.6 g, 8.75 mmol) in $CH_2Cl_2$ (30 mL) at room temperature under nitrogen. The mixture was stirred for 18 h, filtered over a short plug of Celite, and purified by chromatography on a silica gel column using hexane/ethyl acetate (95:5) for elution. The fraction containing the desired product was stripped of all volatiles under vacuum to yield *N*-cyclopropylaniline (0.8 g). NMR (200 MHz, DMSO-$d_6$): $\delta$ 0.37 (m, 2H), 0.68 (m, 2H), 2.30 (m, 1H), 6.03 (br s, 1H), 6.56 (t, $J$ = 7.4 Hz, 1H), 6.70 (d, $J$ = 8.2 Hz, 2H), 7.09 (t, $J$ = 7.8 Hz, 2H).

*N*-Cyclopropylaniline was then coupled with 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotected, and purified by the methods described to give 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-cyclopropyl-*N*-phenylbenzamide as a yellow powder. NMR (200 MHz, DMSO-$d_6$): $\delta$ 0.44 (m, 2H), 0.70 (m, 2H), 0.93 (d, $J$ = 6.1 Hz, 3H), 1.01 (d, $J$ = 5.7 Hz, 3H), 1.74 (dd, $J_1$ = 7.7 Hz, $J_2$ = 11.8 Hz, 1H), 2.05 (dd, $J_1$ = 6.8 Hz, $J_2$ = 11.1 Hz, 1H), 2.39 (br d, $J$ = 10.5 Hz, 1H), 2.41−2.54 (m, 2H), 2.69 (br d, $J$ = 11.8 Hz, 1H), 2.83 (dd, $J_1$ = 6.6 Hz, $J_2$ = 13.6 Hz, 1H), 3.05−3.36 (m, 2H), 4.83 (s, 1H), 5.10 (d, $J$ = 9.8 Hz, 1H), 5.17 (d, $J$ = 17.4 Hz, 1H), 5.70−5.86 (m, 1H), 6.57 (d, $J$ = 7.1 Hz, 1H), 6.63 (s, 1H), 6.65 (d, $J$ = 8.2 Hz, 1H), 7.03−7.38 (m, 10H), 9.34 (s, 1H). Mass spectrum (CI − $CH_4$) *m*/*e*: 496 (M + 1, 100%), 342 (45%), 153 (90%). $[\alpha]^{20}_D$ +7.1° (*c* 1.1, absolute ethanol). The free amine was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 3.95 followed by precipitation with diethyl ether from dichloromethane to give the monohydrochloride salt as a hygroscopic orange powder. Anal. ($C_{32}H_{37}N_3O_2$·HCl·1.50$H_2O$) C, H, N, Cl.

**(+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-*n*-butyl-*N*-phenylbenzamide (18).** *N*-Butylaniline was coupled with 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyloxy)benzyl)-benzoyl chloride, deprotected, and purified by the methods described to give (+)-3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(hydroxybenzyl)-*N*-*n*-butyl-*N*-phenylbenzamide as an off-white solid. NMR (200 MHz, DMSO-$d_6$): $\delta$ 0.87 (t, $J$ = 7.2 Hz, 3H), 0.92 (d, $J$ = 6.3 Hz, 3H), 0.98 (d, $J$ = 6.1 Hz, 3H), 1.29 (m, 2H), 1.48 (m, 2H), 1.70 (dd, $J_1$ = 7.4 Hz, $J_2$ = 10.9 Hz, 1H), 2.05 (dd, $J_1$ = 7.3 Hz, $J_2$ = 10.6 Hz, 1H), 2.30 (d, $J$ = 10.1 Hz, 1H), 2.39−2.54 (m, 2H), 2.67 (br d, $J$ = 10.6 Hz, 1H), 2.86 (dd, $J_1$ = 7.4 Hz, $J_2$ = 13.7 Hz, 1H), 3.19 (dd, $J_1$ = 5.1 Hz, $J_2$ = 13.7 Hz, 1H), 3.83 (t, $J$ = 7.4 Hz, 2H), 4.78 (s, 1H), 5.13 (d, $J$ = 9.9 Hz, 1H), 5.19 (d, $J$ = 16.0 Hz, 1H), 5.71−5.86 (m, 1H), 6.43 (d, $J$ = 7.5 Hz, 1H), 6.57 (s, 1H), 6.65 (d, $J$ = 8.0 Hz, 1H), 7.03−7.33 (m, 10H), 9.34 (s, 1H). MS (CI − $CH_4$) *m*/*e*: 512 (M + 1,30%), 358 (5%), 153 (40%) 79 (100%). $[\alpha]^{20}_D$ +9.5° (*c* 1.0, ethanol). The free amine was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 4.0 followed by precipitation with diethyl ether from dichloromethane to give the monohydrochloride salt as a hygroscopic beige powder. Anal. ($C_{33}H_{41}N_3O_2$·HCl·1.25$H_2O$) C, H, N, Cl.

