Articles

Elucidation of the Bioactive Conformation of the *N*-Substituted *trans*-3,4-Dimethyl-4-(3-hydroxyphenyl)piperidine Class of μ-Opioid Receptor Antagonists

Bertrand Le Bourdonnec,*[,†] Allan J. Goodman,[†,‡] Mathieu Michaut,[†,§] Hai-Fen Ye,[†] Thomas M. Graczyk,[∥] Serge Belanger,[∥] Torsten Herbertz,[†] Glenn P. A. Yap,[⊥] Robert N. DeHaven,[∥] and Roland E. Dolle[†]

Department of Chemistry and Pharmacology, Adolor Corporation, 700 Pennsylvania Drive, Exton, Pennsylvania 19341, and Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716

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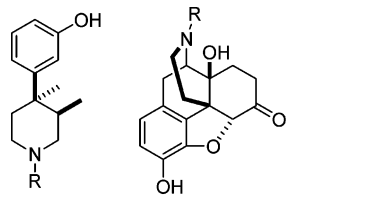
The series of *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines have been widely investigated as opioid receptor antagonists. One of our research goals was to explore the bioactive conformation of the *N*-phenethyl *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine derivative **3**, prototypical μ-opioid antagonist in this series. In this effort, the rotational degrees of freedom of the *N*-substituent of **3** were limited by incorporation of an ethylene bridge between the piperidine 2- or 6-position of **3** and the benzylic position of the *N*-phenethyl moiety. The overall modification led to a novel series of fused bicyclic derivatives of the octahydroquinolizine chemical class, conformationally restricted analogue of **3**. The constrained analogues **6** and **9** showed high affinity toward the μ-opioid receptor. Compound **6** was found to be a μ-opioid antagonist, whereas the constrained analogue **9** displayed potent μ-agonist activity in vitro. This study provides additional information about the molecular determinants for μ recognition, the structural features affecting ligand binding, and the structure function relationships.

Introduction

It is now well-established that a family of G protein-coupled seven transmembrane receptors, designated μ-, κ-, and δ-opioid receptors, mediates the actions of endogenous opioid peptides. In the central, peripheral, and enteric nervous systems, activation of opioid receptors by endogenous opioid peptides plays an important role in both behavioral and homeostatic functions, including nociception, reward, respiration, food intake, and gastrointestinal motility.[1] Thus, opioid antagonists may find therapeutic uses in a number of areas. In particular, these types of compounds could be effective in the treatment of obesity, alcohol dependence, psychosis, depression, and irritable bowel syndrome.[2−7] In 1978, Zimmerman and co-workers described the discovery of opioid antagonist activity in a series of *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**1**).[8] These 4-phenyl piperidine antagonists were structurally unique, since prior to their discovery, opioid antagonists were generally *N*-allyl or *N*-cyclopropylmethyl analogues of oxymorphone (naloxone, **2a**, and naltrexone, **2b**, respectively).

The opioid antagonist activity in the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines was a consequence of substitution at the 3-position of the piperidine ring. The structure−activity relationship (SAR) in this *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine series has focused largely on the substitution of the piperidine nitrogen.[9−12] Hence, it has been determined that maximum potency and selectivity for the μ-opioid receptor was achieved when the *N*-substituent incorporated a lipophilic entity



(phenyl or cyclohexyl rings) separated from the piperidine nitrogen by two or three atoms.[9] A more thorough understanding of the conformational requirements of the *N*-substituent was also investigated using semirigid derivatives.[12] The (+)-*N*-phenethyl *trans*-3(*R*),4(*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine (**3**, Figure 1) has been previously reported to bind cloned human opioid receptors with good affinity [$K_i(\mu) = 1.8$ nM; $K_i(\kappa) = 17$ nM; $K_i(\delta) = 33$ nM].[13] As a result of the fact that the whole phenethyl side chain of **3** can freely rotate relative to the piperidine ring, it is not possible to pinpoint the exact location of this binding site relative to the rest of the molecule. The goal of the current studies was to investigate the bioactive conformation of the prototypical *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine μ-opioid receptor antagonist **3**. In this effort, the design of more structurally constrained molecules was undertaken. Thus, we have carried out a further structural rigidification on this template by linking the piperidine 2- or 6-position of **3** to the benzylic position of the *N*-phenethyl moiety by an ethylene chain linker. This modification yielded a novel series of fused bicyclic structures **4**−**11** (Figure 1). We now wish to report the synthesis, the opioid receptor binding properties, the in vitro functional activity, and the modeling study of this novel series of octahydroquinolizine derivatives.

* To whom correspondence should be addressed. Tel.: 1-484-595-1061. Fax: 1-484-595-1551. E-mail: blebourdonnec@adolor.com.
† Department of Chemistry, Adolor Corporation.
‡ Postdoctoral fellow, 2004−2005.
§ Postdoctoral fellow, 2001−2003.
∥ Department of Pharmacology, Adolor Corporation.
⊥ University of Delaware.

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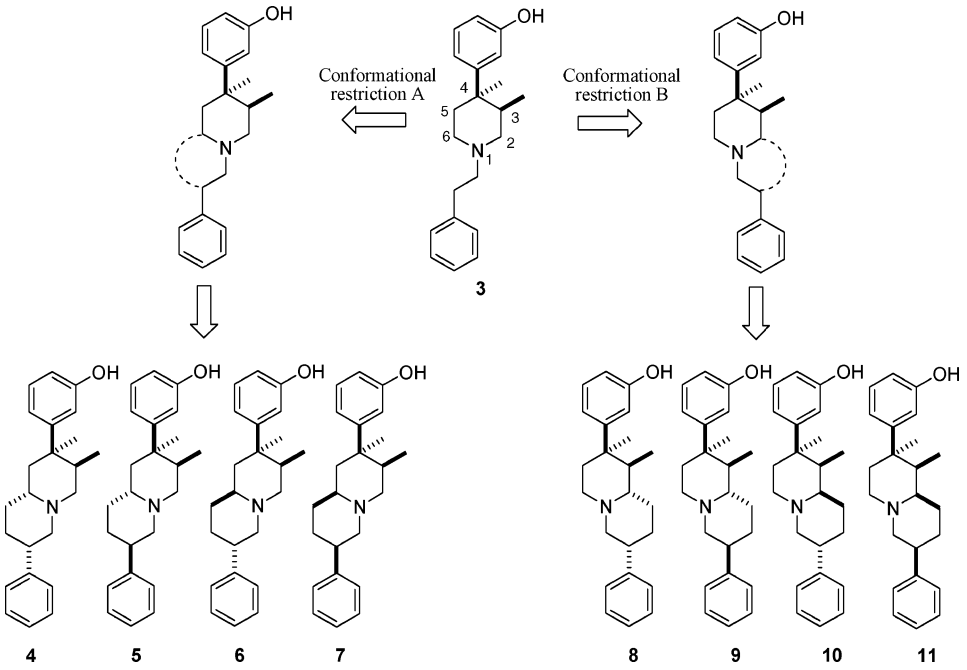
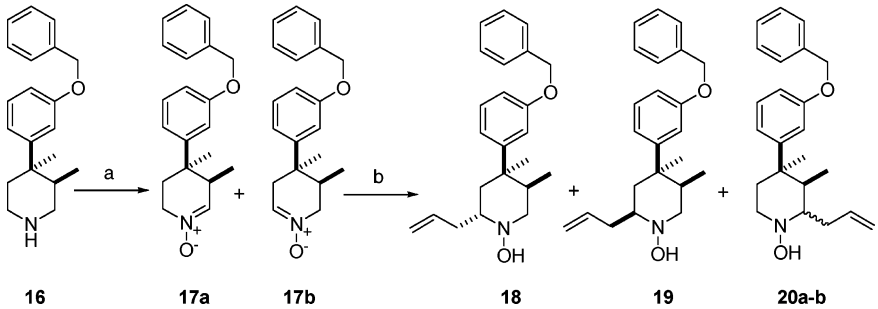


Figure 1. Structures of compounds **4**−**11**, constrained analogues of **3**.

Scheme 1. Synthesis of Key Intermediates **18**, **19**, **20a**,**b**[a]



[a] Reagents and conditions: (a) Na_2WO_4, H_2O_2, $H_2O/CH_2Cl_2/CH_3OH$, 0−25 °C, 68%; (b) $CH_2{=}CHCH_2MgCl$, THF, 0−25 °C, 56% (**18**), 8% (**19**), 11% (**20a**,**b**).

