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Probes for Narcotic Receptor Mediated Phenomena. 41. Unusual Inverse μ-Agonists and Potent μ-Opioid Antagonists by Modification of the N-Substituent in Enantiomeric 5-(3-Hydroxyphenyl)morphans

Kejun Cheng,[†] Yong Sok Lee,[‡] Richard B. Rothman,[§] Christina M. Dersch,[§] Ross W. Bittman,[§] Arthur E. Jacobson,[†] and Kenner C. Rice*,[†]

[†]*Drug Design and Synthesis Section, Chemical Biology Research Branch, National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Department of Health and Human Services, 5625 Fishers Lane, Room 4N03, Bethesda, Maryland 20892-9415, United States,* [‡]*Center for Molecular Modeling, Division of Computational Bioscience, CIT, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20892, United States, and* [§]*Clinical Psychopharmacology Section, Chemical Biology Research Branch, National Institute on Drug Abuse, Addiction Research Center, National Institutes of Health, Department of Health and Human Services, Baltimore, Maryland 21224, United States*

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Conformational restraint in the N-substituent of enantiomeric 5-(3-hydroxyphenyl)morphans was conferred by the addition of a cyclopropane ring or a double bond. All of the possible enantiomers and isomers of the N-substituted compounds were synthesized. Opioid receptor binding assays indicated that some of them had about 20-fold higher μ-affinity than the compound with an *N*-phenylpropyl substituent (K_i = 2−450 nM for the examined compounds with various N-substituents). Most of the compounds acted unusually as inverse agonists in the [^{35}S]GTP-γ-S functional binding assay using nondependent cells that stably express the cloned human μ-opioid receptor. Two of the N-substituted compounds with a cyclopropane ring were very potent μ-opioid antagonists ((+)-**29**, K_e = 0.17 and (−)-**30**, K_e = 0.3) in the [^{35}S]GTP-γ-S functional binding assay. By comparison of the geometry-optimized structures of the newly synthesized compounds, an attempt was made to rationalize their μ-opioid receptor affinity in terms of the spatial position of N-substituents.

Introduction

Opioid enantiomers are known to have pharmacological properties dissimilar in affinity and efficacy to those of the parent racemic mixture, and the N-substituents in these opioids also play a major role in affinity and efficacy. The 1*R*,5*S*-*N*-phenylpropyl- and the 1*S*,5*R*-*N*-phenylpropyl-5-(3-hydroxyphenyl)morphans (Figure 1A and Figure 1B, respectively) were previously found[1,2] to have moderate affinity for the μ-opioid receptor (14 and 27 nM, respectively) and were found to be moderately potent antagonists in the [^{35}S]-GTP-γ-S assay (K_e = 7.5 and 5.5 nM, respectively). A *trans*-oriented (racemic) *N*-phenylcyclopropylmethyl (NPCM[a]) substituent in the phenylpiperidine series (a rotationally restricted N-substituent of LY272922, Figure 1C) has been found to have good affinity (K_i = 1.75 nM) for the μ-opioid receptor, as did a *trans* (*E*)-oriented *N*-phenylpropenyl moiety (Figure 1D).[3] The latter was found to be a potent and selective μ-antagonist with good δ- and κ-antagonist activity as well. Hashimoto et al.[2] found that an *N*-phenethyl substituted 5-(3-hydroxyphenyl)morphan (Figure 1E) had higher μ-affinity than a comparable phenylmorphan with an *N*-phenylpropyl side chain (K_i = 14 nM vs 42 nM, respectively, Figure 1A) in the 1*R*,5*S* enantiomeric series. However the *N*-phenylpropyl-substituted compound was more potent as a pure μ-antagonist (K_e = 3.2 nM vs 7.5 nM for the *N*-phenethyl compound in the [^{35}S]GTP-γ-S binding assay).[2] The *N*-phenylpropyl substituents in the compounds of Hashimoto et al.[2] have unrestricted rotation. We were interested in determining whether conformational restraint of the *N*-phenylpropyl substituent conferred by the addition of a cyclopropane ring or a double-bond effected the receptor affinity and efficacy of enantiomeric 5-(3-hydroxyphenyl)morphans. We now report the synthesis of a series of enantiomeric *N*-arylcyclopropyl and *N*-arylalkenyl substituted 5-(3-hydroxyphenyl)morphans. We

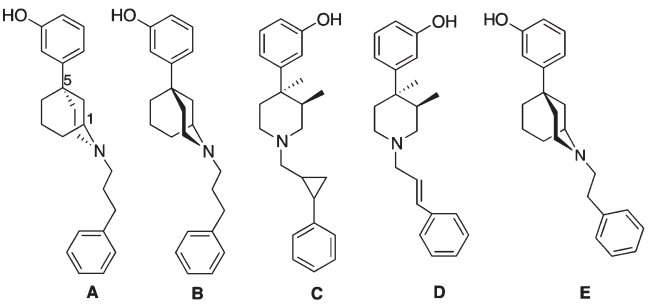

Figure 1. Structures of N-substituted 5-(3-hydroxyphenyl)morphans (A, B, E) and 3-(3*R*,4*R*-dimethylpiperidin-4-yl)phenols (C, D).

*To whom correspondence should be addressed. Phone: 301-496-1856. Fax: 301-402-0589. E-mail: kr21f@nih.gov.

[a] Abbreviations: NPCM, *N*-phenylcyclopropylmethyl; ^{1}H NMR, proton nuclear magnetic resonance; ^{13}C NMR, carbon nuclear magnetic resonance; TLC, thin-layer chromatography; ESI, electrospray ionization; HRMS (TOF MS ES$^+$), high resolution mass spectrometry (time-of-flight mass spectra from electrospray positive ionization).

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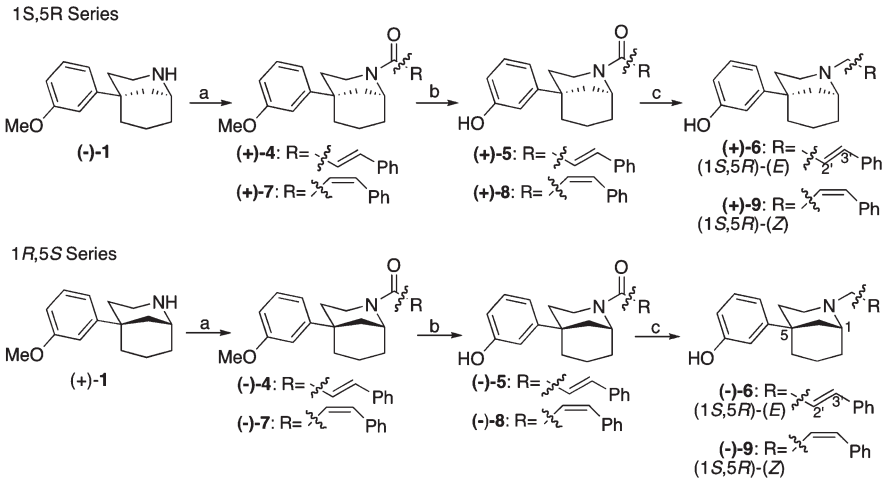
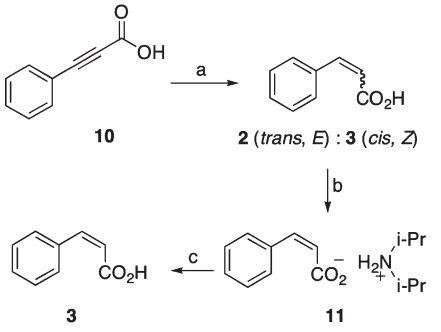
Scheme 1. Synthesis of the 2-(*E*)-Cinnamyl and 2-(*Z*)-3-Phenylallyl) Isomers of the Enantiomers of 3-(2-Azabicyclo[3.1.1]nonan-5-yl)phenol ((+)-**6**, (−)-**6**, (+)-**9**, and (−)-**9**)[a]



[a] Reagents and conditions: (a) compound **2** or **3** (Scheme 2), EDCI/CH_2Cl_2, room temp, 75−81%; (b) 48% HBr/HOAc, reflux, 0.5−1 h, 65−72%; (c) Red-Al, THF, room temp, 1.5 h, 58−68%.

Scheme 2. Synthesis of (*Z*)-3-Phenylacrylic Acid (**3**)[a]



[a] Reagents and conditions: (a) Pd/$CaCO_3$, H_2 (1 equiv at 1 atm), pyridine, room temp; (b) diisopropylamine/Et_2O, recrystallization; (c) HCl/Et_2O; 36% yield in three steps.

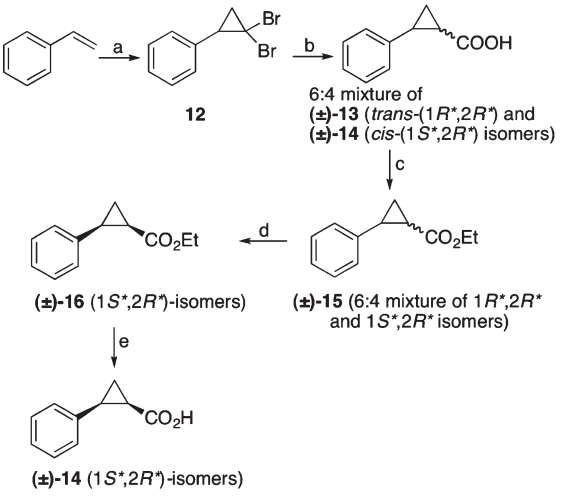
have examined the affinity all of the possible enantiomers and isomers in opioid receptor binding assays and their efficacy in the [^{35}S]GTP-γ-S assay and compared the geometry-optimized structures of the newly synthesized compounds.

Results and Discussion

Chemistry. The enantiomeric starting materials, 1*S*,5*R*-(−)-5-(3-methoxyphenyl)-2-azabicyclo[3.1.1]nonane ((−)-**1**) and 1*R*,5*S*-(+)-5-(3-methoxyphenyl)-2-azabicyclo-[3.1.1]-nonane ((+)-**1**) were prepared as previously described.[4] Reaction of (−)- and (+)-**1** with commercially available cinnamic acid (**2**) and the synthesized (*Z*)-3-phenylacrylic acid (**3**),[5−7] using EDCI in CH_2Cl_2 at room temperature, gave pairs of enantiomeric methoxyphenylamides (+)-**4** (1*S*,5*R*) and (−)-**4** (1*R*,5*S*), and (+)-**7** (1*S*,5*R*) and (−)-**7** (1*R*,5*S*), respectively, in 75−81% yield (Scheme 1). The (*Z*)-3-phenylacrylic acid (**4**) was obtained through Pd/$CaCO_3$ reduction of commercially available 3-phenylpropiolic acid (**10**, Scheme 2).[8] The reduction gave a mixture of both the desired **3** (*Z* isomer) and cinnamic acid **2** (the *E* isomer). Recrystallization of the diisopropylamine salt (**11**) of the isomers gave pure **3** in 36% overall yield.

Conversion of the enantiomeric amides (+)-**4**, (−)-**4**, (+)-**7**, and (−)-**7** to their phenolic relatives (+)-**5**, (−)-**5**, (+)-**8**, and (−)-**8** was achieved in 65−72% yield by refluxing in 48% HBr and acetic acid (Scheme 1). Reduction of the four phenolic amide isomers to the desired enantiomeric amines (+)-**6**, (−)-**6**, (+)-**9**, and (−)-**9**, in 58−68% yield, was carried out using Red/Al in THF (Scheme 1).

Scheme 3. Synthesis of Racemic *cis*-2-Phenylcyclopropanecarboxylic Acid (**14**)[a]



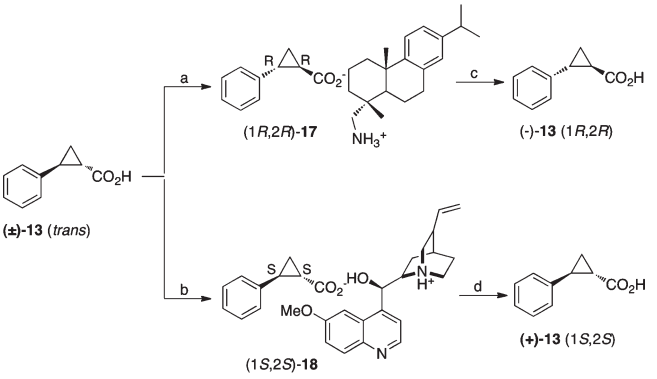
[a] Reagents and conditions: (a) $CHBr_3$, benzyltriethylammonium chloride (TEBA), 50% NaOH aqueous, room temp, 20 h, 78%; (b) synthesis gas (CO/H_2 3:1), toluene, 5 N KOH, $CoCl_2 \cdot 6H_2O$, KCN, $Ni(CN)_2 \cdot 4H_2O$, PEG-400, 90 °C, 3 days, 43%; (c) EtOH, $TsOH \cdot H_2O$, toluene, 115 °C, 8 h, 68%; (d) NaOH, EtOH, H_2O, reflux, 50% based on *cis* isomer; (e) NaOH, EtOH, H_2O, reflux, 70%.

Introduction of the N-substituent bearing a cyclopropyl moiety required the preparation of the phenylcyclopropanecarboxylic acid enantiomers (−)-**13**, and (+)-**13** and their diastereomeric relatives (−)-**14** and (+)-**14**. Although both of the racemic starting materials (±)-**13** and (±)-**14** could be obtained as shown in Scheme 3, 2-phenylcyclopropanecarboxylic acid (±)-**13** was commercially available. The racemic *cis* isomer ((±)-**14**, (1*S**,2*R**)-2-phenylcyclopropanecarboxylic acid) was synthesized from styrene in five steps (Scheme 3) and resolved. (2,2-Dibromocyclopropyl)benzene (**12**, Scheme 3) was obtained in 78% yield using the procedure of Shim et al.[9] Catalytic reductive carbonylation of **12**,

using the procedure of Grushin and Alper,[10] gave a 6:4 mixture of the racemic *cis* and *trans* isomers of 2-phenylcyclopropane carboxylic acid ((±)-**13** and (±)-**14**). Conversion of (±)-**13** and (±)-**14** to the racemic mixture of *trans* and *cis* esters ((±)-**15**) was carried out using the procedure of Kaiser et al.[7] Separation of the racemic *cis* isomer (±)-**16** from (±)-**15** was achieved under reflux conditions using 1 equiv of NaOH in EtOH−H_2O. The *cis* esters were more stable to the alkaline conditions and required 2 equiv of NaOH for hydrolysis to the racemic acid (±)-**14**, with concentrated HCl used for neutralization.