**(+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)phenyl 1,2,3,4-tetrahydro-1-quinolinyl Ketone (19).** 1,2,3,4-Tetrahydroquinoline was coupled with 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotected, and purified by the methods described to give an off-white powder. NMR (200 MHz, DMSO-$d_6$): $\delta$ 0.87 (d, $J$ = 6.1 Hz, 3H), 0.99 (d, $J$ = 6.0 Hz, 3H), 1.65 (dd, $J_1$ = 7.3 Hz, $J_2$ = 10.0 Hz, 1H), 1.86−2.14 (m, 3H), 2.26 (d, $J$ = 11.6 Hz, 1H), 2.28−2.39 (m, 1H), 2.45−2.54 (m, 1H), 2.65 (d, $J$ = 10.9 Hz, 1H), 2.78 (t, $J$ = 6.3 Hz, 2H), 2.83 (m, 1H), 3.17 (dd, $J_1$ = 4.4 Hz, $J_2$ = 9.2 Hz, 1H), 3.73 (t, $J$ = 6.1 Hz, 2H), 4.89 (s, 1H), 5.10 (d, $J$ = 8.4 Hz, 1H), 5.16 (d, $J$ = 18.3 Hz, 1H), 5.66−5.82 (m, 1H), 6.43 (d, $J$ = 8.5 Hz, 1H), 6.56 (s, 1H), 6.62−6.71 (m, 2H), 6.86 (t, $J$ = 7.5 Hz, 1H), 7.00 (t, $J$ = 7.4 Hz, 1H), 7.07 (t, $J$ = 7.8 Hz, 1H), 7.20 (d, $J$ = 7.7 Hz, 1H), 7.25−7.34 (m, 4H), 9.31 (s, 1H). MS (CI − $CH_4$) *m*/*e*: 496 (M + 1,100%), 342 (22%), 153 (33%). $[\alpha]^{20}_D$ +23.2° (*c* 1.2, absolute ethanol). The free amine was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 4.0 followed by precipitation with diethyl ether from dichloromethane to give the monohydrochloride salt as a hygroscopic light-brown powder. Anal. ($C_{32}H_{37}N_3O_2$·HCl·0.75$H_2O$) C, H, N, Cl.

**(+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-benzyl-*N*-methylbenzamide (20).** This compound was prepared from 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyloxy)benzyl)benzoyl chloride and *N*-benzyl-*N*-methylamine as described. NMR (300 MHz, DMSO-$d_6$, 121 °C): $\delta$ 0.93 (d, $J$ = 6.2 Hz, 3H), 1.06 (d, $J$ = 6.2 Hz, 3H), 1.96 (dd, $J_1$ = 6.7 Hz, $J_2$ = 11.0 Hz, 1H), 2.12 (dd, $J_1$ = 7.0 Hz, $J_2$ = 11.0 Hz, 1H), 2.58 (dd, $J_1$ = 2.9 Hz, $J_2$ = 11.4 Hz, 1H), 2.67−2.84 (m, 3H), 2.86 (s, 3H), 2.89 (dd, $J_1$ = 6.6 Hz, $J_2$ = 13.5 Hz, 1H), 3.18 (dd, $J_1$ = 4.0 Hz, $J_2$ = 14.1 Hz, 1H), 4.58 (s, 2H), 4.98 (s, 1H), 5.08 (d, $J$ = 10.2 Hz, 1H), 5.16 (d, $J$ = 17.3 Hz, 1H), 5.74−5.89 (m, 1H), 6.62−6.74 (m, 3H), 7.10 (t, $J$ = 7.8 Hz, 1H), 7.21−7.50 (m, 9H), 8.76 (s, 1H). Mass spectrum (CI − $CH_4$) *m*/*e*: 484 (M + 1,88%), 330 (33%), 153 (100%). $[\alpha]^{20}_D$ +14.3° (*c* 1.25, ethanol). The free amine was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 3.4 followed by precipitation with diethyl ether from dichloromethane to give (+)-3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-benzyl-*N*-methylbenzamide monohydrochloride as a hygroscopic light-yellow powder. Anal. ($C_{31}H_{37}N_3O_2$·HCl·0.75$H_2O$) C, H, N, Cl.