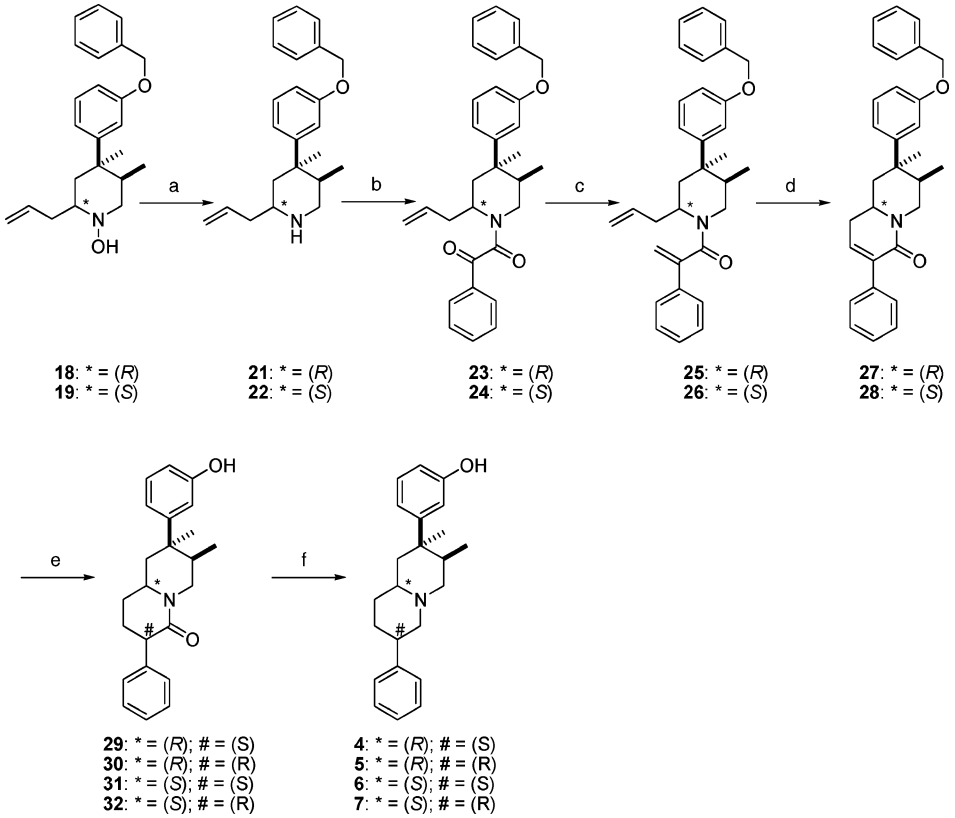
Chemistry

The structures and synthesis of the octahydroquinolizine derivatives **4**−**11** and related analogues **12**−**15** prepared in this investigation are shown in Schemes 1−5. The synthesis of intermediates **18**, **19**, and **20a**,**b** is outlined in Scheme 1. The key step of the chemistry relied on the addition of allylmagnesium chloride to the nitrone derived from (+)-(3*R*,4*R*)-4-(3-(benzyloxy)phenyl)-3,4-dimethylpiperidine (**16**).[12] Oxidation of **16** using sodium tungstate and hydrogen peroxide provided a mixture of nitrones **17a**/**17b** (1:4 ratio, as determined by ^{1}H NMR) that could not be separated by column chromatography.[14] Addition of allylmagnesium chloride to the mixture **17a**/**17b** provided the hydroxylamine derivatives **18**, **19**, and **20a**,**b** that were separated by column chromatography and isolated in 56, 8, and 11% yield, respectively.

Treatment of **18** with zinc powder in acetic acid under sonication conditions afforded the 2α-allyl piperidine derivative **21** (Scheme 2). The absolute regio- and stereochemistry of 3-((2*R*,4*R*,5*R*)-4,5-dimethyl-2-propylpiperidin-4-yl)phenol, obtained from **21** by hydrogenation, was determined by X-ray crystallography,[14] therefore establishing the absolute configuration of **21**. Coupling of **21** with benzoylformic acid in the presence of *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) gave the derivative **23**. This material reacted with the Wittig reagent, potassium methylenetriphenylphosphorane, under standard reaction conditions to provide the diolefin **25**. Ring-closing metathesis (RCM) of compound **25** using a catalytic amount of Grubbs' second-generation catalyst, in refluxing methylene chloride, gave the cyclized compound **27**. Hydrogenation of **27** using palladium on activated carbon generated compounds **29** and **30**, which were separated by column chromatography. Reduction of compound **29** with borane−dimethyl sulfide complex provided the target compound **4**. Similar treatment of compound **30** produced the octahydroquinolizine derivative **5**. Compounds **6** and **7** were prepared from **19** according to synthetic procedures similar to those described for the synthesis of **4** and **5**. The absolute regio- and stereochemistry of the lactam derivative **31** was determined by X-ray crystallography (Figure 2).[15] This crystal structure established by inference the absolute configuration of **32**, the diastereomeric analogue of **31**, the synthetic precursors **19**, **22**, **24**, **26**, and **28**, and the final compounds **6** and **7**.

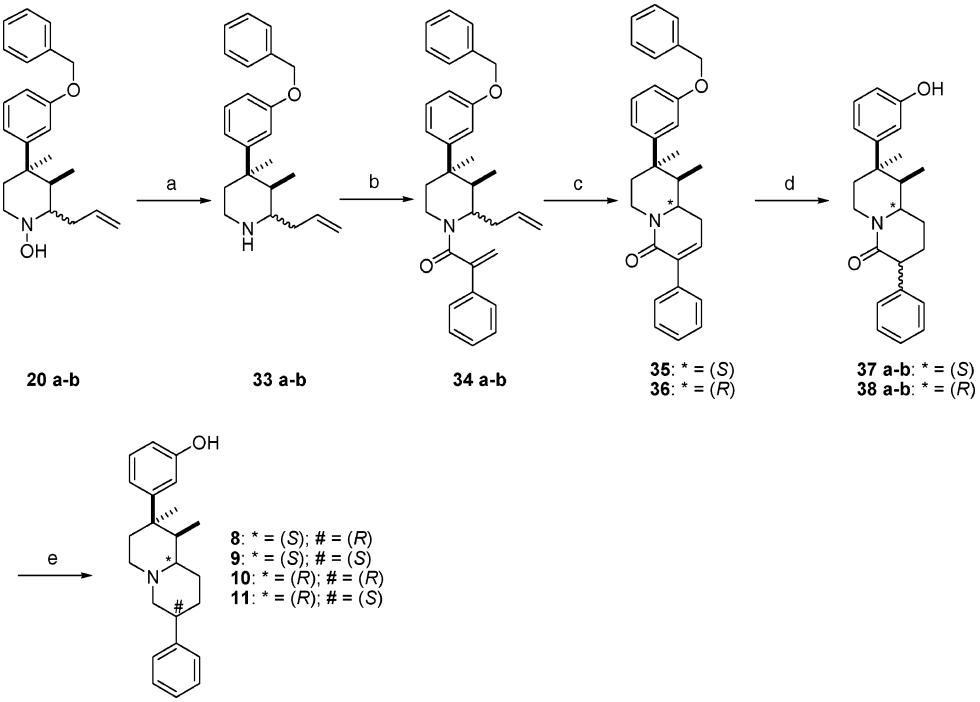
Compounds **8**−**11** were synthesized utilizing similar chemistry to that employed in the synthesis of compounds **4**−**7**, with the exception that the diolefins **34a**,**b**, were prepared in a single-step procedure by condensation of **33a**,**b** with 2-phenylacrylic acid in the presence of TBTU (Scheme 3). The mixture of diastereoisomers **20a**,**b**, **33a**,**b**, or **34a**,**b** could not be separated by column chromatography. However, ring-closing metathesis

Scheme 2. Synthesis of **4**−**7**[a]



[a] Reagents and conditions: (a) Zn, CH_3CO_2H/H_2O, sonication, 25 °C, 96% (**21**), 59% (**22**); (b) $C_6H_5COCO_2H$, TBTU, *i*-Pr_2EtN, CH_3CN, 25 °C, 74% (**23**), 26% (**24**); (c) $(Ph)_3PCH_3Br$, *t*-BuOK, THF, C_6H_6, reflux, 56% (**25**), 71% (**26**); (d) Grubbs' catalyst (second-generation), CH_2Cl_2, 25 °C, 65% (**27**), 95% (**28**); (e) H_2, Pd/C, C_2H_5OH, 25 °C, 59% (**29**), 27% (**30**), 55% (**31**), 15% (**32**); (f) $BH_3S(CH_3)_2$, THF, reflux, 73% (**4**), 66% (**5**), 83% (**6**), 78%d (**7**).

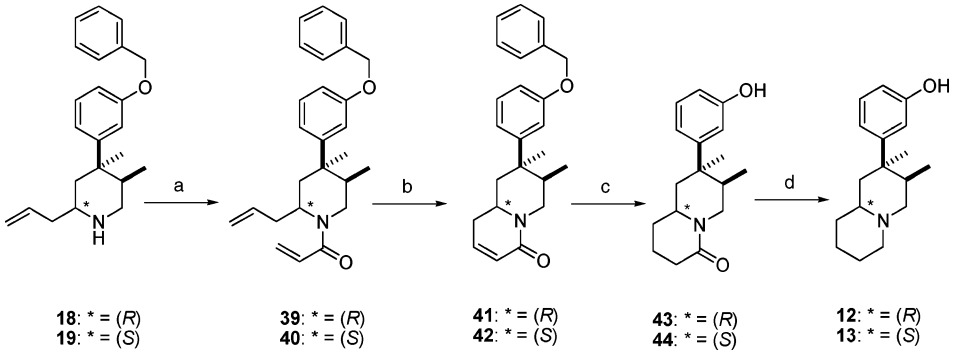
Scheme 3. Synthesis of **8**−**11**[a]



[a] Reagents and conditions: (a) Zn, CH_3CO_2H/H_2O, sonication, 25 °C, 92%; (b) $C_6H_5(C{=}CH_2)CO_2H$, TBTU, *i*-Pr_2EtN, CH_3CN, 25 °C, 76%; (c) Grubbs' catalyst (second-generation), CH_2Cl_2, 25 °C, 45% (**35**), 31% (**36**); (d) H_2, Pd/C, C_2H_5OH, 25 °C, 55% (**37a**,**b**), 79% (**38a**,**b**); (e) $BH_3S(CH_3)_2$, THF, reflux, 46% (**8**), 26% (**9**), 13% (**10**), 8% (**11**).