The commercially available racemic *trans* isomer (±)-**13** was resolved[6,11] as shown in Scheme 4. The 1′*R*,2′*R* and 1′*S*,2′*S* mixture of enantiomers (±)-**13** was separated using (+)-dehydroabietylamine. The 1′*R*,2′*R* salt (**17**) that formed was purified by recrystallization from aqueous methanol. Base hydrolysis of the salt **17** gave the desired (−)-**13** (*trans*-1′*R*,2′*R*, 98% ee via chiral HPLC). The residual material from the 1*R*,2*R* salt formation with (+)-dehydroabietylamine was recovered, and the base was reacted with 1 equiv of quinine in EtOAc. The 1′*S*,2′*S* salt (**18**) that formed was recrystallized from EtOAc; base hydrolysis provided (+)-**13** (*trans*-1′*S*,2′*S*, 98% ee via chiral HPLC).

Scheme 4. Optical Resolution of of *trans*-2-Phenylcyclopropanecarboxylic Acid ((−)-**13** (1*R*,2*R*) and (+)-**13** (1*S*,2*S*))[a]



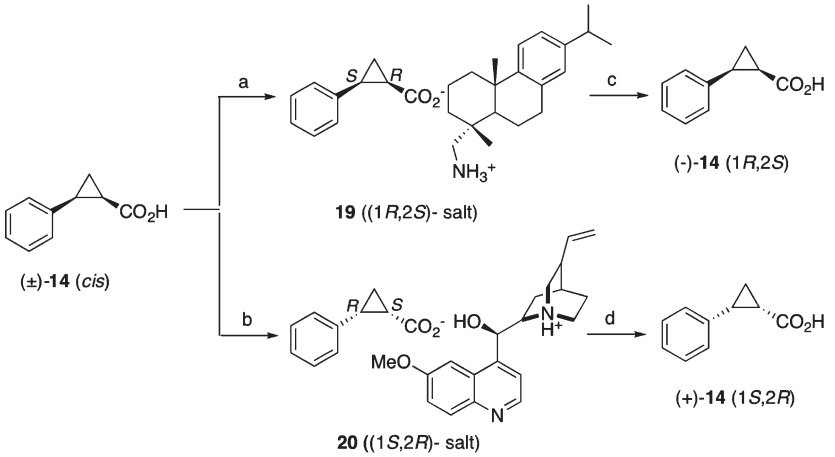
[a] Reagents and conditions: (a) 1.0 equiv of dehydroabietylamine, MeOH, H_2O, recryst 5× from 90% aqueous MeOH, 25%; (b) 1.0 equiv of quinine, EtOAc, recryst 5× from EtOAc, 34%; (c) (i) saturated $NaHCO_3$/Et_2O; (ii) conc HCl/Et_2O, 98%, >98% ee via chiral HPLC; (d) 2 N HCl/Et_2O, 98%, >98% ee via chiral HPLC.

Optical resolution of (±)-**14** (*cis* racemate) was carried out similarly (Scheme 5)[6,11] to give (−)-**14** (*cis*-1′*R*,2′*S*) from the (+)-dehydroabietylamine salt **19** and to give (+)-**14** (*cis*-1′*S*,2′*R*) from the salt with quinine (**20**). Both enantiomers were obtained in 98% ee via chiral HPLC.

With the pure (−)-**13**, (+)-**13**, (−)-**14**, and (+)-**14** enantiomeric acids in hand, the corresponding amides ((−)- and (+)-**21** through **24**) could be prepared as shown in Scheme 6 from the known[4] enantiomeric amines (1*S*,5*R*)- and ((1*R*,5*S*)-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1] nonane ((−)-**1** and (+)-**1**). Reduction of the various amides ((−)- and (+)-**21** through **24**) to the tertiary amines ((−)- and (+)-**25** through **28**) followed by cleavage of the aromatic ether to the corresponding phenol resulted in the formation of four enantiomers in the 1*S*,5*R* series (Scheme 6 top, (−)- and (+)-**29** through **32**) and another set of four amines in the 1*R*,5*S* series (Scheme 6 bottom, (−)- and (+)-**29** through **32**).

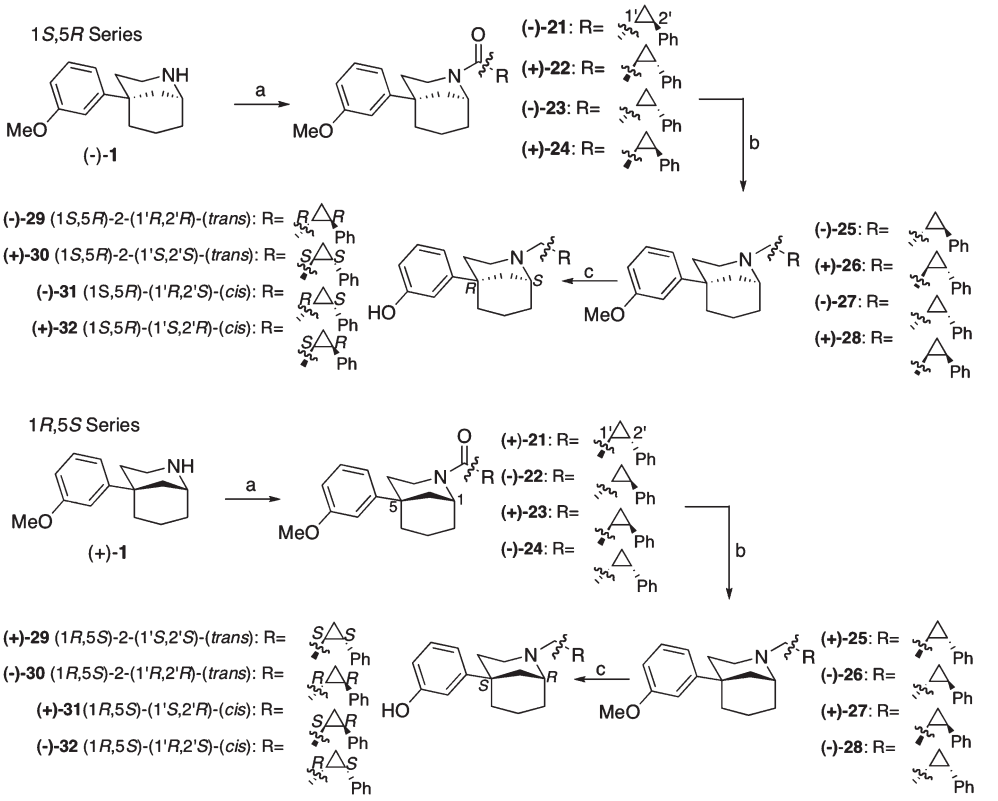
Opioid Receptor Binding and Efficacy Studies. In the series of the *cis*- and *trans*-NPCM substituted compounds ((−)- and (+)-**29** through **32**, Scheme 6), both of the *trans* compounds (+)-**29** and (−)-**30** had high affinity for the μ-receptor (K_i = 3 and 4 nM, respectively, Table 1). All of the compounds in Table 1 had, at most, moderate affinity for δ or κ receptors, and their selectivity for the μ-receptor ranged from 4- to 70-fold. The NPCM substituted compounds were also found to be the most potent μ-antagonists in the [^{35}S]GTP-γ-S binding assays (K_e = 0.17 and 0.31 nM, respectively, Table 2). Figure 2 is an overlay of four NPCM derivatives in the 1*R*,5*S*-phenylmorphan series ((+)-**29**, (−)-**30**, (+)-**31**, and (−)-**32**) obtained by superposing the carbon and nitrogen atoms of the phenylmorphans to those of the geometry optimized naltrexone starting from its X-ray structure.[12] This overlay depicts a spatial position of the NPCM moiety among the four compounds while fixing their essentially invariant phenylmorphan backbone in space with respect to that of naltrexone. Specifically, the extended *trans* isomer (+)-**29** (Figure 2, K_i = 3 nM) is epimeric with respect to the C2 atom of the NCPM of the compact *cis* form (+)-**31** (K_i = 459 nM). The cyclopropyl group of both compounds (+)-**29** and (+)-**31** coincides well with that of naltrexone, suggesting that the ~135-fold lower K_i of (+)-**31** arises from a

Scheme 5. Optical Resolution of *cis*-2-Phenylcyclopropanecarboxylic Acid ((−)-**14** (1*R*,2*S*) and (+)-**14** (1*S*,2*R*))[a]



[a] Reagents and conditions: (a) 1.0 equiv of dehydroabietylamine, MeOH, H_2O, recryst 4× from 90% aqueous MeOH, 16%; (b) 1.0 equiv of quinine, EtOAc, recryst 6× from EtOAc, 9%; (c) (i) saturated $NaHCO_3$/Et_2O; (ii) conc HCl/Et_2O, 98%, >98% ee via chiral HPLC; (d) 2 N HCl/Et_2O, 98%, >98% ee via chiral HPLC.

Scheme 6. Synthesis of the *N*-(2-Phenylcyclopropyl)methyl Enantiomers of (+)- and (−)-2-Azabicyclo[3.3.1]nonan-5-yl)phenol ((+)- and (−)-**29** through **32**)[a]



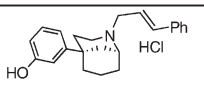
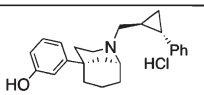
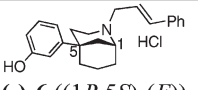
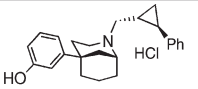
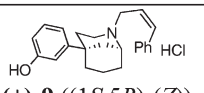
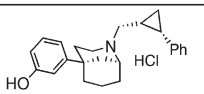
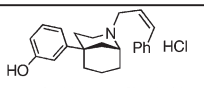
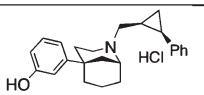
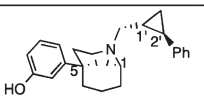
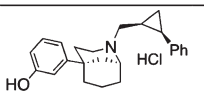
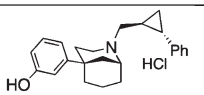
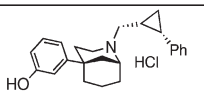
[a] Reagents and conditions: (a) EDCI, CH_2Cl_2, 1.1 equiv of (−)-**13** or (+)-**13** or (−)-**14** or (+)-**14**, room temp, 94−98%; (b) Red-Al, THF, room temp, 1.5 h, 92−96%; (c) 48% HBr/HOAc, reflux, 0.5−1 h, 55−65%.

steric clash between its phenyl group and amino acid residues at the μ-receptor site. Similarly, (−)-**30** (K_i = 4 nM) and (−)-**32** (K_i = 11 nM) are epimeric with respect to the C2 atom of the cyclopropane, while their NPCM groups are enantiomeric to (+)-**29** and (+)-**31**, respectively (Figure 2). The cyclopropyl groups of both (−)-**30** and (−)-**32** do not overlap with that of naltrexone. These comparisons of the spatial NCPM moieties with their binding affinity suggest that the NCPM's 1*S*,2*R* stereochemistry in (+)-**31** needs to be avoided in the design of a higher afffinity ligand. Between the two *trans* stereoisomers ((+)-**29** and (−)-**30**) in the 1*R*,5*S*-phenylmorphan series, little stereospecificity was observed in terms of K_i whereas about a 42-fold difference is seen between the *cis* stereoisomers ((+)-**31**, and (−)-**32**). Also, it was observed that when the stereochemistry of the NPCM side chain is invariant, the (1*R*,5*S*) series tends to have higher affinity at the μ-receptor site, as seen in (−)-**30** (K_i = 4 nM) vs (−)-**29** (K_i = 47 nM) and (−)-**32** (K_i = 11 nM) vs (−)-**31** (K_i = 265 nM) as well as in (+)-**29** (K_i = 3 nM) vs (+)-**30** (K_i = 16 nM). This favorable topology of (1*R*,5*S*) is, however, lost in ((+)-**31** (K_i = 459 nM) vs ((+)-**32** (1*S*,5*R*) (K_i = 76 nM) likely because of the steric repulsion experienced by the phenyl group of (+)-**31**. One of the compounds with moderate affinity for the μ-opioid receptor (+)-**30** (K_i = 16 nM) was found to be equipotent with naloxone as a μ-antagonist, and its enantiomer (−)-**30** had 4-fold higher μ-affinity and was about equipotent with naltrexone as an antagonist in the [^{35}S]GTP-γ-S assay. The most potent NCPM antagonist (+)-**29** was more than 13 times more potent than naloxone. None of the NPCM-substituted compounds had good affinity for either the δ- or κ-opioid receptors (K_i > 70 nM at δ and κ). As shown in Figure 5, all of the NPCM substituted compounds except (−)-**32** were found to have unusual inverse agonist activity in that they showed considerably more inverse agonist activity in non-dependent cells than has been previously found.[13]

In the *N*-phenylpropenyl series (Scheme 3), we have found that the *E* (*trans*) enantiomers of the *N*-phenylpropenyl compounds (+)-**6** and (−)-**6** had higher affinity for the μ-receptor (K_i = 2 and 6 nM, respectively) than the comparable *Z* (*cis*) enantiomers (+)-**9** and (−)-**9** (K_i = 14 and 26 nM, respectively) and that all of them had equivalent or better affinity for μ-receptors than a comparable *N*-phenylpropyl compound. The higher affinity of the *E* (*trans*) enantiomers over the corresponding *Z*-isomers may arise from an improved overlap of the extended *N*-phenylpropenyl group in the *E*-enantiomer with amino acid residues at the active site. Figure 3, obtained by overlaying (−)-**6** and (−)-**9** onto the geometry optimized naloxone,[14] illustrates such an extended and compact *N*-phenylpropenyl group, which spans well beyond the space circumscribed by an allyl moiety of naloxone.

The two *N*-phenylpropenyl compounds in Figure 3 along with the naloxone were further superimposed onto the naltrexone in Figure 2, and this superposition (Figure 4) depicts the spatial position of both the allyl and cyclopropyl moieties as well as phenyl substituents. It illustrates that the double bond in the allyl moiety of naloxone, (−)-**6**, and (−)-**9** literally bisects the cyclopropane ring in naltrexone and in (+)-**29** and (+)-**31**, suggesting that both the double bond and the cyclopropane moiety have a similar effect in binding affinity at the μ receptor via hydrophobic interactions.