**(+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-methyl-*N*-phenethylbenzamide (21).** *N*-Methylphenethylamine was coupled with 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotected, and purified by the methods described above to give (+)-3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-methyl-*N*-phenethylbenzamide as a light-yellow powder. NMR (300 MHz, DMSO-$d_6$, 80 °C): $\delta$ 0.91 (d, $J$ = 5.5 Hz, 3H), 1.08 (d, $J$ = 6.3 Hz, 3H), 1.87 (dd, $J_1$ = 7.1 Hz, $J_2$ = 11.2 Hz, 1H), 2.09 (dd, $J_1$ = 7.1 Hz, $J_2$ = 11.0 Hz, 1H), 2.58 (d, $J$ = 11.3 Hz, 1H), 2.67 (m, 1H), 2.76 (dd, $J_1$ = 6.2 Hz, $J_2$ = 13.2 Hz, 1H), 2.77−2.87 (m, 4H), 2.89 (s, 3H), 3.18 (dd, $J_1$ = 5.5 Hz, $J_2$ = 14.2 Hz, 1H), 3.55 (br s, 2H), 4.97 (s, 1H), 5.10 (d, $J$ = 10.2 Hz, 1H), 5.16 (d, $J$ = 17.3 Hz, 1H), 5.74−5.89 (m, 1H), 6.65−6.73 (m, 3H), 7.07−7.41 (m, 9H), 7.43 (d, $J$ = 7.9 Hz, 1H), 9.07 (s, 1H). Mass spectrum (CI − $CH_4$) *m*/*e*: 498 (M + 1, 88%), 344 (22%), 153 (100%). $[\alpha]^{20}_D$ +3.8° (*c* 1.25, ethanol). The free amine (0.232 g) was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 3.9 followed by precipitation with diethyl ether from dichloromethane to give 0.205 g of the monohydrochloride salt as a hygroscopic light-yellow powder. Anal. ($C_{32}H_{39}N_3O_2$·HCl·$H_2O$) C, H, N, Cl.

**(+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-(3-fluorophenyl)-*N*-methylbenzamide (24).** 3-Fluoro-*N*-methylaniline [NMR (200 MHz, DMSO-$d_6$): $\delta$ 2.76 (s, 3H), 3.42 (s, 1H), 6.51−6.92 (m, 3H), 7.28 (dt, $J_1$ = 7.3 Hz, $J_2$ = 8.0 Hz, 1H)] was prepared from 3-fluoroaniline, coupled with 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethyl-silyloxy)benzyl)-benzoyl chloride, deprotected, and purified by the methods described to give (+)-3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-(3-fluorophenyl)-*N*-methylbenzamide as a light-yellow powder**.** NMR (200 MHz, DMSO-$d_6$): $\delta$ 0.84 (d, $J$ = 6.0 Hz, 3H), 0.97 (d, $J$ = 5.9 Hz, 3H), 1.69 (dd, $J_1$ = 7.7 Hz, $J_2$ = 10.7 Hz, 1H), 2.01 (dd, $J_1$ = 7.4 Hz, $J_2$ = 10.7 Hz, 1H), 2.28 (br d, $J$ = 8.3 Hz, 1H), 2.40−2.52 (m, 2H), 2.67 (br d, $J$ = 10.5 Hz, 1H), 2.82 (dd, $J_1$ = 7.6 Hz, $J_2$ = 13.2 Hz, 1H), 3.17 (br d, $J$ = 14.0 Hz, 1H), 3.34 (s, 3H), 4.80 (s, 1H), 5.10 (d, $J$ = 10.1 Hz, 1H), 5.17 (d, $J$ = 17.3 Hz, 1H), 5.70−5.84 (m, 1H), 6.42 (d, $J$ = 7.1 Hz, 1H), 6.56 (s, 1H), 6.65 (d, $J$ = 8.3 Hz, 1H), 6.90−7.32 (m, 9H), 9.31 (s, 1H). Mass spectrum (CI − $CH_4$) *m*/*e*: 488 (M + 1, 100%), 334 (39%), 153 (87%). $[\alpha]^{20}_D$ +4.9° (*c* 1.2, ethanol). The free amine (0.091 g) was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 3.7 followed by precipitation with diethyl ether from dichloromethane to give 0.072 g (74% recovery) of the monohydrochloride salt as a hygroscopic light-yellow powder. Anal. ($C_{30}H_{34}N_3O_2F$·HCl·1.25$H_2O$) C, H, N, Cl.