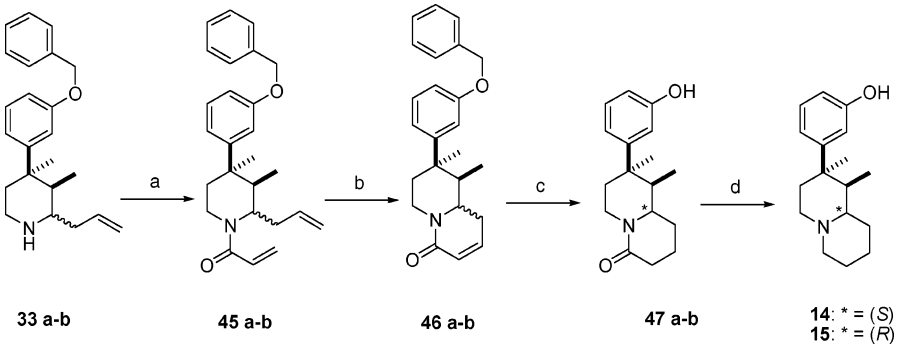
of the diastereomeric mixture **34a**,**b** gave the α,*β*-unsaturated lactam derivatives **35** and **36**, which were readily separated by column chromatography. Hydrogenation of **35** and **36** provided the diastereomeric mixtures **37a**,**b** and **38a**,**b**, respectively. Borane reduction of **37a**,**b** provided the target compounds **8** and **9**, which were separated by column chromatography. Similar

Scheme 4. Synthesis of **12-13**[a]



[a] Reagents and conditions: (a) CH_2=CHCOCl, Et_3N, CH_2Cl_2, 25 °C, 52% (**39**), 45% (**40**); (b) Grubbs' catalyst (second-generation), CH_2Cl_2, 25 °C, 74% (**41**), 95% (**42**); (c) H_2, Pd/C, C_2H_5OH, 25 °C, 100% (**43**), 100% (**44**); (d) $BH_3S(CH_3)_2$, THF, reflux, 41% (**12**), 26% (**13**).

Scheme 5. Synthesis of **14**−**15**[a]



[a] Reagents and conditions: (a) CH_2=CHCOCl, Et_3N, CH_2Cl_2, 25 °C, 65%; (b) Grubbs' catalyst (second-generation), CH_2Cl_2, 25 °C, 100%; (c) H_2, Pd/C, C_2H_5OH, 25 °C, 85%; (d) $BH_3S(CH_3)_2$, THF, reflux, 6% (**14**), 15% (**15**).

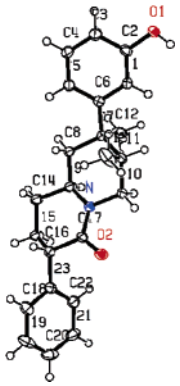


Figure 2. X-ray structure of **31** showing labeling of the nonhydrogen atoms. Displacement ellipsoids are at the 20% probability level.

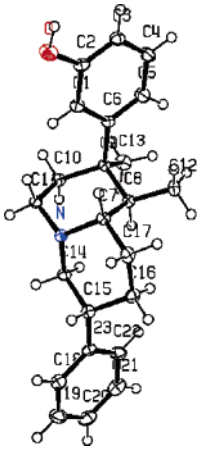


Figure 3. X-ray structure of **8** showing labeling of the nonhydrogen atoms. Displacement ellipsoids are at the 20% probability level.

treatment of the diastereomeric mixture **38a**,**b** produced compounds **10** and **11**. The absolute regio- and stereochemistry of the target compound **8** was also determined by X-ray crystallography (Figure 3),[16] thereby establishing by inference the absolute configuration of its diastereomeric analogue **9**.

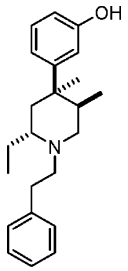
The synthesis of compounds **12** and **13** is outlined in Scheme 4. Condensation of **18** or **19** with acryloyl chloride, followed by ring-closing metathesis of the resulting acrylamide derivatives **39** and **40**, provided the α,β-unsaturated lactam derivatives **41** and **42,** respectively. Hydrogenation of **41** or **42**, followed by borane reduction of the resulting lactams **43** and **44**, provided the compounds **12** and **13**, respectively. The target compounds **14** and **15** were prepared from **33a**,**b**, according to synthetic procedures similar to those described for the synthesis of **12** and **13** (Scheme 5).

Results and Discussion

The synthesis of conformationally restricted analogues of a lead compound often results in improvement of the specific binding affinity for the target molecule.[17−19] A highly conformationally constrained molecule shaped to the complementary binding site of the protein is expected to exhibit high affinity due to the less entropic penalty encountered (compared to the flexible molecule). Restricting the conformation of a biologically active compound is also effective in determining the bioactive conformation.[19] Because the three-dimensional structure of the μ-opioid receptor is not known, one theoretical solution to elucidate the bioactive conformation of a ligand bound to the μ-opioid receptor is to develop sufficiently structurally con-

strained active molecules so as to "freeze" conformational flexibility to a minimum degree. These constrained molecules can then be used as a template for determination of the bioactive conformation for the lesser-constrained version of molecules belonging to the same subset of structures. In view of these considerations, we pursued the approach of conformationally constrained molecules as a mimic of the bioactive conformation and as the basis for designing new μ-opioid receptor antagonists. Compound **3** was an appropriate molecule on which one could apply the concept of conformationally constrained structures as mimics of the bioactive conformation. In this study, the rotational degrees of freedom of the *N*-substituent of **3** were limited by incorporation of an ethylene bridge between the piperidine 2- or 6-position of **3** and the benzylic position of the *N*-phenethyl moiety. The overall modification led to a novel series that may represent a conformationally constrained analogue of **3** and could be a mimic of its bioactive conformation. The derivatives **2**−**15** were tested for their affinities toward the cloned human μ-, δ-, and κ-opioid receptors as measured by their abilities to displace [^{3}H]-diprenorphine from its specific binding sites (see also Experimental Section). The μ-antagonist potencies of the compounds were assessed by their abilities to inhibit agonist (loperamide)-stimulated guanosine 5′-O-(3-[^{35}S]-thio)triphosphate ([^{35}S]GTPγS) binding to membranes containing μ-opioid receptors. The μ-agonist potencies of the target compounds were assessed by their abilities to stimulate [^{35}S]-GTPγS binding to membranes containing μ-opioid receptors.

We reported recently SARs at the 2α-position of the piperidine ring of the *trans*-4,5-dimethyl-4-(3-hydroxyphenyl)-piperidine μ-opioid antagonist series.[14] This study showed that only small linear alkyl groups are tolerated at the 2α-position of the piperidine ring of this series. In particular, introduction of an ethyl group at the 2α position of the piperidine ring of **3** (compound **48**) resulted in a 35-fold decrease in μ-binding [**48**: $K_i(\mu) = 75$ nM].



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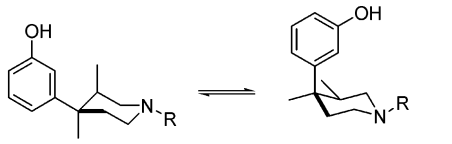
Similarly, the octahydroquinolizine derivatives **4** and **5**, constrained analogues of **48**, bind weakly to the μ-opioid receptor ($K_i = 110$ and 430 nM, respectively). Inversion of the configuration of the chiral center at the α position of the nitrogen atom of **4** resulted in a dramatic increase in μ-opioid receptor binding. The octahydroquinolizine derivative **6**, the diastereoisomeric analogue of **4**, exhibited greater μ binding affinity ($K_i = 0.62$ nM) than the flexible ligand **3** ($K_i = 1.8$ nM). As shown in Table 1, replacement of the phenyl group of **6** with a hydrogen atom (compound **13**, Scheme 4) resulted in over a 1500-fold decrease in μ binding. This result supports the existence of an important lipophilic binding region for the μ receptor in the proximity of the piperidine nitrogen-binding site.[12] Comparison of the μ binding affinity of **6** with the binding affinity of its diastereoisomeric analogue **7** also demonstrated that the *S*-stereochemistry at the carbon atom bearing the phenyl ring was highly preferred. These results showed that the presence

Table 1. Opioid Receptor (M, κ, and δ) Binding Data and in Vitro Antagonist Activity (μ) of Compounds **2**−**15**

compd	$K_i(\mu)^a$ (nM) or % inh.^{b} @ 10 μM	$IC_{50}(\mu)^c$ (nM)	$K_i(\kappa)^a$ (nM) or % inh.^{b} @ 10 μM	$K_i(\delta)^a$ (nM) or % inh.^{b} @ 10 μM
2a	3.7 (3.1−4.5)	7.3 (5.0−10)	9.2 (6.9−13)	33 (27−41)
2b	1.0 (0.78−1.3)	4.1 (1.8−9.1)	4.4 (3.4−5.6)	14 (9.8−20)
3	1.8 (0.76−4.4)	1.1 (0.30−2.0)	17 (12−25)	33 (19−57)
4	110 (99−130)	210 (100−420)	430 (330−550)	900 (730−1100)
5	430 (310−620)	nd^d	1400 (990−2100)	49% ± 2%
6	0.62 (0.41−0.81)	0.54 (0.32−0.89)	9.0 (6.3−12)	31 (21−45)
7	110 (32−410)	110 (30−410)	440 (120−1500)	51% ± 3%
8	73 (43−130)	150 (44−480)	100 (77−130)	190 (130−290)
9	0.90 (0.51−1.6)	^{e}	65 (41−100)	2.1 (1.5−3.0)
10	26 (6.5−100)	190 (65−560)	35 (6.6−180)	25 (7.9−79)
11	37 (16−88)	120 (42−360)	16 (9.1−29)	280 (95−840)
12	710 (430−1200)	nd^d	520 (220−1200)	40% ± 3%
13	940 (130−6900)	nd^d	44% ± 3%	37% ± 3%
14	120 (41−360)	1000 (650−1600)	69 (15−300)	220 (38−1300)
15	43% ± 3%	nd^d	520 (170−1500)	47% ± 3%

^{a} The potencies of the compounds were determined by testing the ability of a range of concentrations of each compound to inhibit the binding of the nonselective opioid antagonist, [^{3}H]diprenorphine, to cloned human μ, κ and δ opioid receptors, expressed in separate cell lines. K_i values are geometric means and 95% confidence intervals computed from at least three separate determinations. ^{b} The % inhibition of [^{3}H]diprenorphine binding to the cloned human μ-, κ-, and δ-opioid receptors using a concentration of the competitor of 10 μM. Mean ± S.E.M. ^{c} The potencies of the antagonists were assessed by their abilities to inhibit agonist (loperamide) stimulated [^{35}S]GTPγS binding to membranes containing the cloned μ opioid receptor. ^{d} nd = not determined. ^{e} Compound **9** is an agonist: $EC_{50}(\mu) = 53$ nM, 95% C. I. = 31−93.