Table 1. ^{125}I-IOXY Opioid Receptor Binding Data[a] (K_i, nM)

	μ	δ	κ		μ	δ	κ
 **(+)-6** ((1*S*,5*R*)-(*E*))	2 ± 0.13	138 ± 5	125 ± 3	 **(+)-30** ((1*S*,5*R*)-2-(1'*S*,2'*S*)-(*trans*))	16 ± 1	183 ± 7	323 ± 15
 **(-)-6** ((1*R*,5*S*)-(*E*))	6 ± 0.39	152 ± 5	225 ± 7	 **(-)-30** ((1*R*,5*S*)-2-(1'*R*,2'*R*)- (*trans*))	4 ± 0.27	200 ± 10	210 ± 13
 **(+)-9** ((1*S*,5*R*)-(*Z*))	26 ± 2	454 ± 25	123 ± 4	 **(-)-31** ((1*S*,5*R*)-2-(1'*R*,2'*S*)-(*cis*))	265 ± 17	610 ± 25	153 ± 7
 **(-)-9** ((1*R*,5*S*)-(*Z*))	14 ± 0.70	359 ± 18	367 ± 18	 **(+)-31** ((1*R*,5*S*)-2-(1'*S*,2'*R*)-(*cis*))	459 ± 14	1980 ± 54	475 ± 33
 **(-)-29** ((1*S*,5*R*)-2-(1'*R*,2'*R*)-(*trans*))	47 ± 3	800 ± 29	390 ± 16	 **(+)-32** ((1*S*,5*R*)-2-(1'*S*,2'*R*)-(*cis*))	76 ± 0.3	547 ± 23	174 ± 12
 **(+)-29** ((1*R*,5*S*)-2-(1'*S*,2'*S*)-(*trans*))	3 ± 0.26	165 ± 7	72 ± 4	 **(-)-32** ((1*R*,5*S*)-2-(1'*R*,2'*S*)-(*cis*))	11 ± 0.9	196 ± 6	322 ± 22

[a] Assays were conducted using ^{125}I-IOXY to label the μ-, δ-, or κ-opioid receptors stably expressed in CHO cells.[17] All results are for $n = 3$ (±SD). For comparison, the K_i of morphine at μ is 2.55 ± 0.01 nM; the K_i of naloxone at μ is 0.98 ± 0.05 nM, at δ is 51 ± 3 nM, and at κ is 3 ± 0.19 nM. Supporting Information (http://pubs.acs.org) contains a complete table of standards for these assays.

In addition, Figure 4 shows the extensive space spanned by the phenyl groups of the NCPM and the *N*-phenylpropenyl compounds. Despite the wide spatial distribution of the conformationally restrained phenyl groups, the K_i of (−)**-6** and (−)**-9** as well as (+)**-29**, (−)**-30**, and (−)**-32** are all in the range of 3−14 nM. This, in turn, suggests that a rather wide binding pocket exists in the μ-receptor binding site that can encompass these phenyl substituents.

All four of the *N*-phenylpropenyl compounds were μ-opioid antagonists, and (+)**-6** was the most potent (K_e = 0.58). Thus, the *N*-phenylpropenyl compounds, like the *N*-phenylpropyl compound of Hashimoto at al.,[2] were opioid antagonists. However, unlike the compound of Hashimoto at al.,[2] three of the four *N*-phenylpropenyl compounds acted as inverse μ-agonists, as determined by the [^{35}S]-GTP-γ-S binding assay (Figure 5). Of the four, only the *N*-phenylpropenyl analogue (−)**-6** had little or no activity as an inverse agonist. We previously reported the full inverse agonist curve for one of the initial compounds that was prepared, (+)**-9**.[15] Although it had low efficacy, it was found to be an inverse agonist at nondependent μ-opioid receptors. This was a rare example of a compound that could act as an inverse agonist at nondependent μ-opioid receptors.[15] Given the low degree of inverse agonist efficacy (∼20%) of the other compounds, generating inverse agonist dose-response curves under such a low signal-to-noise condition was problematic and would have required a larger number of replications than is customary. Under these constraints, we opted to generate a bar graph showing the effect of a single concentration (10 μM) on [^{35}S]-GTP-γ-S binding (Figure 5). The results show that most of the compounds are inverse agonists in nondependent cells. Since the compounds are also μ-antagonists, we have also generated antagonist K_e values for each compound in Table 2. It would be of interest in future studies to examine why (−)**-32** and the *N*-phenylpropenyl substituted compound, (−)**-6**, did not act as inverse agonists. Both of them ((−)**-32** and (−)**-6**) showed moderate to good affinity (Table 1) for the μ-receptor (K_i = 11 and

6 nM, respectively), and both were 4-fold less active as opioid antagonists (Table 2) than naloxone, showing moderate K_e values (8.2 and 6.6 nM). The relationship, if any, between the spatial characteristics of these compounds that enables them to bind with high affinity to the μ-opioid receptor and the inverse agonist activity that results from that binding is not readily apparent.

Conclusion

It is extremely unusual to find compounds that act as μ-inverse agonists in nondependent cells. The ~20% inverse agonist efficacy observed with many of the compounds reported here far exceeds that of previous reports. For example, to our knowledge there is only one report in the literature where a few compounds were found to have extremely minimal inverse agonist activity (3−5%) in nondependent cells.[13] Yet many of the phenylmorphans that we have examined with unsaturated side chains, and/or those with cyclopropyl groups, were found to have this unusual inverse agonist activity in nondependent cells, for reasons that are not apparent. Two of the NCPM compounds, (+)**-29** and (−)**-30**, and one of the *N*-propenyl compounds, (+)**-6**, were found to be potent antagonists more potent than naloxone in the [^{35}S]GTP-γ-S functional binding assay (13-, 7-, and 4-fold more potent, respectively, K_e = 0.17, 0.31, and 0.58 nM). Two others, an *N*-propenyl compound (+)**-9** and an NPCM compound (+)**-30**, were about as potent as naloxone as μ-opioid antagonists (K_e = 3.1 and 2.2 nM, respectively). The overlay of both *N*-phenylpropenyl and *N*-phenylpropyl

Table 2. Functional Data ([^{35}S]GTP-γ-S)[a] for Selected Compounds

[test agent]	K_e (nM)
+2 nM (+)**-6** ((1*S*,5*R*)-(*E*))	0.58 ± 0.07
+6 nM (−)**-6** ((1*R*,5*S*)-(*E*))	6.6 ± 0.7
+10 nM (+)**-9** ((1*S*,5*R*)-(*Z*))	3.1 ± 0.7
+10 nM (−)**-9** ((1*R*,5*S*)-(*Z*))	7.7 ± 1.6
+50 nM (−)**-29** ((1*S*,5*R*)-2-(1′*R*,2′*R*)-(*trans*))	9.4 ± 1.5
+2 nM (+)**-29** ((1*R*,5*S*)-2-(1′*S*,2′*S*)- (*trans*))	0.17 ± 0.02
+16 nM (+)**-30** ((1*S*,5*R*)-2-(1′*S*,2′*S*)-(*trans*))	2.2 ± 0.4
+2 nM (−)**-30** ((1*R*,5*S*)-2-(1′*R*,2′*R*)- (*trans*))	0.31 ± 0.06
+50 nM (−)**-31** ((1*S*,5*R*)-2-(1′*R*,2′*S*)-(*cis*))	8.6 ± 1.9
+50 nM (+)**-31** ((1*R*,5*S*)-2-(1′*S*,2′*R*)-(*cis*))	33 ± 7
+6 nM (+)**-32** ((1*S*,5*R*)-2-(1′*S*,2′*R*)-(*cis*))	18 ± 6
+11 nM (−)**-32** ((1*R*,5*S*)-2-(1′*R*,2′*S*)-(*cis*))	8.2 ± 1.8
naloxone[b]	2.3 ± 0.3
naltrexone	0.34 ± 0.03

[a] [^{35}S]GTP-γ-S binding was conducted as described in Experimental Section. DAMGO dose-response curves (10 points/curve) were generated in the absence and presence of the indicated concentrations of test agents. The data for each experimental condition were pooled and the best-fit estimates of the EC_{50} and E_{MAX} values determined using MLAB-PC. The K_e values were calculated according to the equation [test agent]/($EC_{50\text{-}2}/EC_{50\text{-}1}$ − 1), where $EC_{50\text{-}2}$ is the EC_{50} value in the presence of the test drug and EC_{50-1} is the value in the absence of the test drug. Each parameter value is ±SD. [b] From Kurimura et al.[19]

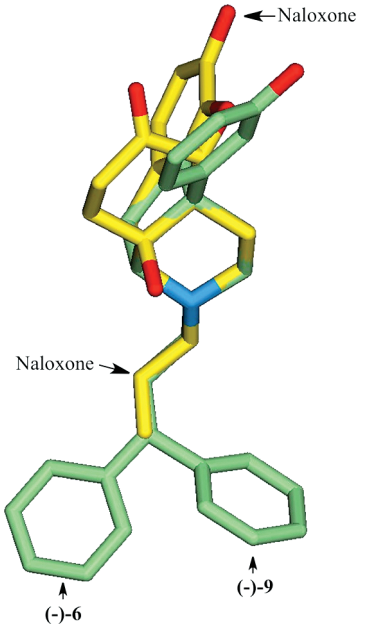


Figure 3. Overlay obtained by fitting the nine heavy (phenethylamine) atoms of two phenylalkenyl-substituted phenylmorphans (−)**-6** (1*R*,5*S*-(*E*)) and (−)**-9** (1*R*,5*S*-(*Z*)) to that of the geometry optimized naloxone. The carbon atoms of naloxone are in yellow. Atoms represented by colors are as follows: green/yellow, carbon; blue, nitrogen; red, oxygen. Hydrogen atoms are not shown.

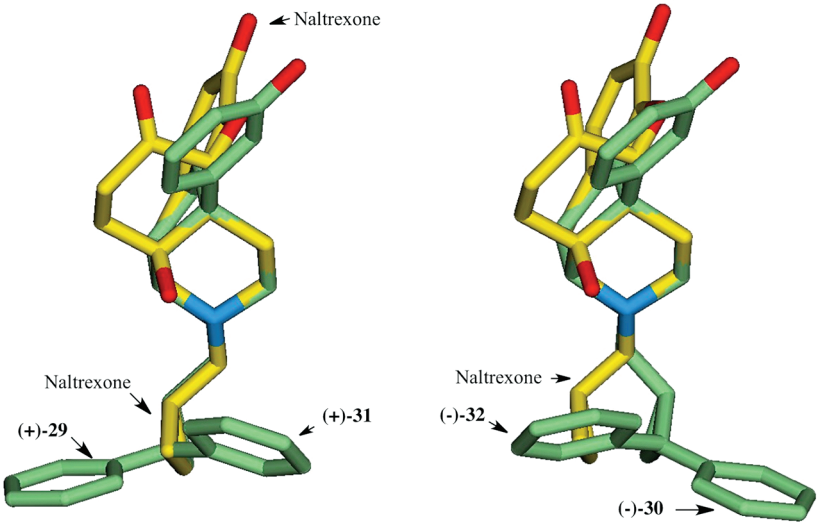


Figure 2. Overlay obtained by fitting the nine heavy (phenethylamine) atoms of each of the four *N*-phenylcyclopropylmethyl-substituted 1*R*,5*S*-phenylmorphans to that of the geometry optimized naltrexone; the carbon atoms of naltrexone are in yellow. Atoms represented by colors are as follows: green/yellow, carbon; blue, nitrogen; red, oxygen. Hydrogen atoms are not shown.

compounds suggests a wide binding or a flexible hydrophobic pocket at the μ-receptor to accommodate the different spatial positions and sizes of the *N*-phenyl substituents. However, the relationship between the topology of these compounds and their inverse agonist activity is not apparent and will be the subject of future studies.

Experimental Section

All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR, 300 MHz) and carbon nuclear magnetic resonance (^{13}C NMR, 75 MHz) spectra were recorded on a Varian Gemini-300 instrument in $CDCl_3$ (unless otherwise noted) with the values given in ppm (TMS as internal standard) and *J* (Hz) assignments of ^{1}H resonance coupling. The high resolution electrospray ionization (ESI) mass spectra were obtained on a Waters LCT Premier time-of-flight (TOF) mass spectrometer. Thin-layer chromatography (TLC) was performed on 0.25 mm Analtech GHLF silica gel. Flash column chromatography was performed with Bodman silica gel LC 60 A. Enantiomeric purity was assessed by HPLC (Shimadzu LC-6A with a Shimadzu SPD-6AV UM detector (at 254 nm) using Daicel's Chiralcel OD and OJ column (250 mm × 4.6 mm)). Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA, and were within ±0.4% for C, H, and N. The elemental analysis, ^{1}H NMR, and ^{13}C NMR were used to confirm ≥95% purity.

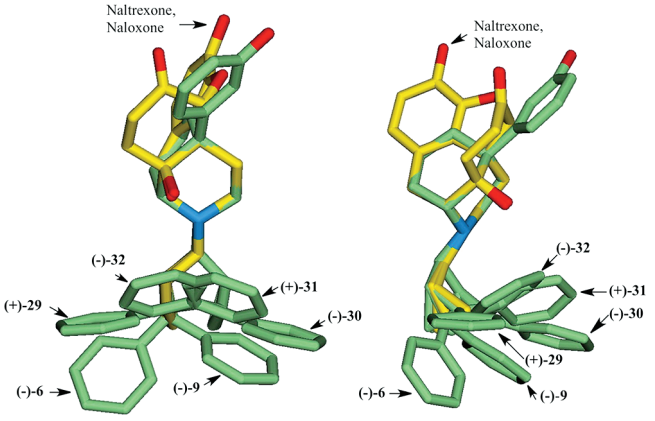
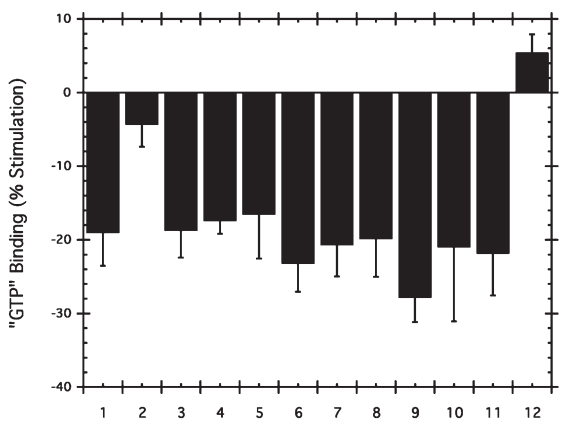


Figure 4. Two views of the obtained by fitting the nine heavy (phenethylamine) atoms of each of the six phenylmorphans ((−)-**6** (1*R*,5*S*)-(*E*), (−)-**9** (1*R*,5*S*)-(*Z*), (+)-**29** (1*R*,5*S*)-2-(1′*S*,2′*S*)-(*trans*), (−)-**30** (1*R*,5*S*)-2-(1′*R*,2′*R*)-(*trans*), (+)-**31** (1*R*,5*S*)-2-(1′*R*,2′*S*)-(*cis*), and (−)-**32** (1*R*,5*S*)-2-(1′*R*,2′*S*)-(*cis*)) and naloxone to that of the geometry optimized naltrexone. The carbon atoms of naltrexone are in yellow. Atoms represented by colors as follows: green/yellow, carbon; blue, nitrogen; red, oxygen. Hydrogen atoms are not shown.