**(+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-(2-fluorophenyl)-*N*-methylbenzamide (25).** 2-Fluoro-*N*-methylaniline [NMR (200 MHz, DMSO-$d_6$): $\delta$ 2.89 (s, 3H), 3.87 (br s, 1H), 6.59−6.78 (m, 2H), 6.91−7.10 (m, 2H)] was prepared from 2-fluoroaniline, coupled with 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotected, and purified by the methods described to give 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-(2-fluorophenyl)-*N*-methylbenzamide as an off-white powder. NMR (200 MHz, DMSO-$d_6$): $\delta$ 0.92 (d, $J$ = 6.1 Hz, 3H), 0.99 (d, $J$ = 6.1 Hz, 3H), 1.69 (dd, $J_1$ = 6.7 Hz, $J_2$ = 10.8 Hz, 1H), 2.05 (dd, $J_1$ = 7.6 Hz, $J_2$ = 11.1 Hz, 1H), 2.30 (br d, $J$ = 11.5 Hz, 1H), 2.41−2.52 (m, 2H), 2.68 (br d, $J$ = 10.4 Hz, 1H), 2.83 (dd, $J_1$ = 7.2 Hz, $J_2$ = 13.8 Hz, 1H), 3.20 (dd, $J_1$ = 6.1 Hz, $J_2$ = 14.2 Hz, 1H), 3.30 (s, 3H), 4.82 (s, 1H), 5.12 (d, $J$ = 9.7 Hz, 1H), 5.18 (d, $J$ = 15.8 Hz, 1H), 5.72−5.86 (m, 1H), 6.45 (d, $J$ = 7.4 Hz, 1H), 6.56 (s, 1H), 6.66 (d, $J$ = 8.0 Hz, 1H), 7.05−7.38 (m, 9H), 9.33 (s, 1H). Mass spectrum (CI − $CH_4$) *m*/*e*: 488 (M + 1, 100%), 334 (45%), 153 (86%). $[\alpha]^{20}_D$ +2.02° (*c* 1.1, absolute ethanol). The free amine was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 4.0 followed by precipitation with diethyl ether from dichloromethane to give the monohydrochloride salt as a hygroscopic beige powder. Anal. ($C_{30}H_{34}N_3O_2F$·HCl·0.75$H_2O$) C, H, N, Cl.