and spatial orientation of the phenyl ring within the binding site relative to the piperidine ring are of critical importance for good binding affinity toward the μ-opioid receptor. In the functional assay, compound **6** was a potent inhibitor of loperamide-stimulated [^{35}S]GTPγS binding with an IC_{50} value of 0.54 nM, superior to the μ in vitro antagonist activity of **3** ($IC_{50} = 1.1$ nM), naloxone ($IC_{50} = 7.3$ nM), and naltrexone ($IC_{50} = 4.1$ nM). Furthermore, compound **6** was found to be a pure μ-opioid antagonist, because no agonist activity was detectable for this ligand at concentrations up to 10 μM. Compound **6** also behaved as a potent κ- and δ-opioid antagonist in the [^{35}S]GTPγS assay [**6**: $IC_{50}(\kappa) = 1.2$ nM, 95% C. I. = 0.41−3.8; $IC_{50}(\delta) = 16$ nM, 95% C. I. = 9.3−26]. We then investigated the opioid binding profile and functional activity of the other set of constrained analogues **8**−**11**. The octahydroquinolizine derivative **8** binds with only weak affinity (K_i = 73 nM) at the μ-opioid receptor. However, inversion of the configuration of the chiral center at the carbon atom bearing the phenyl ring of **8** resulted in a 80-fold increase in μ-opioid receptor binding affinity [**9**: $K_i(\mu) = 0.90$ nM]. Furthermore, the binding data (Table 1) for compound **14** (Scheme 5), which differs from **9** by the absence of the phenyl group, supported the critical importance of this lipophilic substituent for high affinity binding toward the μ-opioid receptor. The octahydro-



3-hydroxyphenyl equatorial piperidine chair 3-hydroxyphenyl axial piperidine chair

Figure 4. Comparison of the structures of the axial and equatorial conformers of *N*-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidines.

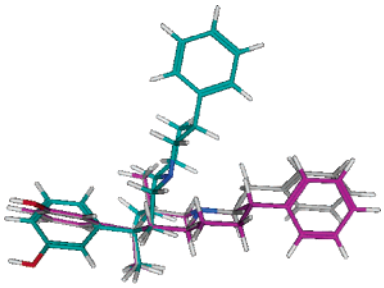


Figure 5. Overlay of lowest energy conformations of **3** (grey), **6** (magenta), and **9** (teal). Compounds were aligned by superposition of the C3−C4−C5 atoms of the piperidine ring (see numbering in Figure 1).

quinolizine derivative **9** exhibited comparable μ binding affinity (K_i = 0.90 nM) to that of the constrained analogue **6** (K_i = 0.62 nM). Surprisingly, in the functional assay, compound **9** did not exhibit any antagonism of loperamide-stimulated [^{35}S]-GTPγS binding. This constrained ligand behaved functionally as a potent full μ-opioid agonist in the functional assay with an EC_{50} = 53 nM. Compound **9** also behaved as a potent δ-opioid agonist and a partial κ-opioid agonist in the [^{35}S]GTPγS assay [**9**: $EC_{50}(\delta)$ = 55 nM, 95% C. I. = 27−65; $EC_{50}(\kappa)$ = 200 nM, 95% C. I. = 170−630].

As illustrated in Figure 4, the 3-hydroxyphenyl moiety in the *N*-substituted 3,4-dimethyl-4-(3-hydroxyphenyl)piperidine analogues can be in either axial or equatorial positions.

Studies showed that both opioid binding affinity and antagonist activity were dependent on a *trans* relative relationship between the 3- and 4-methyl groups in the piperidine ring and that the pure antagonist activity in this series was mediated through a hydroxyphenyl equatorial mode at opioid receptors.[8−10] ^{1}H and ^{13}C NMR studies[20,21] and X-ray crystallographic data[10] confirmed these findings. To examine the conformational behavior of the investigated ligands, a conformational analysis was performed. All calculations were conducted using the MOE software.[22] Stochastic conformational searches using the default MMFF94x force field without solvation were performed to identify the global minimum energy conformers for the prototypical *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine μ-opioid receptor antagonist **3** and the octahydroquinolizine constrained analogues **6** and **9**. All conformers that were within 20 kcal/mol of the lowest-energy conformers were included in this conformational search. As shown in Figure 5, the flexible ligand **3** assumes an extended conformation as its lowest-energy conformer. In this low-energy conformation, the hydroxyphenyl moiety of **3** is positioned in an equatorial orientation. This is in agreement with the hypothesis that a 3-hydroxyphenyl equatorial piperidine chair conformation and the presence of the piperidine 3-methyl axial substituent mediated the antagonist properties of the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine class of opioid antagonists. Extensive work from Ivy Carroll's group supported this hypothesis.[23] In this conformational search, the lowest-energy conformer of **3** in which the hydroxyphenyl moiety is positioned in the axial orientation relative to the piperidine ring is 3.1 kcal/mol higher in energy than the lowest-energy conformer of **3**. The constrained μ-opioid antagonist **6** achieves its lowest-energy conformation with both phenyl rings connected in an equatorial orientation relative to the octahydroquinolizine template. As a result of the added constraints in the bicyclic system, the lowest-energy conformer of **6** containing an axial hydroxyphenyl group is 8.7 kcal/mol higher in energy than the lowest-energy conformer. The availability of the conformationally restricted ligand **6**, in which the hydroxyphenyl, amine, and phenyl have a (relatively) fixed 3D orientation, allowed probing of the binding site for acceptable positions of these pharmacophoric groups. This study provides additional support that the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine opioid antagonists are interacting with the μ-opioid receptor with the hydroxyphenyl group in the equatorial conformation. Furthermore, the low-energy conformation of **3** could be regarded as the bioactive conformation. The high affinity of the rigid octahydroquinolizine derivative **6** strongly supports this assertion. In contrast to the low-energy conformation of the constrained μ-opioid antagonist **6**, the constrained μ-opioid agonist **9** achieves the lowest-energy conformation with the hydroxyphenyl moiety positioned in an axial orientation (Figure 5). In this conformational search, the lowest-energy conformer of **9** with an equatorial hydroxyphenyl group is 3.9 kcal/mol higher in energy. As illustrated in Figure 5, the phenyl moieties of compounds **6** and **9** as well as the central piperidine nitrogen are located in different regions, while the hydroxyphenyl groups overlap reasonably well. This may account for the differences of functional activity between these two ligands.

Seemingly minor changes in the structure of the ligand could then lead to fundamental changes in the nature of the ligand−receptor interaction not only with respect to affinity but also in the expression of efficacy. This study provided compelling evidence that the low-energy conformation of **9** could represent the μ-agonist bioactive conformation and that the 3-hydroxyphenyl axial conformation might trigger the μ-agonist properties of **9**.

Conclusion

To better understand structural requirements for a μ ligand of the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine class to interact with the μ-opioid receptor, constrained analogues of the *N*-phenethyl derivative **3** were prepared. Two of the eight constrained analogues investigated showed high affinity toward the μ-opioid receptor. One of the active constrained analogues, compound **6**, exhibited subnanomolar μ-opioid receptor affinity and potent μ-opioid antagonist activity. The pure antagonist activity of compound **6** provides further evidence that opioid ligands of this class express potent opioid antagonist activity with their 3-hydroxyphenyl in an equatorial position. It is hypothesized that the analogous *linear* arrangement of the pharmacophoric elements (hydroxyphenyl, piperidine nitrogen, and phenyl moieties) reflects a most probable bioactive conformation of the flexible ligand **3**. The other active rigid analogue, compound **9**, which achieves the lowest-energy structure with the hydroxyphenyl moiety positioned in an axial orientation, was found to be a potent μ-opioid agonist. Collectively, these findings may create a basis for further receptor modeling and docking studies with other flexible μ ligands of the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine series. The information provided herein should aid in the design of novel potent, receptor-selective antagonists based upon similar structural architecture.

Experimental Section

A. Chemistry. General. All chemicals were reagent grade and used without further purification. Thin-layer chromatography (TLC) was performed on silica gel 6F glass-backed plates (250 microns) from Analtech and visualized by UV 254 irradiation and iodine. Flash chromatography was conducted using the ISCO CombiFlash with RediSep silica gel cartridges (4 g, 12 g, 40 g, and 120 g). Chromatographic elution solvent systems are reported as volume/volume ratios. All ^{1}H NMR spectra were recorded at ambient temperature on a Bruker 400 MHz spectrometer. They are reported in ppm on the δ scale from TMS. LC-MS data were obtained using a Thermo-Finnigan Surveyor HPLC and a Thermo-Finnigan AQA MS using either positive or negative electrospray ionization. Program (positive); solvent A, 10 mM ammonium acetate, pH 4.5, 1% acetonitrile; solvent B, acetonitrile; column, Michrom Bioresources Magic C18 Macro Bullet; detector, PDA λ = 220−300 nm; gradient, 96% A−100% B in 3.2 min, hold 100% B for 0.4 min. Program (negative); solvent A, 1 mM ammonium acetate, pH 4.5, 1% acetonitrile; solvent B, acetonitrile; column, Michrom Bioresources Magic C18 Macro Bullet; detector, PDA λ = 220−300 nm; gradient, 96% A−100% B in 3.2 min, hold 100% B for 0.4 min. Mass spectra were obtained on a Finnigan 4000 or VG707EHF spectrometer by the mass spectrometry laboratories at the Department of Chemistry, University of Minnesota. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA and are within ± 0.4% of theoretical values.