General Procedure for Syntheses of (*Z*)-3-Phenylacrylic Acid or (*E*)-Cinnamoylamides of the Enantiomers of 5-(3-Methoxyphenyl)-2-azabicyclo[3.3.1]nonane ((−)-1 and (+)-1). The enantiomeric amine[4] (−)-**1** (or (+)-**1**) (2 −3 mmol), (*Z*)-3-phenylacrylic acid (**3**) or cinnamic acid ((*E*) **2**) (1.2 equiv), and EDCI (1.3 equiv) in CH_2Cl_2 (6 mL) were stirred at room temperature overnight. The mixture was diluted with 5% propan-2-ol in CH_2Cl_2, washed with aqueous Na_2CO_3 solution (to ∼pH 10) and brine, dried over Na_2SO_4, and passed through a pad of silica gel. After evaporation, the residue was purified by silica gel column chromatography with hexanes/EtOAc/EtOH (60/30/1.5) to give the amide products.

(*Z*)-3-Phenylacrylic Acid (3).[8] To a solution of 3-phenylpropiolic acid (**10**, 5.85 g, 40 mmol) in anhydrous pyridine (90 mL) was added 5% Pd on calcium carbonate (0.80 g). The mixture was stirred under 1 atm of hydrogen and consumed about 900 mL of hydrogen. The catalyst was removed by filtration and the pyridine distilled from the filtrate under reduced pressure. The residue was acidified with 10% hydrochloric acid (20 mL) and then extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give crude product. Column chromatography of this crude product with CH_2Cl_2−MeOH−acetic acid (75:5:0.4) gave (*Z*)-3-phenylacrylic acid (**3**) with about 10% of cinnamic acid (**2**, 3.5 g, 59% yield). The crude **3** (3.3 g, 22 mmol) was dissolved in anhydrous Et_2O (30 mL), and diisopropylamine (3.4 mL, 24 mmol) was then added to this solution. The resulting mixture was keep at room temperature overnight and gave colorless crystals of diisopropylammonium (*Z*)-3-phenylacrylate (**11**, 3.2 g, 64%). Mp 108.0−109.0 °C; ^{1}H NMR ($CDCl_3$, free base) δ 7.53−7.58 (m, 2H), 7.16−7.26 (m, 3H), 6.38 (d, 1H, J = 12.6 Hz), 6.08 (d, 1H, J = 12.6 Hz), 3.11 (m, 2H), 1.19 (d, 12H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 173.45, 137.26, 130.05, 129.55, 129.04, 127.94, 127.29, 46.19, 19.20. The diisopropylammonium (*Z*)-3-phenylacrylate (**11**, 3.2 g) was acidified with 10% hydrochloric acid (10 mL) and then extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give pure (*Z*)-3-phenylacrylic acid (**3**) as a colorless solid (1.80 g, 95%). Mp 66.0−68.0 °C (lit.[8] mp 65−68 °C); ^{1}H NMR ($CDCl_3$) δ 7.61 (d, 1H, J = 4.5 Hz), 7.58 (d, 1H, J = 1.8 Hz), 7.33−7.38 (m, 3H), 7.07 (d, 1H, J = 12.6 Hz), 5.97 (d, 1H, J = 12.6 Hz); ^{13}C NMR ($CDCl_3$) δ 171.16, 164.00, 134.60, 130.15, 129.60, 128.32, 118.85.



#	Compound
1	**(+)-6** ((1*S*,5*R*)-(*E*))
2	**(-)-6** ((1*R*,5*S*)-(*E*))
3	**(+)-9** ((1*S*,5*R*)-(*Z*))
4	**(-)-9** ((1*R*,5*S*)-(*Z*))
5	**(-)- 29** ((1*S*,5*R*)-2-(1'*R*,2'*R*)-(*trans*))
6	**(+)-29** ((1*R*,5*S*)-2-(1'*S*,2'*S*)-(*trans*))
7	**(+)-30** ((1*S*,5*R*)-2-(1'*S*,2'*S*)-(*trans*))
8	**(-)-30** ((1*R*,5*S*)-2-(1'*R*,2'*R*)-(*trans*))
9	**(-)-31** ((1*S*,5*R*)-2-(1'*R*,2'*S*)-(*cis*))
10	**(+)-31** ((1*R*,5*S*)-2-(1'*S*,2'*R*)-(*cis*))
11	**(+)-32** ((1*S*,5*R*)-2-(1'*S*,2'*R*)-(*cis*))
12	**(-)-32** ((1*R*,5*S*)-2-(1'*R*,2'*S*)-(*cis*))

Figure 5. As described in the Experimental Section, the effect of each test compound (10 μM) on [^{35}S]GTP-γ-S binding to μ-opioid receptors was determined. Each value is the mean ± SD (N = 3). A negative stimulation indicates inverse agonist activity. All changes were significant (p < 0.05) except for no. 12 ((−)-**32**) (Student's t test).

(*E*)-1-((1*S*,5*R*)-5-(3-Methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl)-3-phenylprop-2-en-1-one ((+)-4). Yield, 76.5% as a syrup; $[\alpha]_D^{20}$ +16.5° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.71 (m, 1H), 7.51−7.57 (m, 2H), 7.33−7.42 (m, 3H), 7.24−7.30 (m, 1H), 6.86−6.96 (m, 3H), 6.76 (dd, 1H, *J* = 8.4, 2.4 Hz), 4.70 (br-d, 1H, *J* = 124 Hz), 3.90−4.05 (m, 2H), 3.81 (s, 3H), 1.90−2.30 (m, 7H), 1.50−1.80 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 166.69, 166.27, 159.60, 153.23, 153.00, 142.22, 142.05, 135.51, 129.42, 129.34, 128.73, 127.71, 118.45, 117.93, 117.17, 117.08, 111.52, 111.44, 110.41, 55.16, 49.26, 46.78, 42.44, 39.89, 38.86, 38.53, 36.95, 36.43, 36.20, 35.55, 34.95, 34.71, 31.84, 29.17, 20.45, 20.32; HRMS (TOF MS ES$^+$) calcd for $C_{24}H_{28}NO_2$ (M + H)$^+$ 362.2120, found 362.2117.

(*E*)-1-((1*R*,5*S*)-5-(3-Methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl)-3-phenylprop-2-en-1-one ((−)-4). Yield, 80.5% as syrup; $[\alpha]_D^{20}$ −16.5° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.71 (dd, 1H, *J* = 15.3, 12 Hz), 7.51−7.57 (m, 2H), 7.33−7.42 (m, 3H), 7.24−7.30 (m, 1H), 6.86−6.96 (m, 3H), 6.75 (dd, 1H, *J* = 8.1, 2.4 Hz), 4.70 (br-d, 1H, *J* = 124 Hz), 3.90−4.05 (m, 2H), 3.81 (s, 3H), 1.90−2.30 (m, 7H), 1.50−1.80 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 166.65, 166.23, 159.58, 153.19, 152.97, 142.17, 142.00, 135.48, 129.39, 129.31, 128.70, 127.68, 118.43, 117.91, 117.14, 117.05, 111.49, 111.41, 110.39, 55.13, 49.22, 46.75, 42.40, 39.86, 38.84, 38.50, 36.93, 36.41, 36.17, 35.54, 34.92, 34.69, 31.82, 29.14, 20.44, 20.29; HRMS (TOF MS ES$^+$) calcd for $C_{24}H_{28}NO_2$ (M + H)$^+$ 362.2120, found 362.2117.

General Procedure for Syntheses of Phenolic Amides ((1*S*,5*R*)-(+)-5, (1*R*,5*S*)-(−)-5 and (1*S*,5*R*)-(+)-8, (1*R*,5*S*)-(−)-8) from the Corresponding Methyl Ethers ((1*S*,5*R*)-(+)-4, (1*R*,5*S*)-(−)-4, and (1*S*,5*R*)-(+)-7, (1*R*,5*S*)-(−)-7). A mixture of enantiomeric amide (1−2 mmol), 48% hydrogen bromide (2 mL), and HOAc (3 mL) was refluxed for 30 min to 1 h under argon. The HOAc was removed in vacuo, and the mixture was neutralized with saturated $NaHCO_3$ to pH 10. The mixture was extracted with 5% propan-2-ol in CH_2Cl_2 (3 × 30 mL). The combined extracts were washed with H_2O and brine and then dried over Na_2SO_4. After evaporation, the residue was purified by silica gel column chromatography with hexanes/EtOAc/EtOH (40/28/2) to give the amide products.

(*E*)-1-((1*S*,5*R*)-5-(3-Hydroxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl)-3-phenylprop-2-en-1-one ((+)-5). Yield, 71% as syrup; $[\alpha]_D^{20}$ +22.0° (*c* 0.42, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.72 (m, 1H), 7.48−7.55 (m, 2H), 7.28−7.44 (m, 4H), 7.15−7.22 (m, 1H), 6.81−6.97 (m, 3H), 6.75 (dd, 1H, *J* = 8.4, 2.4 Hz), 4.70 (br-d, 1H, *J* = 124 Hz), 3.75−4.05 (m, 2H), 1.40−2.25 (m, 10H); HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{26}NO_2$ (M + H)$^+$ 348.1964, found 348.1968.

(*E*)-1-((1*R*,5*S*)-5-(3-Hydroxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl)-3-phenylprop-2-en-1-one ((−)-5). Yield, 75% as syrup; $[\alpha]_D^{20}$ −22.3° (*c* 0.68, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.71 (m, 1H), 7.48−7.54 (m, 2H), 7.32−7.40 (m, 3H), 7.14−7.22 (m, 1H), 6.80−6.96 (m, 3H), 6.75 (dd, 1H, *J* = 8.1, 2.4 Hz), 4.70 (br-d, 1H, *J* = 152 Hz), 3.75−4.05 (m, 2H), 1.75−2.25 (m, 7H), 1.50−1.75 (m, 3H); HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{26}NO_2$ (M + H)$^+$ 348.1964, found 348.1961.

General Procedure for Syntheses of Amines ((1*S*,5*R*)-(+)-6, (1*R*,5*S*)-(−)-6 and ((1*S*,5*R*)-(+)-9 and (1*R*,5*S*)-(−)-9) from the Phenolic Amides ((1*S*,5*R*)-(+)-5, (1*R*,5*S*)-(−)-5 and (1*S*,5*R*)-(+)-8, (1*R*,5*S*)-(−)-8).[3] Red-Al (65%, 2.5 equiv) was added to the solution of amide (1−2 mmol) in anhydrous THF (60 mL) dropwise under argon at room temperature, and the mixture was stirred for 2 h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (20 mL), and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of solvent in vacuo, the residue was purified by silica gel column chromatography with hexanes/EtOAc/EtOH (40/40/2) to give the phenolic amides.

3-((1*S*,5*R*)-2-Cinnamyl-2-azabicyclo[3.3.1]nonan-5-yl)phenol ((+)-6). Yield, 61%; HCl salt, mp 202−204 °C (dec); $[\alpha]_D^{20}$ +11.9° (*c* 0.47, MeOH); ^{1}H NMR ($CDCl_3$, free base) δ 8.71 (br, 1H), 7.05−7.40 (m, 6H), 6.54−6.82 (m, 4H), 6.30−6.43 (m, 1H), 3.46 (d, 2H, *J* = 6.6 Hz), 3.34 (br, 1H), 2.95−3.15 (m, 2H), 2.10−2.28 (m, 2H), 1.76−2.06 (m, 5H), 1.20−1.70 (m, 3H); ^{13}C NMR ($CDCl_3$, free base): δ 156.70, 152.40, 136.22, 134.51, 129.21, 128.46, 127.76, 126.46, 124.05, 116.00, 113.56, 112.54, 57.49, 52.29, 49.36, 37.78, 37.20, 35.93, 34.34, 23.71, 22.27; ^{1}H NMR (CD_3OD, free base) δ 7.24−7.32 (m, 2H), 7.06−7.23 (m, 3H), 6.70 (t, 1H, *J* = 7.8 Hz), 6.65−6.75 (m, 2H), 6.45−6.57 (m, 2H), 6.12−6.25 (m, 1H), 3.17−3.22 (m, 1H), 3.09 (br, 1H), 2.98 (d-t, 1H, *J* = 4.8, 12.6 Hz), 2.80 (dd, 1H, *J* = 12.0, 4.8 Hz), 2.10 (br-d, 2H, *J* = 13.8 Hz), 1.70−2.06 (m, 5H), 1.40−1.66 (m, 2H), 1.14−1.40 (m, 2H); ^{13}C NMR (CD_3OD, free base) δ 158.46, 154.67, 138.36, 134.94, 130.35, 129.78, 128.84, 127.55, 127.02, 117.09, 113.77, 112.96, 58.89, 53.67, 50.83, 39.65, 39.48, 38.15, 35.96, 25.14, 24.02; HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{28}NO$ (M + H)$^+$ 334.2171, found 334.2180. Anal. ($C_{23}H_{27}NO\cdot HCl$) C, H, N.

3-((1*R*,5*S*)-2-Cinnamyl-2-azabicyclo[3.3.1]nonan-5-yl)phenol ((−)-6). Yield, 58%; HCl salt, mp 201−203 °C (dec); $[\alpha]_D^{20}$ −12.0° (*c* 0.36, MeOH); ^{1}H NMR ($CDCl_3$, free base) δ 7.05−7.40 (m, 5H), 6.82 (d, 1H, *J* = 7.8 Hz), 6.77 (br-t, 1H, *J* = 2 Hz), 6.64 (dd, 1H, *J* = 8 and 2 Hz), 6.52−6.62 (m, 2H), 6.26−6.38 (m, 1H), 3.41 (m, 2H), 3.25 (br, 1H), 2.90−3.10 (m, 2H), 2.10−2.14 (m, 2H), 1.82−2.07 (m, 5H), 1.50−1.75 (m, 2H), 1.30−1.44 (m, 1H); ^{13}C NMR ($CDCl_3$, free base) δ 156.57, 153.64, 137.03, 133.18, 129.46, 128.74, 127.71, 126.87, 126.59, 116.81, 113.38, 112.64, 58.14, 52.12, 49.83, 38.54, 38.46, 37.10, 34.99, 24.39, 23.09; HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{28}NO$ (M + H)$^+$ 334.2171, found 334.2180. Anal. ($C_{23}H_{27}NO\cdot HCl\cdot 0.25H_2O$) C, H, N.