**(+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-(4-chlorophenyl)-*N*-methylbenzamide (26). 26** was prepared from 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyloxy)benzyl)benzoyl chloride and 4-chloro-*N*-methylaniline as described above. (+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-(4-chlorophenyl)-*N*-methylbenzamide was obtained as a light-yellow powder. NMR (300 MHz, DMSO-$d_6$): $\delta$ 0.89 (d, $J$ = 6.2 Hz, 3H), 0.96 (d, $J$ = 6.1 Hz, 3H), 1.65 (dd, $J_1$ = 7.6 Hz, $J_2$ = 10.8 Hz, 1H), 2.01 (dd, $J_1$ = 7.6 Hz, $J_2$ = 10.4 Hz, 1H), 2.27 (dd, $J_1$ = 1.5 Hz, $J_2$ = 11.4 Hz, 1H), 2.35−2.52 (m, 2H), 2.65 (br d, $J$ = 10.8 Hz, 1H), 2.82 (dd, $J_1$ = 7.6 Hz, $J_2$ = 13.5 Hz, 1H), 3.16 (dd, $J_1$ = 4.5 Hz, $J_2$ = 14.6 Hz, 1H), 3.33 (s, 3H), 4.77 (s, 1H), 5.10 (d, $J$ = 10.2 Hz, 1H), 5.16 (d, $J$ = 17.2 Hz, 1H), 5.70−5.86 (m, 1H), 6.42 (d, $J$ = 8.1 Hz, 1H), 6.56 (s, 1H), 6.64 (d, $J$ = 7.5 Hz, 1H), 7.04−7.25 (m, 5H), 7.13 (d, $J$ = 8.5 Hz, 2H), 7.29 (d, $J$ = 8.5 Hz, 2H), 9.31 (s, 1H). Mass spectrum (CI − $CH_4$) *m*/*e*: 504 ($^{35}$Cl, M + 1, 86%), 350 (28%), 153 (100%). $[\alpha]^{20}_D$ +10.2° (*c* 1.6). The monohydrochloride salt was prepared as described above to give a hygroscopic light-yellow powder. Anal. ($C_{30}H_{34}N_3O_2Cl$·HCl·0.75$H_2O$) C, H, N, Cl.

**(−)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-methyl-*N*-(2-(trifluoromethyl)-phenyl)benzamide (27).** *N*-Methyl-2-(trifluoromethyl)-aniline[35] [NMR (200 MHz, DMSO-$d_6$): $\delta$ 2.75 (s, 3H), 3.40 (s, 1H), 6.70 (t, $J$ = 8.0 Hz, 1H), 6.94−7.16 (br m, 2H), 7.38 (d, $J$ = 7.3 Hz, 1H)] was coupled with 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyloxy)benzyl)-benzoyl chloride, deprotected, and purified by the methods described to give (+)-3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-methyl-*N*-(2-(trifluoromethyl)phenyl)benzamide as a yellow powder. NMR (200 MHz, DMSO-$d_6$): $\delta$ 0.90 (d, $J$ = 6.0 Hz, 3H), 0.97 (d, $J$ = 6.0 Hz, 3H), 1.64 (m, 1H), 2.05 (m, 1H), 2.27 (br d, $J$ = 10.5 Hz, 1H), 2.40−2.84 (m, 4H), 3.18 (br d, $J$ = 13.5 Hz, 1H), 3.29 (s, 3H), 4.79 (s, 1H), 5.11 (d, $J$ = 10.2 Hz, 1H), 5.18 (d, $J$ = 17.0 Hz, 1H), 5.70−5.82 (m, 1H), 6.42 (d, $J$ = 7.6 Hz, 1H), 6.65 (d, $J$ = 7.7 Hz, 1H), 6.67 (s, 1H), 7.04−7.83 (m, 9H), 9.32 (s, 1H). Mass spectrum (CI − $CH_4$) *m*/*e*: 538 (M + 1, 82%), 384 (13%), 153 (100%). $[\alpha]^{20}_D$ −1.8° (*c* 1.0, ethanol). The free amine was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 3.7 followed by precipitation with diethyl ether from dichloromethane to give the monohydrochloride salt as a hygroscopic beige powder. Anal. ($C_{31}H_{34}N_3O_2F_3$·HCl·0.75$H_2O$) C, H, N, Cl.