(4*R*,5*R*)-4-(3-Benzyloxy-phenyl)-4,5-dimethyl-2,3,4,5-tetrahydro-pyridine 1-oxide (17a) and (3*R*,4*R*)-4-(3-Benzyloxy-phenyl)-3,4-dimethyl-2,3,4,5-tetrahydro-pyridine 1-oxide (17b). To a stirred solution of **16** (29.35 g, 99.49 mmol) in methanol (200 mL) and methylene chloride (200 mL) was added a solution of sodium tungstate (1.50 g, 3.98 mmol) in water (50 mL). To this solution was then added hydrogen peroxide (35 mL, 298.47 mmol), and the reaction mixture was stirred at room temperature for 18 h. The mixture was then poured into a saturated ammonium chloride solution (500 mL) and extracted with methylene chloride. The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated. The crude product was purified by column chromatography on silica, eluting with 0−5% methanol in methylene chloride to give the mixture of **17a** and **17b** as a yellow gum (20.76 g, 68%). ^{1}H NMR ($CDCl_3$) δ 0.75 and 0.83 (d, J = 7 Hz, 3H, regioisomers), 1.39 and 1.43 (s, 3H, regioisomers), 2.33 (m, 1H), 2.58 (dd, J = 2 and 20 Hz, 1H), 2.92 (d, J = 20 Hz, 1H), 3.41 (dd, J = 3 and 15 Hz, 1H), 3.94 (d, J = 15 Hz, 1H), 5.06 (s, 2H), 6.82−6.89, (m, 3H), 7.26−7.43 (m, 6H); LCMS (ESI) m/z 310 [M + H]$^+$.

(2*R*,4*R*,5*R*)-2-Allyl-4-(3-benzyloxy-phenyl)-4,5-dimethyl-piperidin-1-ol (18). An oven-dried flask was charged with a solution of **17a** and **17b** (25 g, 80.91 mmol) in anhydrous THF (500 mL), and the solution, under a nitrogen atmosphere, was cooled in an ice bath. To this solution was then added, dropwise, a 2 M solution of allylmagnesium chloride in THF (122 mL, 244 mmol). The ice bath was removed after the addition, and the reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was then poured into a mixture of a saturated ammonium chloride solution (250 mL) and a saturated sodium bicarbonate solution (250 mL). This mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated. The crude material was purified by silica gel chromatography, eluting with 0−50% ethyl acetate in hexanes to give **18** (15.90 g, 56%) as a yellow oil, **19** (2.16 g, 8%) as an orange solid, and an inseparable mixture of **20a** and **20b** (3.02 g, 11%) as a yellow oil. **18:** ^{1}H NMR ($CDCl_3$) δ 1.04 (d, J = 7 Hz, 3H), 1.28 (s, 3H), 1.40 (m, 1H), 1.94 (br s, 1H), 2.12 (m, 1H), 2.24 (d, J = 14 Hz, 1H), 2.64 (br m, 2H), 2.85 (br s, 1H), 2.98, (d, J = 9 Hz, 1H), 5.05 (s, 2H), 5.09 (m, 2H), 5.83 (m, 1H), 6.52 (br s, 1H), 6.81 (d, J = 7 Hz, 1H), 7.00 (s, 2H), 7.18−7.22 (m, 1H), 7.32−7.45 (m, 5H); LCMS (ESI) m/z 352 [M + H]$^+$.

(2*S*,4*R*,5*R*)-2-Allyl-4-(3-benzyloxy-phenyl)-4,5-dimethyl-piperidin-1-ol (19). ^{1}H NMR ($CDCl_3$) δ 0.73 (d, J = 7 Hz, 3H), 1.36 (s, 3H), 1.41 (m, 0.5H), 1.58 (m, 0.5H), 1.78 (d, J = 14 Hz, 1H), 1.97 (t, J = 13 Hz, 0.5H), 2.06−2.13 (br m, 1.5H), 2.24 (m, 0.5H), 2.78−2.82, (br m, 2H), 3.08 (d, J = 10 Hz 0.5H), 3.18 (d, J = 11 Hz, 0.5H), 3.65 (t, J, = 6 Hz, 0.5H), 5.05 (s, 2H), 5.08−5.17 (m, 2H), 5.88 (m, 1H), 6.13 (br s, 1H), 6.79 (d, J = 8 Hz, 1H), 6.84 (br d, J = 7 Hz, 2H), 7.23 (t, J = 8 Hz, 1H), 7.33−7.45 (m, 5H); LCMS (ESI) m/z 352 [M + H]$^+$.

(2*R*,3*R*,4*R*)-2-Allyl-4-(3-benzyloxy-phenyl)-3,4-dimethyl-piperidin-1-ol (20a) and (2*S*,3*R*,4*R*)-2-Allyl-4-(3-benzyloxy-phenyl)-3,4-dimethyl-piperidin-1-ol (20b). ^{1}H NMR ($CDCl_3$) δ 0.59 (d, J = 7 Hz, 1.2H), 1.05 (d, J = 7 Hz, 1.6H), 1.32 (s, 3H), 1.53 (m, 0.5H), 1.73−2.00 (br m, 2H), 2.06−2.14 (br m, 0.5H), 2.23−2.33 (br m, 1H), 2.63−2.97 (br m, 3H), 3.14 (dt, J = 11 and 3 Hz, 0.5H), 3.23 (br m, 0.5H), 5.06 (s, 2H), 5.99 (m, 1H), 6.81 (m, 1H), 7.04 (m, 2H), 7.18−7.26 (m, 1H), 7.33−7.46 (m, 5H); LCMS (ESI) m/z 352 [M + H]$^+$.

(2*R*,4*R*,5*R*)-2-Allyl-4-(3-(benzyloxy)phenyl)-4,5-dimethylpiperidine (21). To a solution of **18** (3 g, 8.55 mmol) in acetic acid/water (1:1; 30 mL) was added zinc dust (2.8 g, 42.75 mmol), and the reaction mixture was sonicated for 3 h at room temperature. The mixture was then filtered through Celite, and the Celite was washed with warm methanol. The filtrate was concentrated under reduced pressure, and the residue was basified with a saturated sodium bicarbonate solution. The mixture was extracted with ethyl acetate, and the combined organic extracts were washed with saturated brine, dried (Na_2SO_4), filtered, and evaporated to give the desired product as a yellow oil (2.74 g, 96%). ^{1}H NMR ($CDCl_3$) δ 1.01 (d, J = 7 Hz, 3H), 1.33 (s, 3H), 1.37 (m, 1H), 1.84 (m, 1H), 2.14 (m, 3H), 2.79 (m, 2H), 2.95 (m, 1H), 5.09 (m, 4H), 5.75 (m, 1H), 6.81 (d, J = 8 Hz, 1H), 7.03 (m, 1H), 7.21 (t, J = 9 Hz, 2H), 7.33 (m, 1H), 7.39 (t, J = 7 Hz, 2H), 7.44 (d, J = 7 Hz, 2H); LCMS (ESI) m/z 336 [M + H]$^+$.

(2*S*,4*R*,5*R*)-2-Allyl-4-(3-(benzyloxy)phenyl)-4,5-dimethylpiperidine (22). Compound **22** was synthesized in a manner similar to compound **21**, using compound **19** as starting material: yield 59% (colorless oil); ^{1}H NMR ($CDCl_3$) δ 0.67 (d, J = 7 Hz, 3H), 1.36 (s, 3H), 1.58 (d, J = 13 Hz, 1H), 1.74 (t, J = 12 Hz, 2H), 1.89 (m, 1H), 2.22 (m, 2H), 2.76 (d, J = 13 Hz, 1H), 2.94 (m, 1H), 3.29 (dd, J = 13 and 3 Hz, 1H), 5.04 (s, 2H), 5.12 (m, 2H), 5.86 (m, 1H), 6.79 (d, J = 7 Hz, 1H), 6.89 (m, 1H), 7.31 (t, J = 8 Hz, 1H), 7.35 (t, J = 7 Hz, 2H), 7.44 (t, J = 13 Hz, 1H); LCMS (ESI) m/z 336 [M + H]$^+$.

1-((2*R*,4*R*,5*R*)-2-Allyl-4-(3-(benzyloxy)phenyl)-4,5-dimethylpiperidin-1-yl)-2-phenylethane-1,2-dione (23). To a stirred solution of **21** (1 g, 2.99 mmol) in acetonitrile (15 mL) under a nitrogen atmosphere was added, sequentially, *N*,*N*-diisopropylethylamine (1.6 mL, 8.97 mmol), phenylglyoxalic acid (0.54 g, 3.58 mmol), and TBTU (1.44 g, 4.49 mmol). The reaction mixture was stirred at room temperature for 16 h, poured into a saturated ammonium chloride solution, and extracted with ethyl acetate. The combined organic extracts were washed with saturated brine, dried (Na_2SO_4), filtered, and evaporated. The crude material was purified by flash column chromatography on silica, eluting with 0−20% ethyl acetate in hexanes to give **23** as a purple foam (1.03 g, 74%). ^{1}H NMR ($CDCl_3$) δ 0.61 (d, J = 7 Hz, 1.7H), 0.79 (d, J = 7 Hz, 1.3H), 1.49 (s, 1.7H), 1.52 (s, 1.3H), 1.57 (s, 1H), 1.83 (d, J = 14 Hz, 0.4H), 1.94 (d, J = 14 Hz, 0.6H), 2.25 (m, 1H), 2.35 (dd, J = 14 and 6 Hz, 0.6H), 2.62, (m, 1.4H), 2.75 (m, 0.6H), 3.23 (dd, J = 14 Hz and 3 Hz, 0.6H), 3.42 (dd, J = 14 Hz and 3 Hz, 0.4H), 3.77 (dd, J = 14 Hz and 3 Hz, 0.6H), 3.85 (q, J = 8 Hz, 0.4H), 4.49 (dd, J = 14 Hz and 3 Hz, 0.4H), 5.03 (m, 3H), 5.20 (m, 1H), 5.56 (m, 0.5H), 5.96 (m, 0.5H), 6.82 (m, 3H), 7.24 (t, J = 9 Hz 1H), 7.33 (m, 1H), 7.37 (t, J = 7 Hz, 2H), 7.41 (m, 2H), 7.48 (m, 2H), 7.62 (m, 1H), 7.98 (m, 2H); LCMS (ESI) m/z 468 [M + H]$^+$.