(*Z*)-1-((1*S*,5*R*)-5-(3-Methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl)-3-phenylprop-2-en-1-one ((+)-7). Yield, 74.7% as syrup; $[\alpha]_D^{20}$ +45.4° (*c* 0.95, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.37−7.45 (m, 2H), 7.19−7.35 (m, 4H), 6.70−6.83 (m, 3H), 6.63 (d, 1H, *J* = 12.6 Hz), 6.86−6.96 (m, 3H), 6.09 (dd, 1H, *J* = 12.6, 8.4 Hz), 4.62 (d-m, 1H, *J* = 180 Hz), 3.79 (d, 3H, *J* = 2.7 Hz), 3.42−3.78 (m, 2H), 1.80−2.20 (m, 5H), 1.48−1.80 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 168.80, 168.65, 159.78, 153.27, 152.77, 136.07, 135.74, 133.02, 132.61, 129.48, 128.73, 128.63, 128.58, 128.36, 124.68, 123.95, 117.31, 117.19, 111.66, 111.53, 110.68, 110.57, 55.38, 50.46, 45.93, 43.02, 39.89, 38.60, 38.04, 37.47, 36.46, 35.93, 35.28, 31.21, 28.76, 21.52, 20.77; HRMS (TOF MS ES$^+$) calcd for $C_{24}H_{28}NO_2$ (M + H)$^+$ 362.2120, found 362.2108.

(*Z*)-1-((1*R*,5*S*)-(−)-5-(3-methoxyphenyl)-2-azabicyclo[3.3.1]-nonan-2-yl)-3-phenylprop-2-en-1-one ((−)-7). Yield, 78.0% as syrup; $[\alpha]_D^{20}$ −45.3° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.37−7.43 (m, 2H), 7.19−7.35 (m, 4H), 6.70−6.83 (m, 3H), 6.63 (d, 1H, *J* = 12.6 Hz), 6.86−6.96 (m, 3H), 6.09 (dd, 1H, *J* = 12.6, 8.4 Hz), 4.62 (d-m, 1H, *J* = 180 Hz), 3.79 (d, 3H, *J* = 2.7 Hz), 3.42−3.72 (m, 2H), 1.80−2.20 (m, 5H), 1.46−1.80 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 168.80, 168.65, 159.78, 153.27, 152.77, 136.07, 135.74, 133.02, 132.61, 129.48, 128.73, 128.63, 128.58, 128.36, 124.68, 123.95, 117.31, 117.19, 111.66, 111.53, 110.68, 110.57, 55.38, 50.46, 45.93, 43.02, 39.89, 38.60, 38.04, 37.47, 36.46, 35.93, 35.28, 31.21, 28.76, 21.52, 20.77; HRMS (TOF MS ES$^+$) calcd for $C_{24}H_{28}NO_2$ (M + H)$^+$ 362.212, found 362.2117.

(*Z*)-1-((1*S*,5*R*)-5-(3-Hydroxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl)-3-phenylprop-2-en-1-one ((+)-8). Yield, 72% as syrup; $[\alpha]_D^{20}$ +46.3° (*c* 0.95, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.08−7.42 (m, 6H), 6.60−6.88 (m, 4H), 6.07 (dd, 1H, *J* = 12.6, 7.2 Hz), 4.62 (d-m, 1H, *J* = 198 Hz), 3.36−3.70 (m, 2H), 1.40−2.20 (m, 10H); HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{26}NO_2$ (M + H)$^+$ 348.1964, found 348.1962.

(*Z*)-1-((1*R*,5*S*)-(−)-5-(3-Hydroxyphenyl)-2-azabicyclo[3.3.1]-nonan-2-yl)-3-phenylprop-2-en-1-one ((−)-8). Yield, 65.0% as syrup; $[\alpha]_D^{20}$ −46.4° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.64 (s, 1H), 7.20−7.40 (m, 5H), 7.05−7.14 (m, 1H), 6.60−6.78 (m, 4H), 6.07 (dd, 1H, *J* = 12.6, 7.2 Hz), 4.55 (d-m, 1H, *J* = 198 Hz),

3.35−3.70 (m, 2H), 1.40−2.20 (m, 10H); HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{26}NO_2$ $(M + H)^+$ 348.1964, found 348.1948.

3-((1*S*,5*R*)-2-((*Z*)-3-phenylallyl)-2-azabicyclo[3.3.1]nonan-5-yl)-phenol ((+)-9). Yield, 68%; HCl salt, mp 201−203 °C (dec); $[\alpha]_D^{20}$ +27.3° (*c* 0.42, MeOH); ^{1}H NMR ($CDCl_3$, free base) δ 7.20−7.40 (m, 5H), 7.11 (t, 1H, J = 7.8 Hz), 6.79 (d, 1H, J = 7.8 Hz), 6.76 (br, 1H), 6.64 (dd, 1H, J = 7.8, 2.1 Hz), 6.57 (d, 1H, J = 11.7 Hz), 5.86 (d-t, 1H, J = 12.6, 6.3 Hz), 3.55 (m, 2H), 3.23 (br, 1H), 2.96 (m, 2H), 2.14 (d-br, 1H, J = 12.6 Hz), 1.76−2.06 (m, 6H), 1.20−1.70 (m, 3H); ^{13}C NMR ($CDCl_3$, free base) δ 156.64, 153.61, 137.25, 131.53, 129.55, 129.41, 129.07, 128.36, 127.09, 116.67, 113.34, 112.67, 53.21, 52.26, 49.75, 38.46, 37.03, 34.86, 24.45, 22.99; HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{28}NO$ $(M + H)^+$ 334.2171, found 334.2176. Anal. ($C_{23}H_{27}NO\cdot HCl\cdot 0.25H_2O$) C, H, N.

3-((1*R*,5*S*)-2-((*Z*)-3-phenylallyl)-2-azabicyclo[3.3.1]nonan-5-yl)phenol ((−)-9). Yield, 60%; HCl salt, mp 200−202 °C (dec); $[\alpha]_D^{20}$ −27.0° (*c* 0.42, MeOH); ^{1}H NMR ($CDCl_3$, free base) δ 7.70 (br, 1H), 7.18−7.40 (m, 5H), 7.10 (t, 1H, J = 7.8 Hz), 6.78 (d, 1H, J = 7.8 Hz), 6.72 (br, 1H), 6.60 (dd, 1H, J = 7.8, 1.8 Hz), 5.56 (d, 1H, J = 12.6 Hz), 5.86 (d-t, 1H, J = 12.6, 6.3 Hz), 3.54 (m, 2H), 3.22 (br, 1H), 2.96 (m, 2H), 2.14 (d-br, 1H, J = 12.6 Hz), 1.700−2.04 (m, 6H), 1.44−1.62 (m, 2H), 1.20−1.36 (m, 1H); ^{13}C NMR ($CDCl_3$, free base) δ 156.70, 153.52, 137.22, 131.55, 129.45, 129.40, 129.06, 128.35, 127.07, 116.58, 113.53, 112.80, 53.16, 52.24, 49.73, 38.35, 37.00, 34.81, 24.40, 22.96; HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{28}NO$ $(M + H)^+$ 334.2171, found 334.2182. Anal. ($C_{23}H_{27}NO\cdot HCl\cdot 0.5H_2O$) C, H, N.

(2,2-Dibromocyclopropyl)benzene (12).[9] A 3 L round-bottomed flask equipped with a mechanical stirrer was charged with styrene (99.9 g, 0.96 mmol) and bromoform (485 g, 1.92 mol). Benzyltriethylammonium chloride (TEBA, 46 g, 0.2 mol) and 50% aqueous NaOH (500 mL) were added to the solution, and the resulting mixture was stirred vigorously at room temperature for 20 h. The reaction mixture was then treated with H_2O (1 L) and extracted with Et_2O (3 × 500 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo. Distillation of the residue gave **12** as a yellow oil (86−88 °C/~2 mmHg, 206 g, 78%). ^{1}H NMR ($CDCl_3$) δ 7.20−2.40 (m, 5H), 2.95 (dd, 1H, J = 10.5, 8.1 Hz), 2.13 (dd, 1H, J = 10.5, 8.1 Hz), 2.01 (t, 1H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 135.95, 128.88, 128.27, 127.59, 35.89, 28.41, 27.19.

2-Phenylcyclopropanecarboxylic Acid ((±)-13 (*trans*-1*R,2*R**) and (±)-14 (*cis*-1*S**,2*R**)).**[10] Synthesis gas (CO/H_2, 3:1) was bubbled through a vigorously stirred mixture of 5 N KOH (1100 mL), toluene (600 mL), cobalt(II) chloride hexahydrate (14.28 g, 60 mmol), potassium cyanide (7.81 g, 120 mmol), nickel(II) cyanide tetrahydrate (10.97 g, 60 mmol), and PEG-400 (5 mL, 15 mmol) at 95 °C for 2 h. A solution of **12** (82.8 g, 300 mmol) in toluene (200 mL) was added, and the resulting mixture was stirred vigorously, continuously bubbling in additional synthesis gas for 2 days at 95 °C. After cooling to room temperature, the mixture was filtered through Celite. The aqueous layer was separated, washed with Et_2O (2 × 200 mL), acidified with 6 N hydrochloric acid to pH 1, and extracted with Et_2O (3 × 120 mL). The combined extracts were washed with brine and dried over $MgSO_4$. Removal of solvent gave a 6:4 mixture of isomers (±)-**13** and (±)-**14** as a light yellow solid (21 g, 43%).

(1*S*,2*S*)-2-Phenylcyclopropane-1-carboxylic acid (*trans*-(+)-13). A solution of (+)-(1*S*,2*S*)-enriched (±)-**13** (19 g, 117 mmol) and quinine (40.1 g, 124 mmol) in EtOAc (760 mL) was refluxed until most of the solid was dissolved. The solution was filtered, and the filtrate was allowed to stand at room temperature for 5 days. The precipitate was collected and recrystallized from EtOAc five times to yield 10.2 g (34%) of (1*S*,4*S*)-2-((*R*)-hydroxy(6-methoxyquinolin-4-yl)methyl)-8-vinyl-1-azoniabicyclo[2.2.2]octane (1*S*,2*S*)-2-phenylcyclopropanecarboxylate ((−)-**18**) as colorless crystals. Mp 152.0−152.5 °C; $[\alpha]_D^{20}$ −10.2° (*c* 1.0, EtOH). The free acid was liberated from the salt by treatment with 2 N HCl. Extraction with Et_2O and removal of solvent in vacuo gave 3.2 g of (+)-**13** as an oil, which solidified on standing. Mp 45−46 °C; $[\alpha]_D^{20}$ +406.0° (*c* 1.0, $CHCl_3$); >98% ee in chiral HPLC [Chiralcel OD column; hexane/propan-2-ol/TFA 91:9:0.2; flow rate 1 mL/min; detection 254 nm; retention time 8.18 min].

(1*R*,2*R*)-2-Phenylcyclopropanecarboxylic Acid (*trans*-(−)-13).[11] A warm solution of commercially available *trans*-2-phenylcyclopropane-1-carboxylic acid ((±)-**13**, 24 g, 147 mmol) in MeOH (150 mL) was added to a solution of dehydroabietylamine (41.7 g, 147 mmol) in warm MeOH (120 mL). The mixture was cooled to room temperature and the precipitate was collected and dried to afford a white solid, which was recrystallized from 90% aqueous MeOH five times to give 8.2 g (25%) of ((1*R*,4a*S*)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)methanaminium (1*R*,2*R*)-2-phenylcyclopropanecarboxylate ((−)-**17**) as colorless crystals. Mp 167.5−168 °C, $[\alpha]_D^{20}$ −80.8° (*c* 0.61, MeOH). The free acid was liberated from the salt by treatment with a saturated $NaHCO_3$ solution and extraction with Et_2O. Acidification of the aqueous fraction with cold, 37% hydrochloric acid, extraction with Et_2O, and removal of solvent in vacuo gave 2.9 g of crude (−)-**13**. One recrystallization from acetone gave 2.8 g of (−)-**13**, mp 47−48 °C (lit.[6] mp 49.5−50 °C; $[\alpha]_D^{20}$ −401.0° (*c* 0.88, $CHCl_3$) (lit.[6] $[\alpha]_D^{25}$ −309° (*c* 1, 95% EtOH); >98% ee in chiral HPLC [Chiralcel OD column; hexane/propan-2-ol/TFA 91:9:0.2; flow rate 1 mL/min; detection 254 nm; retention time 5.56 min].

(1*S,2*R**)-2-Phenylcyclopropanecarboxylic Acid (*cis*-((±)-14).**[7] A 500 mL flask equipped with a 30 cm Vigreux column, to which was attached a partial takeoff distilling head with a reflux condenser, was charged with (1*S**,2*R**)-(±)-**16** (20.0 g, 0.105 mol), H_2O (75 mL), NaOH (8.4 g, 0.21 mol), and EtOH (100 mL). The mixture was refluxed for 5 h, during which time 120 mL of distillate was obtained. After cooling to room temperature, the mixture was washed with benzene (30 mL), and then benzene (40 mL) and concentrated hydrochloric acid (20 mL) were added. The organic layer was separated, and the aqueous layer was extracted with benzene (2 × 30 mL). The combined organic layer was dried over $MgSO_4$. Removal of solvent afforded (±)-**14** as colorless crystals (12 g, 70% yield). Mp 86−87 °C (lit.[7] mp 106−109 °C); ^{1}H NMR ($CDCl_3$) δ 7.35 − 7.55 (m, 5H), 3.86 (q, 2H, J = 7.2 Hz), 2.57 (dd, 1H, J = 16.5, 9.0 Hz), 2.03−2.12 (m, 1H), 1.67−1.74 (m, 1H), 1.28−1.36 (m, 1H), 0.965 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 171.52, 136.75, 129.49, 128.06, 126.82, 60.35, 25.64, 21.99, 14.20, 11.29.