**(+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-(4-methoxyphenyl)-*N*-methylbenzamide (28).** 4-Methoxy-*N*-methylaniline was coupled with 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotected, and purified by the methods described to give 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-(4-methoxyphenyl)-*N*-methylbenzamide as a light-purple powder. NMR (200 MHz, DMSO-$d_6$): $\delta$ 0.89 (d, $J$ = 6.0 Hz, 3H), 0.96 (d, $J$ = 6.1 Hz, 3H), 1.66 (dd, $J_1$ = 6.5 Hz, $J_2$ = 11.0 Hz, 1H), 2.00 (dd, $J_1$ = 7.1 Hz, $J_2$ = 10.4 Hz, 1H), 2.27 (br d, $J$ = 11.4 Hz, 1H), 2.36−2.54 (m, 2H), 2.64 (d, $J$ = 11.6 Hz, 1H), 2.82 (dd, $J_1$ = 6.9 Hz, $J_2$ = 13.6 Hz, 1H), 3.18 (dd, $J_1$ = 5.4 Hz, $J_2$ = 12.8 Hz, 1H), 3.30 (s, 3H), 3.68 (s, 3H), 4.76 (s, 1H), 5.11 (d, $J$ = 10.6 Hz, 1H), 5.18 (d, $J$ = 17.1 Hz, 1H), 5.66−5.88 (m, 1H), 6.42 (d, $J$ = 7.1 Hz, 1H), 6.58 (s, 1H), 6.63 (d, $J$ = 7.4 Hz, 1H), 6.78 (d, $J$ = 8.8 Hz, 2H), 6.97−7.24 (m, 7H), 9.34 (s, 1H). Mass spectrum (CI − $CH_4$) *m*/*e*: 500 (M + 1, 79%), 346 (49%), 153 (100%). $[\alpha]^{20}_D$ +9.6° (*c* 1.0, absolute ethanol). The free amine was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 4.0 followed by precipitation with diethyl ether from dichloromethane to give the monohydrochloride salt as a hygroscopic light-purple powder. Anal. ($C_{31}H_{37}N_3O_3$·HCl·$H_2O$) C, H, N, Cl.

**(+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-methyl-*N*-(4-nitrophenyl)benzamide (29).** *N*-Methyl-4-nitroaniline was coupled with 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-

butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotected, and purified by the methods described to give 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-methyl-*N*-(4-nitrophenyl)benzamide as a light-yellow powder. NMR (200 MHz, DMSO-$d_6$): $\delta$ 0.88 (d, $J$ = 6.0 Hz, 3H), 0.94 (d, $J$ = 6.0 Hz, 3H), 1.66 (dd, $J_1$ = 7.3 Hz, $J_2$ = 11.1 Hz, 1H), 1.98 (dd, $J_1$ = 7.7 Hz, $J_2$ = 10.9 Hz, 1H), 2.27 (br d, $J$ = 11.5 Hz, 1H), 2.36−2.56 (m, 2H), 2.65 (dd, $J_1$ = 2.5 Hz, $J_2$ = 8.4 Hz, 1H), 2.82 (dd, $J_1$ = 7.4 Hz, $J_2$ = 14.5 Hz, 1H), 3.17 (dd, $J_1$ = 5.5 Hz, $J_2$ = 14.1 Hz, 1H), 3.45 (s, 3H), 4.79 (s, 1H), 5.12 (d, $J$ = 8.8 Hz, 1H), 5.17 (d, $J$ = 15.2 Hz, 1H), 5.67−5.89 (m, 1H), 6.41 (d, $J$ = 7.4 Hz, 1H), 6.50 (s, 1H), 6.62 (d, $J$ = 6.5 Hz, 1H), 7.03 (t, $J$ = 7.6 Hz, 1H), 7.09−7.42 (m, 6H), 8.11 (d, $J$ = 9.0 Hz, 2H), 9.32 (s, 1H). MS (CI − $CH_4$) *m/e*: 515 (M + 1, 76%), 361 (26%), 153 (100%). $[\alpha]^{20}_D$ +5.9° (*c* 1.3, absolute ethanol). The free amine was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 4.0 followed by precipitation with diethyl ether from dichloromethane to give the monohydrochloride salt as a hygroscopic light-yellow powder. Anal. ($C_{30}H_{34}N_4O_4$·HCl·0.5$H_2O$) C, H, N, Cl.