1-((2*S*,4*R*,5*R*)-2-Allyl-4-(3-(benzyloxy)phenyl)-4,5-dimethylpiperidin-1-yl)-2-phenylethane-1,2-dione (24). Compound **24** was synthesized in a manner similar to compound **23**, using compound **22** as starting material: yield 26% (orange oil); ^{1}H NMR ($CDCl_3$) δ 0.40 (d, J = 7 Hz, 3H), 1.39 (s, 1H), 1.44 (s, 3H), 1.93 (m, 1H), 2.08 (m, 1H), 2.46 (m, 2H), 2.92 (dd, J = 11 and 3 Hz, 1H), 3.40 (dd, J = 15 and 7 Hz, 1H), 4.58 (m, 1H), 5.06 (s, 2H), 5.17 (m,

2H), 5.92 (m, 1H), 6.81 (dd, J = 8 and 3 Hz, 1H), 6.87 (m, 2H), 7.22 (t, J = 8 Hz, 1H), 7.33 (t, J = 7 Hz, 1H), 7.38 (t, J = 7 Hz, 3H), 7.44 (d, J = 7 Hz, 2H), 7.52 (t, J = 8 Hz, 2H), 7.65 (t, J = 8 Hz, 1H), 7.99 (d, J = 7 Hz, 2H); LCMS (ESI) m/z 468 $[M + H]^+$.

1-((2*R*,4*R*,5*R*)-2-Allyl-4-(3-(benzyloxy)phenyl)-4,5-dimethylpiperidin-1-yl)-2-phenylprop-2-en-1-one (25). To a suspension of methyl triphenylphosphonium bromide (0.42 g, 1.2 mmol) in anhydrous THF (10 mL) under a nitrogen atmosphere was added potassium *tert*-butoxide (0.15 g, 1.3 mmol) in one portion. The bright yellow mixture was stirred at room temperature for 30 min before being transferred by syringe to a solution of **23** (0.5 g, 1.1 mmol) in anhydrous benzene (10 mL). The reaction mixture was then heated to reflux for 1.5 h. The solvents were removed under reduced pressure, and the crude product was purified by silica gel column chromatography, eluting with 0−20% ethyl acetate in hexanes to give the titled product as a colorless oil (0.28 g, 56%). ^{1}H NMR ($CDCl_3$) δ 0.61 (d, J = 7 Hz, 1.8H), 0.79 (d, J = 7 Hz, 1.2H), 1.49 (s, 1.6H), 1.52 (s, 1.4H), 1.83 (d, J = 14 Hz, 0.5H), 1.94 (d, J = 14 Hz, 0.5H), 2.04 (m, 0.5H), 2.25 (m, 1H), 2.35 (dd, J = 14 and 7 Hz, 0.5H), 2.61 (m, 1.5H), 2.74 (m, 0.5H), 3.23 (dd, J = 14 and 2 Hz, 0.5H), 3.42 (dd, J = 14 and 3 Hz, 0.5H), 3.77 (dd, J = 14 and 3 Hz, 0.5H), 4.48 (dd, J = 14 and 2 Hz, 0.5H), 5.02 (m, 3.8H), 5.19 (m, 1.2H), 5.57 (m, 0.4H), 5.96 (m, 0.6H), 6.82 (m, 3H), 7.24 (t, J = 8 Hz 1H), 7.33 (m, 1H), 7.38 (m, 3H), 7.42 (m, 3H), 7.49 (m, 2H), 7.63 (t, J = 7 Hz, 1H), 7.97 (m, 2H); LCMS (ESI) m/z 466 $[M + H]^+$.

1-((2*S*,4*R*,5*R*)-2-Allyl-4-(3-(benzyloxy)phenyl)-4,5-dimethylpiperidin-1-yl)-2-phenylprop-2-en-1-one (26). Compound **26** was synthesized in a manner similar to compound **25**, using compound **24** as starting material: yield 71% (yellow oil); ^{1}H NMR ($CDCl_3$) δ 0.34 (br s, 3H), 1.34 (s, 3H), 1.73−1.84 (m, 2H), 1.99 (d, J = 14 Hz, 1H), 2.38−2.43 (m, 2H), 2.78 (t, J = 13 Hz, 1H), 3.65 (br s, 1H), 4.55 (br s, 1H), 5.04 (s, 2H), 5.07 (m, 2H), 5.37 (s, 1H), 5.71 (s, 1H), 5.84 (br s, 1H), 6.79 (dd, J = 8 and 2 Hz, 1H), 6.86 (s, 2H), 7.20 (t, J = 8 Hz, 1H), 7.31−7.38 (m, 6H), 7.42 (d, J = 13 Hz, 2H), 7.48 (d, J = 8 Hz, 2H); LCMS (ESI) m/z 466 $[M + H]^+$.

(7*R*,8*R*,9α*R*)-8-(3-(Benzyloxy)phenyl)-7,8-dimethyl-3-phenyl-7,8,9,9α-tetrahydro-1*H*-quinolizin-4(6*H*)-one (27). A solution of **25** (0.77 g, 1.66 mmol) in anhydrous methylene chloride (40 mL) was purged with nitrogen for 20 min. Grubbs' second-generation catalyst (0.07 g, 0.08 mmol) was then added to the reaction mixture, which was heated to reflux for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography, eluting with 0−20% ethyl acetate in hexanes to give **27** as a colorless oil (0.47 g, 65%). ^{1}H NMR ($CDCl_3$) δ 1.10 (d, J = 7 Hz, 3H), 1.37 (s, 3H), 1.62 (d, J = 14 Hz, 0.5H), 1.68 (d, J = 14 Hz, 0.5H), 1.92 (m, 1H), 2.23 (dd, J = 14 and 3 Hz, 1.2H), 2.33 (dd, J = 14 and 3 Hz, 0.8H), 2.47 (t, J = 6 Hz, 0.6H), 2.52 (t, J = 6 Hz, 0.4H), 2.80 (t, J = 14 Hz, 1H), 3.79 (m, 1H), 4.20 (dd, J = 14 Hz and 5 Hz, 1H), 5.06 (s, 2H), 6.55 (q, J = 3 Hz, 1H), 6.84 (dd, J = 9 and 3 Hz, 1H), 7.01 (m, 2H), 7.24 (m, 2H), 7.32 (m, 3H), 7.38 (m, 3H), 7.43 (m 3H); LCMS (ESI) m/z 438 $[M + H]^+$.

(7*R*,8*R*,9α*S*)-8-(3-(Benzyloxy)phenyl)-7,8-dimethyl-3-phenyl-7,8,9,9α-tetrahydro-1*H*-quinolizin-4(6*H*)-one (28). Compound **28** was synthesized in a manner similar to compound **27**, using compound **26** as starting material: yield 95% (yellow oil); ^{1}H NMR ($CDCl_3$) δ 0.72 (d, J = 7 Hz, 3H), 1.41 (s, 3H), 1.56 (s, 1H), 1.83 (dd, J = 13 and 3 Hz, 1H), 2.18 (m, 2H), 2.49 (m, 1H), 2.61 (t, J = 6 Hz, 0.6H), 2.65 (t, J = 6 Hz, 0.4H), 3.32 (dd, J = 14 and 3 Hz, 1H), 3.89 (m, 1H), 4.30 (dd, J = 14 and 2 Hz, 1H), 5.07 (s, 2H), 6.62 (dd, J = 6 and 2 Hz, 1H), 6.83 (dd, J = 8 and 2 Hz, 1H), 6.91 (m, 1H), 7.26−7.35 (m, 5H), 7.38−7.47 (m, 6H); LCMS (ESI) m/z 438 $[M + H]^+$.

(3*S*,7*R*,8*R*,9α*R*)-8-(3-Hydroxyphenyl)-7,8-dimethyl-3-phenylhexahydro-1*H*-quinolizin-4(6*H*)-one (29) and (3*R*,7*R*,8*R*,9α*R*)-8-(3-Hydroxyphenyl)-7,8-dimethyl-3-phenyl-hexahydro-1*H*-quinolizin-4(6*H*)-one (30). To a solution of **27** (0.47 g, 1.07 mmol) in ethanol (30 mL) was added 10% palladium on charcoal (catalytic), and the mixture was stirred at room temperature under a hydrogen atmosphere for 16 h. The mixture was then filtered through Celite. The Celite was washed with warm methanol. The filtrate was then concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography, eluting with 0−50% ethyl acetate in hexanes. Compound **29** was obtained as a white solid (0.22 g, 59%). Compound **30** was obtained as a colorless oil (0.1 g, 27%).

29: ^{1}H NMR ($CDCl_3$) δ 1.28 (d, J = 7 Hz, 3H), 1.38 (s, 3H), 1.54 (m, 2H), 1.68 (m, 2H), 1.94 (m, 2H), 2.17 (d, J = 14 Hz, 1H), 2.98 (d, J = 14 Hz, 1H), 3.48 (m, 1H), 3.84 (m, 1H), 4.69 (dd, J = 14 and 4 Hz, 1H), 6.67 (d, J = 7 Hz, 1H), 7.10 (s, 1H), 7.16 (d, J = 13 Hz, 1H), 7.22 (m, 3H), 7.33 (m, 3H); LCMS (ESI) m/z 350 $[M + H]^+$.

30: ^{1}H NMR ($CDCl_3$) δ 1.05 (d, J = 7 Hz, 3H), 1.30 (s, 3H), 1.53 (t, J = 14 Hz, 2H), 1.78 (m, 1H), 1.88 (m, 1H), 1.99 (m, 1H), 2.13 (m, 2H), 2.78 (t, J = 13 Hz, 1H), 3.60 (q, J = 5 Hz, 1H), 3.72 (m, 1H), 4.49 (dd, J = 14 and 5 Hz, 1H), 6.53 (dd, J = 8 and 2 Hz, 1H), 6.85 (d, J = 8 Hz, 1H), 6.92 (s, 1H), 7.08 (t, J = 8 Hz, 1H), 7.13 (d, J = 7 Hz, 2H), 7.18 (d, J = 7 Hz, 1H), 7.24 (t, J = 7 Hz, 2H), 7.53 (br s, 1H); LCMS (ESI) m/z 350 $[M + H]^+$.