(1*R*,2*S*)-2-Phenylcyclopropanecarboxylic Acid ((−)-14). Optical Resolution of ((1*S,2*R**)-2-phenylcyclopropanecarboxylic Acid (±)-14).** The (±)-**14** (14.8 g, 91.6 mmol)[7] was added to a boiling solution of (+)-dehydroabietylamine (26.2 g, 91.6 mmol) in MeOH (1300 mL) and H_2O (330 mL). The mixture was cooled to room temperature, and the precipitate was collected and dried to afford the light yellow solid, which was recrystallized from 90% aqueous methanol four times to give 3.3 g (16%) of ((1*R*,4a*S*)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)methanaminium (1*R*,2*S*)-2-phenylcyclopropanecarboxylate ((+)-**19**) as colorless crystals. Mp 189−190 °C; $[\alpha]_D^{20}$ +37.1° (*c* 1.0, EtOH). The free acid was liberated from the salt by treatment with a saturated $NaHCO_3$ solution and extracted with Et_2O. The aqueous fraction was acidified with cold, concentrated hydrochloric acid and extracted with Et_2O. The ethereal solutions were combined and the solvent was removed to give 1.1 g of (−)-**14** as colorless crystals. Mp 82.5−83.5 °C (lit.[6] mp 83−84 °C); $[\alpha]_D^{20}$ −28.4° (*c* 1.0, $CHCl_3$) (lit.[6] $[\alpha]_D^{20}$ −28° (*c* 1.023, $CHCl_3$)); >98% ee in chiral HPLC (Chiralcel OJ column; hexane/propan-2-ol/TFA 95:5:0.1; flow rate 1 mL/min; detection 254 nm; retention time 12.87 min).

(1*S*,2*R*)-2-Phenylcyclopropane-1-carboxylic Acid ((+)-14). A solution of (+)-(1*S*,2*R*) enriched *cis*-2-phenylcyclopropanecarboxylic acid (13.2 g, 81.4 mmol) and quinine (27.9 g, 86.2 mmol)

in EtOAc (530 mL) was refluxed until most of solid was dissolved. The solution was filtered, and the filtrate was allowed to stand at room temperature overnight. The precipitate was collected and recrystallized from EtOAc six times to yield 3.8 g (9%) of (1*S*,4*S*)-2-((*R*)-hydroxy(6-methoxyquinolin-4-yl)methyl-8-vinyl-1-azoniabicyclo[2.2.2]octane (1*S*,2*R*)-2-phenylcyclopropanecarboxylate ((−)-**20**) as colorless crystals. Mp 142−144 °C; $[\alpha]_D^{20}$ −116.5° (*c* 1.0, EtOH). The free acid was liberated from the salt by treatment with 2 N HCl and extracted with Et_2O. Removal of solvent gave 1.2 g of (+)-**14** as colorless crystals. Mp 83−84 °C; $[\alpha]_D^{20}$ +28.4° (*c* 1.0, $CHCl_3$); > 98% ee in chiral HPLC (Chiralcel OJ column; hexane/propan-2-ol/TFA 95:5:0.1; flow rate 1 mL/min; detection 254 nm; retention time 13.95 min).

Ethyl 2-Phenylcyclopropanecarboxylate (*trans*/*cis* (±)-15).[7] A 1 L round-bottomed flask equipped with a short fractionating column connected to a downward condenser was charged with the *trans*/*cis* mixture ((±)-**13** and (±)-**14**, 89 g, 0.55 mol), *p*-toluenesulfonic acid (3.0 g), absolute EtOH (165 mL), and toluene (100 mL). The mixture was heated in an oil bath at 115 °C, and an azeotropic mixture of EtOH, toluene, and H_2O was collected in a flask containing anhydrous K_2CO_3 (70 g) until the temperature at the top of the column rose to 78 °C. The distillate was shaken thoroughly with K_2CO_3, filtered, and then returned to the reaction flask. The mixture was heated until the temperature at the top of the column rose to 78−80 °C. The residue was distilled at 84−91 °C/0.5 mmHg to give a 6:4 *trans*-(1*R**,2*R**)/*cis*-(1*S**,2*R**) mixture of the isomers of (±)-**15** (71 g, 68%) as a colorless oil.

(1*S,2*R**)-Ethyl 2-phenylcyclopropanecaboxylate ((±)-16).** A 500 mL three-neck round-bottomed flask equipped with a dropping funnel, stirrer, and a 30 cm Vigreux column, to which was attached a partial takeoff distilling head with reflux condenser, was charged with (±)-**15** (83.3 g, 0.438 mol), EtOH (107 mL), H_2O (35 mL), and NaOH (13.1 g, 0.328 mol). The mixture was refluxed for 5 h during which time 107 mL of EtOH was slowly distilled from the mixture and replaced by an equal volume of H_2O, added through a dropping funnel. After cooling to room temperature, H_2O (120 mL) and benzene (80 mL) were added. The organic layer was separated, and the aqueous layer was extracted with benzene (2 × 30 mL). The combined organic layers were dried over $MgSO_4$. Removal of solvent gave a crude *trans*/*cis*-mixture (1:9) of ethyl 2-phenylcyclopropanecarboxylate as a light yellow solid (23 g). Purification of the crude material by column chromatography with 2% EtOAc in hexanes afforded (±)-**16** as a light yellow oil (20 g, 50% yield, based on the (1*S**,2*R**)-*cis*-isomer (±)-**16**). ^{1}H NMR ($CDCl_3$) δ 7.35−7.55 (m, 5H), 3.86 (q, 2H, J = 7.2 Hz), 2.57 (dd, 1H, J = 16.5, 9.0 Hz), 2.03−2.12 (m, 1H), 1.67−1.74 (m, 1H), 1.28−1.36 (m, 1H), 0.965 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 171.52, 136.75, 129.49, 128.06, 126.82, 60.35, 25.64, 21.99, 14.20, 11.29.

General Procedure for Syntheses of the Enantiomers of 5-(3-Methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2- yl((*cis* or *trans*)-2-phenylcyclopropyl)methanone ((+)- and (−)-21 through 24). A mixture of the enantiomeric amine (−)-**1** or (+)-**1** (2 −3 mmol), chiral 2-phenylcyclopropane-1-carboxylic acid (1.2 equiv), and EDCI (1.3 equiv) in CH_2Cl_2 (6 mL) was stirred at room temperature overnight. The mixture was diluted with 5% propan-2-ol in CH_2Cl_2, washed with aqueous Na_2CO_3 solution (to ∼pH 10) and brine, dried over Na_2SO_4, and passed through a pad of silica gel. After removal of solvent in vacuo, the residue was purified by silica gel column chromatography with hexanes/EtOAc/EtOH (60/30/1.5) to give the amide products.

((1*R*,5*S*)-5-(3-Methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl)-((1′*S*,2′*S*)-2-phenylcyclopropyl)methanone ((+)-21). Yield, 90% as a colorless resin; $[\alpha]_D^{20}$ +547.0° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.16−7.32 (m, 4H), 7.10−7.16 (m, 2H), 6.83−6.93 (m, 2H), 6.71−6.76 (m, 1H), 4.43−4.83 (m, 1H), 3.80−3.94 (m, 2H), 3.77−3.80 (m, 3H), 2.54 (m, 1H), 1.80−2.24 (m, 8H), 1.42−1.78 (m, 4H), 1.22−1.34 (m, 1H); HRMS (TOF MS ES$^+$) calcd for $C_{25}H_{30}NO_2$ (M + H)$^+$ 376.2277, found 376.2256.

(1*S*,5*R*)-5-(3-Methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl)((1′*R*,2′*R*)-2-phenylcyclopropyl)methanone ((−)-21). Yield, 90% as colorless resin; $[\alpha]_D^{20}$ −546.5° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.16−7.32 (m, 4H), 7.10−7.16 (m, 2H), 6.84−6.92 (m, 2H), 6.72−6.76 (m, 1H), 4.62 (d-m, 1H, J = 100 Hz), 3.81−3.94 (m, 2H), 3.79 (m, 3H), 2.54 (m, 1H), 1.82−2.24 (m, 8H), 1.42−1.80 (m, 4H), 1.20−1.34 (m, 1H); HRMS (ESI) calcd for $C_{25}H_{30}NO_2$ (M + H)$^+$ 376.2277, found 376.2260.

((1*S*,5*R*)-5-(3-Methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl)((1′*S*,2′*S*)-2-phenylcyclopropyl)methanone ((+)-22). Yield, 90% as colorless resin; $[\alpha]_D^{20}$ +565.5° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.16−7.32 (m, 4H), 7.08−7.16 (m, 2H), 6.84−6.94 (m, 2H), 6.72−6.78 (m, 1H), 4.64 (d-m, 1H, J = 100 Hz), 3.74−3.96 (m, 5H), 2.42−2.54 (m, 1H), 1.80−2.24 (m, 8H), 1.42−1.76 (m, 4H), 1.23−1.31 (m, 1H); HRMS (TOF MS ES$^+$) calcd for $C_{25}H_{30}NO_2$ (M + H)$^+$ 376.2277, found 376.2261.

((1*R*,5S)-5-(3-Methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl)((1′*R*,2′*R*)-2-phenylcyclopropyl)methanone ((−)-22). Yield, 88% as a colorless resin; $[\alpha]_D^{20}$ −564.5° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.15−7.32 (m, 4H), 7.08−7.15 (m, 2H), 6.83−6.92 (m, 2H), 6.71−6.76 (m, 1H), 4.64 (d-m, 1H, J = 100 Hz), 3.71−3.95 (m, 5H), 2.40−2.55 (m, 1H), 1.80−2.25 (m, 8H), 1.42−1.76 (m, 4H), 1.21−1.30 (m, 1H); HRMS (TOF MS ES$^+$) calcd for $C_{25}H_{30}NO_2$ (M + H)$^+$ 376.2277, found 376.2261.

((1*R*,5*S*)-5-(3-Methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl)((1′*S*,2′*R*)-2-phenylcyclopropyl)methanone ((+)-23). Yield, 79% as a colorless resin; $[\alpha]_D^{20}$ +103.0° (*c* 0.76, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.14−7.28 (m, 4H), 7.07−7.14 (m, 2H), 6.68−6.88 (m, 3H), 4.50−4.60 (m, 1H), 3.45−3.92 (m, 5H), 2.38−2.50 (m, 1H), 1.75−2.30 (m, 6H), 1.24−1.75 (m, 7H); HRMS (TOF MS ES$^+$) calcd for $C_{25}H_{30}NO_2$ (M + H)$^+$ 376.2277, found 376.2287.

((1*S*,5*R*)-5-(3-Methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl)((1′*R*,2′*S*)-2-phenylcyclopropyl)methanone ((−)-23). Yield, 71% as a colorless resin; $[\alpha]_D^{20}$ −102° (*c* 0.50, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.14−7.28 (m, 4H), 7.07−7.14 (m, 2H), 6.68−6.88 (m, 3H), 4.50−4.60 (m, 1H), 3.45−3.92 (m, 5H), 2.38−2.50 (m, 1H), 1.75−2.30 (m, 6H), 1.24−1.75 (m, 7H); HRMS (TOF MS ES$^+$) calcd for $C_{25}H_{30}NO_2$ (M + H)$^+$ 376.2277, found 376.2281.

((1*S*,5*R*)-5-(3-Methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl)((1′*S*,2′*R*)-2-phenylcyclopropyl)methanone ((+)-24). Yield, 72% as a colorless resin; $[\alpha]_D^{20}$ +139.0° (*c* 0.59, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.10−7.28 (m, 6H), 6.67−6.86 (m, 3H), 4.42−4.54 (m, 1H), 3.36−4.02 (m, 2H), 3.79 (s, 3H), 2.40−2.50 (m, 1H), 2.10−2.24 (m, 1H), 1.62−2.05 (m, 7H), 1.02−1.44 (m, 4H), 0.60−0.78 (m, 1H); HRMS (TOF MS ES$^+$) calcd for $C_{25}H_{30}NO_2$ (M + H)$^+$ 376.2277, found 376.2273.

((1*R*,5*S*)-5-(3-Methoxyphenyl)-2-azabicyclo[3.3.1]nonan-2-yl)((1′*R*,2′*S*)-2-phenylcyclopropyl)methanone ((−)-24). Yield, 75% as a colorless resin; $[\alpha]_D^{20}$ −138.1° (*c* 0.65, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.10−7.28 (m, 6H), 6.67−6.86 (m, 3H), 4.42−4.54 (m, 1H), 3.36−4.02 (m, 2H), 3.79 (s, 3H), 2.40−2.50 (m, 1H), 2.10−2.24 (m, 1H), 1.62−2.05 (m, 7H), 1.02−1.44 (m, 4H), 0.60−0.78 (m, 1H); HRMS (TOF MS ES$^+$) calcd for $C_{25}H_{30}NO_2$ (M + H)$^+$ 376.2277, found 376.2278.

General Procedure for the Synthesis of the Enantiomers of 5-(3-Methoxyphenyl)-2-(((*trans* or *cis*)-2-phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonane ((+)- and (−)-25 through 28).[2] Red-Al (65%, 2.0 equiv) was added dropwise to a solution of chiral amide (2−3 mmol) in anhydrous THF (80 mL) under argon at room temperature, and the mixture was stirred for 1 h at room temperature. The reaction was quenched with saturated Na_2CO_3 (20 mL), and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of solvent in vacuo, the residue was purified by silica gel column chromatography using hexanes/EtOAc/acetone (60/35/5).

(1*R*,5*S*)-5-(3-Methoxyphenyl)-2-(((1′*S*,2′*S*)-2-phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonane ((+)-25)). Yield, 98% as a light yellow oil; $[\alpha]_D^{20}$ +204.0° (*c* 0.83, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.19−7.28 (m, 3H), 7.10−7.16 (m, 1H), 7.03−7.08 (m, 2H), 6.91−6.96 (m, 1H), 6.89 (t, 1H, *J* = 2.4 Hz), 6.72 (ddd, 1H, *J* = 8.1, 2.7, 0.90 Hz), 3.79 (s, 3H), 3.26 (m, 1H), 2.98−3.06 (m, 2H), 2.79 (dd, 1H, *J* = 12.6, 5.7 Hz), 2.49 (dd, 1H, *J* = 12.6, 7.2 Hz), 1.84−2.18 (m, 7H), 1.56−1.76 (m, 3H), 1.20−1.42 (m, 2H), 0.95 (dt, 1H, *J* = 8.4, 5.1 Hz), 0.86 (dt, 1H, *J* = 8.4, 5.1 Hz); ^{13}C NMR ($CDCl_3$) δ 158.64, 154.11, 143.30, 129.26, 128.47, 125.89, 125.58, 117.48, 111.55, 110.47, 60.47, 55.34, 52.95, 49.63, 39.12, 38.63, 37.61, 35.33, 25.07, 23.21, 23.09, 22.16, 14.99; HRMS (TOF MS ES$^+$) calcd for $C_{25}H_{32}NO$ (M + H)$^+$ 362.2484, found 362.2495.