**(+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-ethyl-*N*-(4-fluorophenyl)benzamide (30).** 4-Fluoro-*N*-ethylaniline [NMR (200 MHz, DMSO-$d_6$): $\delta$ 1.25 (t, $J$ = 7.1 Hz, 3H), 3.12 (q, $J$ = 7.1 Hz, 2H), 3.24 (br s, 1H), 6.57 (dd, $J_1$ = 4.5 Hz, $J_2$ = 9.0 Hz, 2H), 6.90 (t, $J$ = 8.9 Hz, 2H)] was coupled with 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyloxy)benzyl)-benzoyl chloride, deprotected, and purified by the methods described to give (+)-3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-ethyl-*N*-(4-fluorophenyl)-benzamide as an off-white powder. NMR (200 MHz, DMSO-$d_6$): $\delta$ 0.91 (d, $J$ = 6.1 Hz, 3H), 0.98 (d, $J$ = 6.0 Hz, 3H), 1.08 (t, $J$ = 7.0 Hz, 3H), 1.71 (dd, $J_1$ = 7.0 Hz, $J_2$ = 11.3 Hz, 1H), 2.05 (dd, $J_1$ = 7.2 Hz, $J_2$ = 10.8 Hz, 1H), 2.31 (d, $J$ = 11.4 Hz, 1H), 2.36−2.57 (m, 2H), 2.69 (dd, $J_1$ = 2.2 Hz, $J_2$ = 10.7 Hz, 1H), 2.85 (dd, $J_1$ = 7.0 Hz, $J_2$ = 13.9 Hz, 1H), 3.18 (dd, $J_1$ = 5.3 Hz, $J_2$ = 13.9 Hz, 1H), 3.84 (q, $J$ = 7.0 Hz, 2H), 4.78 (s, 1H), 5.11 (d, $J$ = 10.0 Hz, 1H), 5.18 (d, $J$ = 16.4 Hz, 1H), 5.65−5.88 (m, 1H), 6.46 (d, $J$ = 7.4 Hz, 1H), 6.58 (s, 1H), 6.65 (d, $J$ = 8.1 Hz, 1H), 7.01−7.27 (m, 9H), 9.33 (s, 1H). Mass spectrum (CI − $CH_4$) *m/e*: 502 (M + 1, 90%), 348 (15%), 153 (100%). $[\alpha]^{20}_D$ + 6.30° (*c* 1.1, absolute ethanol). The free amine (0.313 g) was dissolved in ethanol and titrated with ethanolic hydrogen chloride to pH 3.95 followed by precipitation with diethyl ether from dichloromethane to give 0.263 g of the monohydrochloride salt as a hygroscopic white powder. Anal. ($C_{31}H_{36}N_3O_2F$·HCl·$H_2O$) C, H, N, Cl.

**(+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-(4-fluorophenyl)-*N*-propylbenzamide (31).** 4-Fluoro-*N*-propylaniline was coupled with 3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyloxy)benzyl)benzoyl chloride, deprotected, and purified by the methods described to give (+)-3-((α-*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-(4-fluorophenyl)-*N*-propylbenzamide as a light-beige solid. NMR (200 MHz, DMSO-$d_6$): $\delta$ 0.87 (t, $J$ = 7.4 Hz, 3H), 0.92 (d, $J$ = 6.0 Hz, 3H), 0.99 (d, $J$ = 6.1 Hz, 3H), 1.50 (m, 2H), 1.69 (dd, $J_1$ = 7.3 Hz, $J_2$ = 10.7 Hz, 1H), 2.04 (dd, $J_1$ = 6.6 Hz, $J_2$ = 10.3 Hz, 1H), 2.31 (d, $J$ = 10.2 Hz, 1H), 2.39−2.53 (m, 2H), 2.69 (br d, $J$ = 11.5 Hz, 1H), 2.89 (dd, $J_1$ = 7.1 Hz, $J_2$ = 13.9 Hz, 1H), 3.18 (dd, $J_1$ = 5.0 Hz, $J_2$ = 14.3 Hz, 1H), 3.77 (t, $J$ = 7.2 Hz, 2H), 4.78 (s, 1H), 5.12 (d, $J$ = 10.1 Hz, 1H), 5.19 (d, $J$ = 16.2 Hz, 1H), 5.71−5.84 (m, 1H), 6.47 (d, $J$ = 7.3 Hz, 1H), 6.59 (s, 1H), 6.65 (d, $J$ = 8.0 Hz, 1H), 7.03−7.28 (m, 9H), 9.35 (s, 1H). $[\alpha]^{20}_D$ +5.6° (*c* 1.1, absolute ethanol). Anal. ($C_{32}H_{38}FN_3O_2$·HCl·0.75$H_2O$) C, H, N, Cl.