(3*S*,7*R*,8*R*,9α*S*)-8-(3-Hydroxyphenyl)-7,8-dimethyl-3-phenyl-hexahydro-1*H*-quinolizin-4(6*H*)-one (31). Compound **31** was synthesized in a manner similar to compound **29**, using compound **28** as starting material: yield 55% (white solid); ^{1}H NMR (CD_3OD) δ 0.73 (d, J = 7 Hz, 3H), 1.44 (s, 3H), 1.65 (m, 1H), 1.77 (d, J = 12 Hz, 1H), 1.93 (m, 1H), 2.03 (m, 2H), 2.20 (m, 2H), 3.24 (dd, J = 13 and 3 Hz, 1H), 3.81 (m, 2H), 4.57 (dd, J = 13 and 2 Hz, 1H), 6.61 (dd, J = 8 and 2 Hz, 1H), 6.73 (s, 1H), 6.78 (d, J = 13 Hz, 1H), 7.13 (t, J = 8 Hz, 1H), 7.21 (m, 3H), 7.31 (t, J = 7 Hz, 1H); LCMS (ESI) m/z 350 $[M + H]^+$.

(3*R*,7*R*,8*R*,9α*S*)-8-(3-Hydroxyphenyl)-7,8-dimethyl-3-phenyl-hexahydro-1*H*-quinolizin-4(6*H*)-one (32). Compound **32** was synthesized in a manner similar to compound **29**, using compound **28** as starting material: yield 15% (white solid); ^{1}H NMR (CD_3OD) δ 0.64 (d, J = 7 Hz, 3H), 1.47 (s, 3H), 1.80 (d, J = 13 Hz, 2H), 2.18 (m, 3H), 3.28 (dd, J = 13 and 3 Hz, 1H), 3.33 (s, 2H), 3.67 (dd, J = 10 and 5 Hz, 1H), 3.92 (m, 1H), 4.54 (dd, J = 13 and 3 Hz, 1H), 6.63 (dd, J = 7 and 2 Hz, 1H), 6.77 (s, 1H), 6.81 (d, J = 8 Hz, 1H), 7.16 (t, J = 8 Hz, 1H), 7.23 (m, 3H), 7.32 (t, J = 8 Hz, 2H); LCMS (ESI) m/z 350 $[M + H]^+$.

3-((2*R*,3*R*,7*S*,9α*R*)-2,3-Dimethyl-7-phenyl-octahydro-1*H*-quinolizin-2-yl)phenol (4). To a solution of (**29**; 0.22 g, 0.63 mmol) in anhydrous THF (10 mL) was added borane−dimethyl sulfide complex (2 M anhydrous solution in THF, 0.63 mL, 1.26 mmol), and the reaction mixture was heated to reflux under a nitrogen atmosphere for 16 h. The mixture was then cooled to 0 °C and methanol (10 mL) was added. The reaction mixture was stirred at 0 °C for 1 h. A 2 M anhydrous solution of HCl in diethyl ether was then added to the reaction mixture, which was heated to reflux for 1 h. The solvents were removed under reduced pressure, and the residue was taken up in methanol and stripped of solvent under reduced pressure (this process was repeated five times). The residue was then basified with a 1 M aqueous solution of NaOH (5 mL) and extracted with a 10% solution of methanol in methylene chloride. The combined organic extracts were washed with saturated brine, dried (Na_2SO_4), filtered, and evaporated. Purification of the crude product by silica gel flash column chromatography, eluting with 0−50% ethyl acetate in hexanes, afforded the desired product as a white solid (0.155 g, 73%): ^{1}H NMR (CD_3OD) δ 0.89 (d, J = 7 Hz, 3H), 1.15 (s, 3H), 1.27 (m, 2H), 1.45 (m, 1H), 1.52 (m, 1H), 1.66 (m, 2H), 1.75 (m, 2H), 1.91 (m, 1H), 2.32 (dd, J = 12 and 4 Hz, 3H), 2.77 (t, J = 4 Hz, 1H), 2.98 (dd, J = 12 and 4 Hz, 1H), 3.43 (dt, J = 10 and 3 Hz, 2H), 6.47 (dd, J = 8 and 2 Hz, 1H), 6.78 (d, J = 9 Hz, 1H), 6.83 (m, 1H), 6.94 (t, J = 8 Hz, 1H), 6.99 (t, J = 8 Hz, 1H), 7.11 (t, J = 8 Hz, 2H), 7.37 (d, J = 7 Hz, 1H); LCMS (ESI) m/z 336 $[M + H]^+$. Anal. ($C_{23}H_{29}NO \cdot 0.66H_2O$) C, H, N.

3-((2*R*,3*R*,7*R*,9α*R*)-2,3-Dimethyl-7-phenyl-octahydro-1*H*-quinolizin-2-yl)phenol (5). Compound **5** was synthesized in a manner similar to compound **4**, using compound **30** as starting material:

yield 66% (white solid); ^{1}H NMR (CD_3OD) δ 1.07 (d, J = 7 Hz, 3H), 1.33 (s, 3H), 1.40 (m, 1H), 1.50 (t, J = 14 Hz, 1H), 1.59 (m, 1H), 1.75 (m, 1H), 1.88 (m, 1H), 2.03 (m, 1H), 2.11 (dd, J = 14 and 3 Hz, 1H), 2.18 (d, J = 9 Hz, 1H), 2.31 (m, 2H), 2.52 (dd, J = 14 and 4 Hz, 1H), 2.87 (m, 1H), 6.60 (m, 1H), 6.93 (m, 2H), 7.09 (t, J = 8 Hz, 1H), 7.17 (m, 3H), 7.25 (m, 2H); LCMS (ESI) m/z 336 $[M + H]^+$. Anal. ($C_{23}H_{29}NO \cdot 0.2H_2O$) C, H, N.

3-((2*R*,3*R*,7*S*,9α*S*)-2,3-Dimethyl-7-phenyl-octahydro-1*H*-quinolizin-2-yl)phenol (6). Compound **6** was synthesized in a manner similar to compound **4**, using compound **31** as starting material: yield 83% (white solid); ^{1}H NMR (CD_3OD) δ 0.85 (d, J = 7 Hz, 3H), 1.28 (s, 1H), 1.33 (s, 3H), 1.36 (s, 1H), 1.49 (dd, J = 13 and 2 Hz, 1H), 1.90 (m, 3H), 2.04 (m, 1H), 2.22 (m, 1H), 2.52 (d, J = 13 Hz, 2H), 2.68 (dd, J = 11 and 3 Hz, 1H), 3.05 (d, J = 12 Hz, 2H), 6.56 (dd, J = 8 and 2 Hz, 1H), 6.72 (m, 1H), 6.75 (d, J = 8 Hz, 1H), 7.09 (m, 2H), 7.20 (t, J = 8 Hz, 2H), 7.63 (d, J = 7 Hz, 2H); LCMS (ESI) m/z 336 $[M + H]^+$. Anal. ($C_{23}H_{29}NO$) C, H, N.

3-((2*R*,3*R*,7*R*,9α*S*)-2,3-Dimethyl-7-phenyl-octahydro-1*H*-quinolizin-2-yl)phenol (7). Compound **7** was synthesized in a manner similar to compound **4**, using compound **32** as starting material: yield 78% (white solid); ^{1}H NMR (CD_3OD) δ 0.79 (d, J = 7 Hz, 3H), 1.38 (s, 3H), 1.57 (m, 1H), 1.67 (m, 2H), 1.83 (m, 1H), 1.98 (m, 2H), 2.09 (m, 1H), 2.33 (m, 1H), 2.42 (m, 1H), 2.68 (d, J = 7 Hz, 1H), 2.92 (m, 3H), 6.59 (dd, J = 8 and 2 Hz, 1H), 6.73 (m, 1H), 6.77 (d, J = 7 Hz, 1H), 7.11 (t, J = 8 Hz, 1H), 7.19 (m, 1H), 7.27 (m, 4H); LCMS (ESI) m/z 336 $[M + H]^+$. Anal. ($C_{23}H_{29}NO \cdot 0.5H_2O$) C, H, N.

(2*S*,3*R*,4*R*)-2-Allyl-4-(3-(benzyloxy)phenyl)-3,4-dimethylpiperidine (33a) and (2*R*,3*R*,4*R*)-2-Allyl-4-(3-(benzyloxy)phenyl)-3,4-dimethylpiperidine (33b). Compounds **33a** and **33b** were synthesized in a manner similar to compound **21**, using **20a**,**b** as starting material: yield 92% (yellow oil); ^{1}H NMR ($CDCl_3$) δ 0.59 (d, J = 7 Hz, 1.6H), 1.01 (d, J = 7 Hz, 1.4H), 1.32 (s, 1.6H), 1.37 (s, 1.4H), 1.48 (m, 0.7H), 1.62 (m, 0.3H), 1.79 (m, 0.5H), 1.88 (m, 0.5H), 2.05 (m, 2H), 2.50 (d, J = 13 Hz, 1H), 2.69 (dt, J = 13 and 3 Hz, 1H), 2.91 (m, 1H), 2.99 (m, 1H), 5.06 (s, 2H), 5.16 (m, 1H), 6.81 (m, 1H), 7.06 (m, 2H), 7.23 (m, 1H), 7.34 (m, 1H), 7.39 (t, J = 7 Hz, 2H), 7.44 (m, 2H); LCMS (ESI) m/z 336 $[M + H]^+$.