(1*S*,5*R*)-5-(3-Methoxyphenyl)-2-(((1′*R*,2′*R*)-2-phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonane ((−)-25). Yield, 94% as a light yellow oil; $[\alpha]_D^{20}$ −202.5° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.19−7.28 (m, 3H), 7.10−7.16 (m, 1H), 7.03−7.08 (m, 2H), 6.91−6.96 (m, 1H), 6.89 (t, 1H, *J* = 2.4 Hz), 6.71 (ddd, 1H, *J* = 8.1, 2.7, 0.90 Hz), 3.79 (s, 3H), 3.25 (m, 1H), 2.97−3.06 (m, 2H), 2.79 (dd, 1H, *J* = 12.6, 5.7 Hz), 2.49 (dd, 1H, *J* = 12.6, 7.2 Hz), 1.84−2.18 (m, 7H), 1.56−1.76 (m, 3H), 1.20−1.42 (m, 2H), 0.94 (dt, 1H, *J* = 8.4, 5.1 Hz), 0.85 (dt, 1H, *J* = 8.4, 5.1 Hz); ^{13}C NMR ($CDCl_3$) δ 159.46, 153.93, 143.11, 129.00, 128.22, 125.66, 125.32, 117.24, 111.30, 110.22, 60.27, 55.09, 52.72, 49.39, 38.95, 38.41, 37.43, 35.10, 24.88, 22.96, 22.87, 22.01, 14.77; HRMS (TOF MS ES$^+$) calcd for $C_{25}H_{32}NO$ (M + H)$^+$ 362.2484, found 362.2495.

(1*S*,5*R*)-5-(3-Methoxyphenyl)-2-(((1′*S*,2′*S*)-2-phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonane ((+)-26)). Yield, 98% as light yellow oil; $[\alpha]_D^{20}$ +230.1° (*c* 0.90, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.20−7.28 (m, 3H), 7.12−7.17 (m, 1H), 7.03−7.07 (m, 2H), 6.92−6.96 (m, 1H), 6.89 (t, 1H, *J* = 2.4 Hz), 6.72 (ddd, 1H, *J* = 8.4, 2.4, 0.9 Hz), 3.79 (s, 3H), 3.27 (m, 1H), 3.02 (dd, 2H, *J* = 9.6, 3.9 Hz), 2.74 (dd, 1H, *J* = 12.6, 6.3 Hz), 2.56 (dd, 1H, *J* = 12.6, 6.3 Hz), 1.80−2.20 (m, 8H), 1.56−1.76 (m, 3H), 1.20−1.44 (m, 2H), 0.98 (dt, 1H, *J* = 8.4, 5.1 Hz), 0.87 (dt, 1H, *J* = 8.4, 5.1 Hz); ^{13}C NMR ($CDCl_3$) δ 159.70, 154.15, 143.39, 129.27, 128.51, 125.83, 125.58, 117.46, 111.52, 110.50, 59.99, 55.35, 51.95, 49.99, 39.11, 38.61, 37.66, 35.33, 24.82, 23.12, 22.46, 22.29, 15.60; HRMS (TOF MS ES$^+$) calcd for $C_{25}H_{32}NO$ (M + H)$^+$ 362.2484, found 362.2480.

(1*R*,5S)-5-(3-Methoxyphenyl)-2-(((1′*R*,2′*R*)-2-phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonane ((−)-26). Yield, 97% as a light yellow oil; $[\alpha]_D^{20}$ −232.0° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.20−7.29 (m, 3H), 7.10−7.18 (m, 1H), 7.02−7.08 (m, 2H), 6.91−6.96 (m, 1H), 6.89 (t, 1H, *J* = 2.4 Hz), 6.71 (ddd, 1H, *J* = 8.4, 2.4, 0.9 Hz), 3.79 (s, 3H), 3.27 (m, 1H), 3.02 (dd, 2H, *J* = 9.6, 3.9 Hz), 2.74 (dd, 1H, *J* = 12.6, 6.3 Hz), 2.56 (dd, 1H, *J* = 12.6, 6.3 Hz), 1.80−2.20 (m, 8H), 1.56−1.76 (m, 3H), 1.20−1.40 (m, 2H), 0.98 (dt, 1H, *J* = 8.4, 5.1 Hz), 0.87 (dt, 1H, *J* = 8.4, 5.1 Hz); ^{13}C NMR ($CDCl_3$) δ 159.48, 153.97, 143.21, 129.04, 128.28, 125.60, 125.35, 117.25, 111.30, 110.27, 59.81, 55.12, 51.75, 49.77, 38.93, 38.41, 37.49, 35.13, 24.64, 22.90, 22.22, 22.13, 15.39; HRMS (ESI) calcd for $C_{25}H_{32}NO$ (M + H)$^+$ 362.2484, found 362.2469.

(1*R*,5*S*)-5-(3-Methoxyphenyl)-2-(((1′*S*,2′*R*)-2-phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonane ((+)-27)). Yield, 93% as a light yellow oil; $[\alpha]_D^{20}$ +15.4° (*c* 0.35, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.14−7.32 (m, 6H), 6.90−6.95 (m, 1H), 6.87 (t, 1H, *J* = 2.4 Hz), 6.71 (ddd, 1H, *J* = 7.8, 2.4, 0.9 Hz), 3.79 (s, 3H), 3.23 (m, 1H), 2.70−2.80 (m, 2H), 2.50 (dd, 1H, *J* = 12.9, 5.1 Hz), 1.64−2.22 (m, 9H), 1.48−1.62 (m, 2H), 1.22−1.36 (m, 2H), 1.09 (dt, 1H, *J* = 5.1, 8.1 Hz), 0.84 (q, 1H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 159.67, 154.27, 139.32, 129.22, 129.19, 128.07, 125.92, 117.47, 111.53, 110.41, 55.33, 54.62, 51.77, 49.58, 38.95, 38.64, 37.58, 35.30, 24.83, 22.93, 20.51, 17.62, 9.75; HRMS (TOF MS ES$^+$) calcd for $C_{25}H_{32}NO$ (M + H)$^+$ 362.2484, found 362.2490.

(1*S*,5*R*)-5-(3-Methoxyphenyl)-2-(((1′*R*,2′*S*)-2-phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonane ((−)-27). Yield, 94% as a light yellow oil; $[\alpha]_D^{20}$ −15.2° (*c* 0.50, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.15−7.31 (m, 6H), 6.89−6.94 (m, 1H), 6.87 (t, 1H, *J* = 2.4 Hz), 6.71 (ddd, 1H, *J* = 7.8, 2.4, 0.9 Hz), 3.79 (s, 3H), 3.23 (m, 1H), 2.70−2.79 (m, 2H), 2.49 (dd, 1H, *J* = 12.9, 5.4 Hz), 1.64−2.22 (m, 9H), 1.50−1.62 (m, 2H), 1.22−1.36 (m, 2H), 1.08 (dt, 1H, *J* = 4.8, 8.1 Hz), 0.84 (q, 1H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 159.66, 154.26, 139.31, 129.21, 129.18, 128.06, 125.92, 117.46, 111.52, 110.41, 55.32, 54.62, 51.76, 49.57, 38.95, 38.63, 37.57, 35.30, 24.82, 22.92, 20.51, 17.62, 9.75; HRMS (TOF MS ES$^+$) calcd for $C_{25}H_{32}NO$ (M + H)$^+$ 362.2484, found 362.2485.

(1*S*,5*R*)-5-(3-Methoxyphenyl)-2-(((1′*S*,2′*R*)-2-phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonane ((+)-28). Yield, 95% as a light yellow oil; $[\alpha]_D^{20}$ +48.5° (*c* 0.60, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.14−7.32 (m, 6H), 6.90−6.95 (m, 1H), 6.88 (t, 1H, *J* = 2.4 Hz), 6.72 (ddd, 1H, *J* = 7.8, 2.4, 0.9 Hz), 3.79 (s, 3H), 2.82−3.04 (m, 3H), 2.54 (dd, 1H, *J* = 12.9, 5.1 Hz), 1.64−2.23 (m, 9H), 1.48−1.62 (m, 2H), 1.04−1.36 (m, 3H), 0.83 (q, 1H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 159.66, 154.25, 139.27, 129.29, 129.22, 128.09, 125.92, 117.47, 111.55, 110.39, 55.53, 55.33, 52.70, 49.58, 38.98, 38.69, 37.54, 35.27, 25.03, 23.03, 20.49, 17.61, 10.16; HRMS (TOF MS ES$^+$) calcd for $C_{25}H_{32}NO$ (M + H)$^+$ 362.2484, found 362.2489.

(1*R*,5*S*)-5-(3-Methoxyphenyl)-2-(((1′*R*,2′*S*)-2-phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonane ((−)-28)). Yield, 94% as a light yellow oil; $[\alpha]_D^{20}$ −49.1° (*c* 0.60, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.14−7.32 (m, 6H), 6.90−6.95 (m, 1H), 6.88 (t, 1H, *J* = 2.4 Hz), 6.71 (ddd, 1H, *J* = 7.8, 2.4, 0.9 Hz), 3.79 (s, 3H), 2.82−3.04 (m, 3H), 2.54 (dd, 1H, *J* = 12.9, 5.1 Hz), 1.64−2.23 (m, 9H), 1.48−1.62 (m, 2H), 1.04−1.36 (m, 3H), 0.83 (q, 1H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 159.66, 154.28, 139.32, 129.30, 129.22, 128.09, 125.92, 117.47, 111.56, 110.39, 55.54, 55.33, 52.72, 49.58, 39.02, 38.71, 37.58, 35.29, 25.07, 23.03, 20.51, 17.67, 10.15; HRMS (TOF MS ES$^+$) calcd for $C_{25}H_{32}NO$ (M + H)$^+$ 362.2484, found 362.2491.

General Procedure for the Synthesis of the *N*-(2-Phenylcyclopropyl)methyl enantiomers of (+)- and (−)-2-azabicyclo[3.3.1]-nonan-5-yl)phenol ((+)- and (−)-29 through 32). The enantiomeric methoxyphenyl ether (1−2 mmol, ((+)- and (−)-**25** through **28**), 48% hydrogen bromide (2 mL), and acetic acid (3 mL) were refluxed for 30 min to 1 h under argon. The acetic acid was removed in vacuo, and the residue was neutralized with saturated $NaHCO_3$ to pH 10. The mixture was extracted with 5% propan-2-ol in CH_2Cl_2 (3 × 30 mL). The combined extracts were washed with H_2O and brine and dried over Na_2SO_4. After removal of solvent, the residue was purified by silica gel column chromatography using hexanes/EtOAc/EtOH (40/28/2) to give the phenolic amide products.

3-((1*R*,5*S*)-2-(((1′*S*,2′*S*)-2-Phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonan-5-yl)phenol ((+)-29). Yield, 60% as HCl salt; mp 232−234 °C (dec); $[\alpha]_D^{20}$ +62.0° (*c* 0.38, MeOH); ^{1}H NMR ($CDCl_3$, free base) δ 7.22 (br-s, 1H), 7.19 (br-s, 1H), 7.08−7.16 (m, 1H), 7.03 (br-s, 1H), 7.01 (br-s, 1H), 6.99 (d, 1H, *J* = 8.1 Hz), 6.76 (d, 1H, *J* = 8.1 Hz), 6.70 (t, 1H, *J* = 1.8 Hz), 6.48 (dd, 1H, *J* = 7.8, 2.4 Hz), 3.30 (br-s, 1H), 2.90−3.10 (m, 2H), 2.83 (dd, 1H, *J* = 12.6, 5.7 Hz), 2.49 (dd, 1H, *J* = 12.6, 5.7 Hz), 2.15 (br-t, 2H, *J* = 12.6 Hz), 1.50−2.02 (m, 8H), 1.24−1.46 (m, 2H), 0.96 (dt, 1H, *J* = 8.7, 5.1 Hz), 0.87 (dt, 1H, *J* = 8.7, 5.1 Hz); ^{13}C NMR ($CDCl_3$, free base) δ 156.61, 153.59, 142.95, 129.31, 128.51, 125.89, 125.65, 116.93, 113.88, 113.20, 60.15, 52.77, 49.69, 38.35, 37.06, 34.89, 24.50, 23.31, 23.07, 21.46, 14.95; HRMS (TOF MS ES$^+$) calcd for $C_{24}H_{30}NO$ (M + H)$^+$ 348.2327, found 348.2327. Anal. ($C_{23}H_{29}NO\cdot HCl\cdot 0.25H_2O$) C, H, N.

3-((1*S*,5*R*)-2-(((1′*R*,2′*R*)-2-Phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonan-5-yl)phenol ((−)-29). Yield, 60% as HCl salt; mp 222−224 °C (dec); $[\alpha]_D^{20}$ −62.6° (*c* 0.52, MeOH); ^{1}H NMR ($CDCl_3$, free base) δ 7.08−7.30 (m, 4H), 6.96−7.06 (m, 2H), 6.68−6.80 (m, 2H), 6.49 (dd, 1H, *J* = 8.1, 2.1 Hz), 3.30 (br, 1H), 2.90−3.10 (m, 2H), 2.84 (dd, 1H, *J* = 12.6, 5.7 Hz), 2.49 (dd, 1H, *J* = 12.6, 7.2 Hz), 2.15 (br-t, 2H, *J* = 12.6 Hz),

1.50−2.02 (m, 8H), 1.20−1.46 (m, 2H), 0.94 (dt, 1H, J = 8.7, 5.1 Hz), 0.87 (dt, 1H, J = 8.7, 5.1 Hz); ^{13}C NMR ($CDCl_3$, free base) δ 156.64, 153.52, 142.92, 129.31, 128.51, 125.89, 125.66, 116.90, 113.90, 113.21, 60.13, 52.77, 49.70, 38.34, 37.01, 34.87, 24.46, 23.32, 23.06, 21.40, 14.97; HRMS (TOF MS ES$^+$) calcd for $C_{24}H_{30}NO$ (M + H)$^+$ 348.2327, found 348.2330. Anal. ($C_{23}H_{29}NO\cdot HCl\cdot 0.25H_2O$) C, H, N.