**(+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-(3-fluorophenyl)-*N*-methylbenzylamine (32).** Allane was generated in situ by slow addition of an $H_2SO_4$ solution (concentrated $H_2SO_4$ diluted to 1 M in THF, 386 $\mu$L) to 1 M $LiAlH_4$ in THF (771 $\mu$L) at 0 °C, under nitrogen. After 1 h, 125 mg (0.257 mmol) of (+)-3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-(3-fluorophenyl)-*N*-methylbenzamide (**24**) in THF was added. After 1 h, with slow warming to room temperature, the reaction was quenched with 155 $\mu$L of 33% $H_2O$ in THF (CAUTION: gas evolution), then with 77 $\mu$L of 30% aqueous NaOH, and finally with 77 $\mu$L of $H_2O$. After 1 h of stirring, all solids were filtered off. After the mixture was dried with $Na_2SO_4$, all volatiles were removed under vacuum to give 111 mg of (+)-3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*-(3-fluorophenyl)-*N*-methylbenzylamine as a fluffy white solid. $[\alpha]^{20}_D$ +25.0° (*c* 1.4, ethanol). The free amine (0.085 g) was dissolved in ethanol and treated with ethanolic HCl, followed by precipitation with diethyl ether from dichloromethane to give 0.059 g of the monohydrochloride salt as a hygroscopic off-white powder. Mass spectrum (CI − $CH_4$) *m/e*: 474 (M + 1, 100). Anal. ($C_{30}H_{36}N_3O_2F$·HCl·1.25$H_2O$) C, H, N, Cl.

**(+)-3-((α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*,*N*-diethylbenzamide (4).** By use of diethylamine and the methods described above, (+)-3-((α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*,*N*-diethylbenzamide was prepared and isolated as an off-white solid. $[\alpha]^{20}_D$ +20° (*c* 2, methanol). NMR (400 MHz, DMSO-$d_6$): $\delta$ 0.91 (d, $J$ = 6.2 Hz, 3H), 0.99 (br s, 3H), 1.05 (d, $J$ = 6.2 Hz, 3H), 1.09 (br s, 3H), 1.84 (dd, $J_1$ = 7.3 Hz, $J_2$ = 10.9 Hz, 1H), 2.06 (dd, $J_1$ = 7.3 Hz, $J_2$ = 10.9 Hz, 1H), 2.48 (m, 1H), 2.51 (dd, $J_1$ = 2.7 Hz, $J_2$ = 10.9 Hz, 1H), 2.58 (br s, 1H), 2.70 (dd, $J_1$ = 2.7 Hz, $J_2$ = 10.9 Hz, 1H), 2.81 (dd, $J_1$ = 7.0 Hz, $J_2$ = 13.9 Hz, 1H), 3.12 (br s, 2H), 3.15 (dd, $J_1$ = 5.1 Hz, $J_2$ = 13.9 Hz, 1H), 3.38 (br s, 2H), 4.97 (br s, 1H), 5.07 (d, $J$ = 10.2 Hz, 1H), 5.14 (d, $J$ = 16.9 Hz, 1H), 5.70−5.82 (m, 1H), 6.64 (dd, $J_1$ = 2.1 Hz, $J_2$ = 8.0 Hz, 1H), 6.65 (s, 1H), 6.68 (d, $J$ = 7.7 Hz, 1H), 7.11 (t, $J$ = 8.0 Hz, 1H), 7.14 (d, $J$ = 7.6 Hz, 1H), 7.30 (s, 1H), 7.33 (t, $J$ = 7.6 Hz, 1H), 7.39 (d, $J$ = 8.0 Hz, 1H), 9.31 (s, 1H). Mass spectrum (CI − $CH_4$) *m/e*: 436 (M + 1, 53%). The free amine was dissolved in absolute ethanol and titrated with ethanolic hydrogen chloride (7 and 1 M) to a pH of 3.95. The solvent was removed, and the residue was redissolved in dichloromethane. Diethyl ether was added with vigorous stirring to precipitate a gummy product that solidified upon stirring overnight under nitrogen. The product was collected by filtration and dried under vacuum at 55 °C to give the monohydrochloride salt. Anal. ($C_{27}H_{37}N_3O_2$·HCl·$H_2O$) C, H, N, Cl.

**Supporting Information Available:** Crystallographic data, atomic coordinates and isotropic displacement parameters, bond lengths and bond angles, anisotropic displacement parameters, and hydrogen coordinates of **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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