3-((1*S*,5*R*)-2-(((1′*S*,2′*S*)-2-Phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonan-5-yl)phenol ((+)-30). Yield, 58% as HCl salt; mp 255−260 °C (dec); $[\alpha]_D^{20}$ +69.8° (*c* 0.38, MeOH); ^{1}H NMR ($CDCl_3$, free base) δ 7.22 (br-s, 1H), 7.19 (br-s, 1H), 7.09−7.16 (m, 1H), 7.05 (d, 1H, J = 8.1 Hz), 7.02 (d, 1H, J = 1.5 Hz), 6.99 (br-s, 1H), 6.76 (d, 1H, J = 8.1 Hz), 6.70 (t, 1H, J = 1.8 Hz), 6.56 (dd, 1H, J = 7.8, 2.4 Hz), 3.34 (br-s, 1H), 2.93−3.10 (m, 2H), 2.76 (dd, 1H, J = 12.6, 6.3 Hz), 2.60 (dd, 1H, J = 12.6, 6.3 Hz), 2.14 (br-t, 2H, J = 12.6 Hz), 1.50−2.02 (m, 8H), 1.24−1.46 (m, 2H), 0.96 (dt, 1H, J = 8.7, 5.1 Hz), 0.88 (dt, 1H, J = 8.7, 5.1 Hz); ^{13}C NMR ($CDCl_3$, free base) δ 156.76, 153.49, 142.94, 129.37, 128.51, 125.85, 125.68, 116.61, 113.68, 112.93, 59.59, 51.82, 49.96, 38.36, 38.21, 36.96, 34.88, 24.28, 22.99, 22.63, 21.24, 15.61; HRMS (TOF MS ES$^+$) calcd for $C_{24}H_{30}NO$ (M + H)$^+$ 348.2327, found 348.2307. Anal. ($C_{23}H_{29}NO\cdot HCl\cdot 0.25H_2O$) C, H, N.

3-((1*R*,5*S*)-2-(((1′*R*,2′*R*)-2-Phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonan-5-yl)phenol ((−)-30). Yield, 62% as HCl salt; mp 250−255 °C (dec); $[\alpha]_D^{20}$ −70.4° (*c* 0.44, MeOH); ^{1}H NMR ($CDCl_3$, free base) δ 7.22 (br-s, 1H), 7.20 (br-s, 1H), 7.09−7.16 (m, 2H), 7.06 (d, 1H, J = 8.1 Hz), 7.02 (d, 1H, J = 1.5 Hz), 6.78 (d, 1H, J = 8.1 Hz), 6.70 (t, 1H, J = 1.8 Hz), 6.56 (dd, 1H, J = 7.8, 2.4 Hz), 3.32 (m, 1H), 2.93−3.06 (m, 2H), 2.75 (dd, 1H, J = 12.6, 6.3 Hz), 2.59 (dd, 1H, J = 12.6, 6.3 Hz), 2.13 (br-t, 2H, J = 12.6 Hz), 1.50−2.02 (m, 8H), 1.24−1.46 (m, 2H), 0.97 (dt, 1H, J = 8.7, 5.1 Hz), 0.88 (dt, 1H, J = 8.7, 5.1 Hz); ^{13}C NMR ($CDCl_3$, free base) δ 156.73, 153.56, 142.98, 129.35, 128.50, 125.83, 125.65, 116.64, 113.68, 112.96, 59.63, 51.75, 49.98, 38.38, 38.26, 37.01, 34.90, 24.28, 23.03, 22.62, 21.33, 15.62; HRMS (TOF MS ES$^+$) calcd for $C_{24}H_{30}NO$ (M + H)$^+$ 348.2327, found 348.2332. Anal. ($C_{23}H_{29}NO\cdot HCl$) C, H, N.

3-((1*R*,5*S*)-2-(((1′*S*,2′*R*)-2-Phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonan-5-yl)phenol ((+)-31). Yield, 64% as HCl salt; mp 135−138 °C; $[\alpha]_D^{20}$ +4.6° (*c* 0.41, MeOH); ^{1}H NMR ($CDCl_3$, free base) δ 7.24−7.32 (m, 2H), 7.16−7.23 (m, 2H), 7.10 (t, 1H, J = 8.1 Hz), 6.76 (d, 1H, J = 8.1 Hz), 6.70 (br-t, 1H, J = 2.1 Hz), 6.58 (dd, 1H, J = 8.1, 2.1 Hz), 3.31 (br-s, 1H), 2.78−2.88 (m, 1H), 2.67 (dt, 1H, J = 5.1, 12.3 Hz), 2.57 (dd, 1H, J = 12.9, 4.8 Hz), 2.04−2.22 (m, 2H), 1.70−2.00 (m, 7H), 1.44−1.62 (m, 2H), 1.28−1.40 (m, 2H), 1.09 (dt, 1H, J = 5.1, 8.4 Hz), 0.87 (q, 1H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$, free base) δ 156.79, 153.73, 139.03, 129.33, 129.14, 128.16, 126.06, 116.73, 113.61, 113.02, 54.41, 51.82, 49.53, 38.44, 38.22, 36.98, 34.91, 24.26, 22.87, 20.46, 16.84, 9.81; HRMS (TOF MS ES$^+$) calcd for $C_{24}H_{30}NO$ (M + H)$^+$ 348.2327, found 348.2339. Anal. ($C_{23}H_{29}NO\cdot HCl\cdot 0.75H_2O$) C, H, N.

3-((1*S*,5*R*)-2-(((1′*R*,2′*S*)-2-Phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonan-5-yl)phenol ((−)-31). Yield, 61% as HCl salt; mp 136−138 °C; $[\alpha]_D^{20}$ −4.8° (*c* 0.42, MeOH); ^{1}H NMR ($CDCl_3$, free base) δ 7.24−7.32 (m, 2H), 7.16−7.23 (m, 2H), 7.10 (t, 1H, J = 8.1 Hz), 6.76 (d, 1H, J = 8.1 Hz), 6.71 (br-t, 1H, J = 2.1 Hz), 6.59 (dd, 1H, J = 8.1, 2.1 Hz), 3.31 (br-s, 1H), 2.78−2.88 (m, 1H), 2.67 (dt, 1H, J = 4.8, 12.3 Hz), 2.57 (dd, 1H, J = 12.9, 4.8 Hz), 2.02−2.22 (m, 3H), 1.70−2.02 (m, 6H), 1.44−1.62 (m, 2H), 1.26−1.40 (m, 2H), 1.08 (dt, 1H, J = 5.1, 8.1 Hz), 0.87 (q, 1H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$, free base) δ 156.75, 153.76, 139.05, 129.34, 129.14, 128.16, 126.06, 116.77, 113.60, 113.02, 54.43, 51.82, 49.54, 38.45, 38.24, 37.00, 34.93, 24.27, 22.88, 20.46, 16.87, 9.81; HRMS (TOF MS ES$^+$) calcd for $C_{24}H_{30}NO$ (M + H)$^+$ 348.2327, found 348.2321. Anal. ($C_{23}H_{29}NO\cdot HCl\cdot 1.0H_2O$) C, H, N.

3-((1*S*,5*R*)-2-(((1′*S*,2′*R*)-2-Phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonan-5-yl)phenol ((+)-32). Yield, 61% as HCl salt. Mp 157−160 °C; $[\alpha]_D^{20}$ +69.5° (*c* 0.60, MeOH); ^{1}H NMR ($CDCl_3$, free base) δ 7.14−7.30 (m, 4H), 7.10 (t, 1H, J = 8.1 Hz), 6.77 (d, 1H, J = 8.1 Hz), 6.71 (br-t, 1H, J = 2.1 Hz), 6.58 (dd, 1H, J = 8.1, 2.1 Hz), 3.13 (br-s, 1H), 2.98−3.08 (m, 1H), 2.87 (dt, 1H, J = 5.1, 12.3 Hz), 2.65 (dd, 1H, J = 12.9, 4.2 Hz), 2.04−2.22 (m, 2H), 1.70−2.00 (m, 7H), 1.44−1.62 (m, 2H), 1.30−1.40 (m, 1H), 1.16−1.24 (m, 1H), 1.09 (dt, 1H, J = 5.1, 8.4 Hz), 0.87 (q, 1H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$, free base) δ 156.80, 153.70, 138.99, 129.34, 129.23, 128.22, 126.07, 116.66, 113.62, 113.00, 55.49, 52.61, 49.75, 38.50, 38.31, 36.92, 34.92, 24.40, 23.03, 20.37, 16.74, 10.41; HRMS (TOF MS ES$^+$) calcd for $C_{24}H_{30}NO$ (M + H)$^+$ 348.2327, found 348.2334. Anal. ($C_{23}H_{29}NO\cdot HCl\cdot 1.25H_2O$) C, H, N.

3-((1*R*,5*S*)-2-(((1′*R*,2′*S*)-2-Phenylcyclopropyl)methyl)-2-azabicyclo[3.3.1]nonan-5-yl)phenol ((−)-32). Yield, 66% as HCl salt; mp 158−162 °C; $[\alpha]_D^{20}$ −70.0° (*c* 0.58, MeOH); ^{1}H NMR ($CDCl_3$, free base) δ 7.14−7.30 (m, 4H), 7.10 (t, 1H, J = 8.1 Hz), 6.77 (d, 1H, J = 8.1 Hz), 6.71 (br-t, 1H, J = 2.1 Hz), 6.58 (dd, 1H, J = 8.1, 2.1 Hz), 3.13 (br-s, 1H), 2.98−3.08 (m, 1H), 2.87 (dt, 1H, J = 5.1, 12.3 Hz), 2.65 (dd, 1H, J = 12.9, 4.2 Hz), 2.06−2.22 (m, 2H), 1.70−2.00 (m, 7H), 1.44−1.62 (m, 2H), 1.30−1.40 (m, 1H), 1.16−1.24 (m, 1H), 1.09 (dt, 1H, J = 5.1, 8.4 Hz), 0.87 (q, 1H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$, free base) δ 156.77, 153.71, 139.00, 129.33, 129.23, 128.22, 126.06, 116.68, 113.60, 112.99, 55.49, 52.60, 49.75, 38.51, 38.32, 36.94, 34.93, 24.41, 23.04, 20.38, 16.76, 10.41; HRMS (TOF MS ES$^+$) calcd for $C_{24}H_{30}NO$ (M + H)$^+$ 348.2327, found 348.2328. Anal. ($C_{23}H_{29}NO\cdot HCl\cdot 1.5H_2O$) C, H, N.

Quantum Chemistry and Superposition Study. The starting geometries of the NPCM compounds (Figure 2) and the *N*-phenylalkenyl compounds (Figure 3) were constructed from the respective X-ray structure of naltrexone and naloxone. The geometry optimization for these compounds, in their protonated form, was done in the gaseous phase with the density functional theory at the level of B3LYP/6-31G*.[16] The conformation of the cyclopropyl moiety in (+)-**29** and (+)-**31** as well as the alkenyl in (−)-**6** (1*R*,5*S*)-(*E*) and (−)-**9** (1*R*,5*S*)-(*Z*) was assumed to resemble the respective conformation of these moieties shown in the X-ray structure of naltrexone and naloxone; thus, a conformation search was not carried out to find the lowest energy conformer for these compounds. However, the conformation of the *N*-cyclopropylmethyl moiety in (+)-**30** and (−)-**32** was varied by changing the dihedral angles of C1−N−C−C1′ and N−C−C1′−C2′, and their respective low energy conformers were chosen after the geometry optimization. For the superposition study, the optimized structures of the NPCM compounds (+)-**29**, (−)-**30**, (+)-**31**, and (−)-**32** in Figure 2 were overlaid onto naltrexone while the *N*-phenylalkenyl compounds (−)-**6** (1*R*,5*S*)-(*E*) and (−)-**9** (1*R*,5*S*)-(*Z*) were overlaid onto naloxone with the rigid fit of Quanta 2008 (Accelrys) using the nine heavy atoms of the phenylmorphan as a common docking site. The root-mean-square deviations of such fit for each compound were all less than 0.12 Å. The root-mean-square deviation for the rigid fit of the optimized naloxone to the optimized naltrexone was less than 0.01 Å.

Binding and Efficacy Assays. Cell Culture and Membrane Preparation. As noted previously,[17] the recombinant CHO cells (hMOR-CHO, hDOR-CHO, and hKOR-CHO) were produced by stable transfection with the respective human opioid receptor cDNA and were provided by Dr. Larry Toll (SRI International, CA). The cells were grown on plastic flasks in DMEM (100%) (hDOR-CHO and hKOR-CHO) or DMEM/F-12 (50%/50%) medium (hMOR-CHO) containing 10% FBS, and G-418 (0.10−0.2 mg/mL) under 95% air/5% CO_2 at 37 °C. Cell monolayers were harvested and frozen at −80 °C.

[^{35}S]GTP-γ-S Binding Assays. The assays were conducted with minor modifications of published methods.[18] In this description, buffer "A" is 50 mM Tris-HCl, pH 7.4, containing 100 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA and buffer "B" is buffer A plus 1.67 mM DTT and 0.15% BSA. On the day of the assay,

cells were thawed on ice for 15 min and homogenized using a Polytron in 50 mM Tris-HCl, pH 7.4, containing 4 μg/mL leupeptin, 2 μg/mL chymostatin, 10 μg/mL bestatin, and 100 μg/mL bacitracin. The homogenate was centrifuged at 30000*g* for 10 min at 4 °C and the supernatant discarded. The membrane pellets were resuspended in buffer B and used for [^{35}S]GTP-γ-S binding assays. Test tubes received the following additions: 50 μL of buffer A plus 0.1% BSA, 50 μL of GDP in buffer A/0.1% BSA (final concentration of 40 μM), 50 μL of drug in buffer A/0.1% BSA, 50 μL of [^{35}S]-GTP-γ-S in buffer A/0.1% BSA (final concentration of 50 pM), and 300 μL of cell membranes (50 μg of protein) in buffer B. The final concentrations of reagents in the [^{35}S]GTP-γ-S binding assays were 50 mM Tris-HCl, pH 7.4, containing 100 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA, 1 mM DTT, 40 μM GDP, and 0.1% BSA. Incubations proceeded for 3 h at 25 °C. Nonspecific binding was determined using GTP-γ-S (40 μM). Bound and free [^{35}S]GTP-γ-S were separated by vacuum filtration (Brandel) through GF/B filters. The filters were punched into 24-well plates to which was added 0.6 mL of LSC-cocktail (Cytoscint). Samples were counted, after an overnight extraction, in a Trilux liquid scintillation counter at 27% efficiency.

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Supporting Information Available: Elemental analysis for compounds (+)- and (−)-**6**, (+)- and (−)-**9**, and (+)- and (−)-**29**−**32**; additional data for Table 1 on opioid receptor binding. This material is available free of charge via the Internet at http://pubs.acs.org.

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