1-((2*S*,3*R*,4*R*)-2-Allyl-4-(3-(benzyloxy)phenyl)-3,4-dimethylpiperidin-1-yl)-2-phenylprop-2-en-1-one (34a) and 1-((2*R*,3*R*,4*R*)-2-Allyl-4-(3-(benzyloxy)phenyl)-3,4-dimethylpiperidin-1-yl)-2-phenylprop-2-en-1-one (34b). To a stirred solution of **33a**,**b** (1.26 g, 3.76 mmol) in acetonitrile (20 mL) under a nitrogen atmosphere was added, sequentially, *N*,*N*-diisopropylethylamine (2.0 mL, 11.28 mmol), α-methylene benzeneacetic acid (670 mg, 4.51 mmol), and TBTU (1.81 g, 5.64 mmol). The reaction mixture was stirred at room temperature for 16 h, poured into a saturated ammonium chloride solution, and extracted with ethyl acetate. The combined organic extracts were washed with saturated brine, dried (Na_2SO_4), filtered, and evaporated. The crude material was purified by flash chromatography on silica, eluting with 0−20 ethyl acetate in hexanes to give **34a**,**b** as a colorless oil (1.33 g, 76%): ^{1}H NMR ($CDCl_3$) δ 0.22 (d, J = 7 Hz, 0.8H), 0.67 (d, J = 7 Hz, 2.2H), 1.42 (s, 2.4H), 1.44 (s, 0.6H), 1.62 (m, 0.3H), 1.71 (s, 0.7H), 2.03 (m, 1H), 2.17 (q, J = 7 Hz, 1H), 2.59−2.75 (m, 2H), 2.99 (dt, J = 13 and 2 Hz, 3H), 3.31 (dt, J = 13 and 2 Hz, 0.7H), 3.67 (m, 0.3H), 3.76 (d, J = 14 Hz, 0.7H), 4.77 (t, J = 14 Hz, 0.7H), 4.83 (d, J = 15 Hz, 0.3H), 5.01 (s, 0.6H), 5.02 (s, 1.4H), 5.33 (s, 0.8H), 5.35 (s, 0.2H), 5.51 (m, 0.3H), 5.63 (s, 0.3H), 5.73 (s, 0.7H), 5.97 (m, 0.7H), 6.78 (m, 3H), 7.24 (t, J = 13 Hz, 1H), 7.28−7.51 (m, 11H); LCMS (ESI) m/z 466 $[M + H]^+$.

(8*R*,9*R*,9α*S*)-8-(3-(Benzyloxy)phenyl)-8,9-dimethyl-3-phenyl-7,8,9,9α-tetrahydro-1*H*-quinolizin-4(6*H*)-one (35) and (8*R*,9*R*,9α*R*)-8-(3-(Benzyloxy)phenyl)-8,9-dimethyl-3-phenyl-7,8,9,9α-tetrahydro-1*H*-quinolizin-4(6*H*)-one (36). Compounds **35** and **36** were synthesized in a manner similar to compound **27**, using compounds **34a**,**b** as starting material. Compound **35** was obtained as a brown oil in 45% yield. Compound **36** was obtained as a brown foam in 31% yield.

35: ^{1}H NMR ($CDCl_3$) δ 0.76 (d, J = 7 Hz, 3H), 1.43 (s, 3H), 1.78 (m, 2H), 2.16 (m, 1H), 2.24 (m, 1H), 2.50 (t, J = 7 Hz, 0.5H), 2.54 (t, J = 7 Hz, 0.5H), 3.65 (m, 1H), 3.75 (m, 2H), 5.03 (s, 1H), 5.06 (s, 2H), 6.59 (m, 1H), 6.84 (d, J = 7 Hz, 1H), 7.00 (m, 2H), 7.24 (m, 1H), 7.28−7.39 (m, 4H), 7.45 (m, 4H); LCMS (ESI) m/z 438 $[M + H]^+$.

36: ^{1}H NMR ($CDCl_3$) δ 0.66 (d, J = 7 Hz, 3H), 1.35 (s, 3H), 1.64 (m, 1H), 2.07 (m, 2H), 2.37 (m, 1H), 2.69 (t, J = 6 Hz, 0.6H), 2.73 (t, J = 6 Hz, 0.4H), 3.05 (dt, J = 14 and 3 Hz, 1H), 3.54 (m, 1H), 4.44 (m, 1H), 5.07 (s, 2H), 6.61 (m, 1H), 6.84 (dd, J = 9 and 2 Hz, 1H), 7.02 (m, 2H), 7.27−7.33 (m, 4H), 7.39 (t, J = 7 Hz, 2H), 7.44 (t, J = 7 Hz, 4H); LCMS (ESI) m/z 438 $[M + H]^+$.

(3*R*,8*R*,9*R*,9α*S*)-8-(3-Hydroxyphenyl)-8,9-dimethyl-3-phenyl-hexahydro-1*H*-quinolizin-4(6*H*)-one (37a) and (3*S*,8*R*,9*R*,9α*S*)-8-(3-Hydroxyphenyl)-8,9-dimethyl-3-phenyl-hexahydro-1I-quinolizin-4(6*H*)-one (37b). Compounds **37a**,**b** were synthesized in a manner similar to compound **29**, using compound **35** as starting material: yield 55% (colorless oil); ^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 7 Hz, 0.7H), 0.95 (d, J = 7 Hz, 2.3H), 1.39 (s, 1.2H), 1.41 (s, 1.8H), 1.50 (m, 1H), 1.65 (m, 1H), 1.76 (m, 1H), 1.90 (m, 1H), 2.02 (m, 1H), 2.21 (m, 1H), 3.04 (m, 1H), 3.09 (m, 1H), 3.14 (m, 1H), 3.59 (m, 1H), 3.71 (m, 0.4H), 3.84 (m, 0.6H), 4.34 (m, 0.4H), 4.57 (t, J = 5 Hz, 0.4H), 4.61 (t, J = 5 Hz, 0.2H), 6.67 (m, 1H), 6.93 (m, 0.5H), 6.98 (m, 1.5H), 7.14−7.25 (m, 4H), 7.28−7.37 (m, 2H); LCMS (ESI) m/z 350 $[M + H]^+$.

(3*R*,8*R*,9*R*,9α*R*)-8-(3-Hydroxyphenyl)-8,9-dimethyl-3-phenyl-hexahydro-1*H*-quinolizin-4(6*H*)-one (38a) and (3*S*,8*R*,9*R*,9α*R*)-8-(3-Hydroxyphenyl)-8,9-dimethyl-3-phenyl-hexahydro-1*H*-quinolizin-4(6*H*)-one (38b). Compounds **38a**,**b** were synthesized in a manner similar to compound **29**, using compound **36** as starting material: yield 79% (white solid); ^{1}H NMR ($CDCl_3$) δ 0.60 (d, J = 7 Hz, 3H), 1.37 (s, 3H), 1.57 (m, 2H), 1.91 (br s, 2H), 2.02 (br s, 2H), 2.15 (m, 1H), 2.87 (br s, 1H), 3.39 (br s, 0.7H), 3.46 (br s, 0.3H), 3.92 (br s, 1H), 4.78 (br s, 0.3H), 4.89 (br s, 0.7H), 6.67 (d, J = 8 Hz, 1H), 6.91 (m, 2H), 7.18 (t, J = 8 Hz, 1H), 7.25 (m, 3H), 7.35 (m, 2H); LCMS (ESI) m/z 350 $[M + H]^+$.

3-((1*R*,2*R*,7*R*,9α*S*)-1,2-Dimethyl-7-phenyl-octahydro-1*H*-quinolizin-2-yl)phenol (8) and 3-((1*R*,2*R*,7*S*,9α*S*)-1,2-Dimethyl-7-phenyl-octahydro-1*H*-quinolizin-2-yl)phenol (9). Compounds **8** and **9** were synthesized in a manner similar to compound **4**, using compounds **37a**,**b** as starting materials. Compound **8** was obtained as a white solid in 46% yield. Compound **9** was obtained as a white solid in 26% yield.

8: ^{1}H NMR (CD_3OD) δ 1.06 (d, J = 7 Hz, 3H), 1.34 (s, 3H), 1.45 (br s, 1H), 1.77 (m, 3H), 1.93 (m, 3H), 2.58 (m, 4H), 2.92 (d, J = 4 Hz, 1H), 3.15 (dd, J = 15 and 4 Hz, 1H), 6.58 (m, 1H), 6.97 (m, 2H), 7.08 (t, J = 8 Hz, 1H), 7.14 (m, 1H), 7.26 (t, J = 8 Hz, 2H), 7.49 (t, J = 7 Hz, 2H); LCMS (ESI) m/z 336 $[M + H]^+$. Anal. ($C_{23}H_{29}NO \cdot 0.2H_2O$) C, H, N.

9: ^{1}H NMR (CD_3OD) δ 1.13 (d, J = 7 Hz, 3H), 1.36 (s, 3H), 1.59 (dd, J = 13 and 3 Hz, 1H), 1.67 (m, 1H), 1.90 (m, 1H), 1.97 (m, 1H), 2.05 (m, 1H), 2.14 (m, 1H), 2.23 (t, J = 11 Hz, 1H), 2.40 (t, J = 12 Hz, 1H), 2.63 (m, 1H), 2.85 (m, 2H), 6.58 (m, 1H), 6.96 (m, 2H), 7.09 (t, J = 8 Hz, 1H), 7.16 (m, 1H), 7.24 (m, 4H); LCMS (ESI) m/z 336 $[M + H]^+$. Anal. ($C_{23}H_{29}NO \cdot 0.5H_2O$) C, H, N.

3-((1*R*,2*R*,7*R*,9α*R*)-1,2-Dimethyl-7-phenyl-octahydro-1*H*-quinolizin-2-yl)phenol (10) and 3-((1*R*,2*R*,7*S*,9α*R*)-1,2-Dimethyl-7-phenyl-octahydro-1*H*-quinolizin-2-yl)phenol (11). Compounds **10** and **11** were synthesized in a manner similar to compound **4**, using compounds **38a**,**b** as starting materials. Compound **10** was obtained as a white solid in 13% yield. Compound **11** was obtained as a white solid in 8% yield.

10: ^{1}H NMR (CD_3OD) δ 0.56 (d, J = 7 Hz, 3H), 1.30 (s, 3H), 1.34 (s, 1H), 1.47 (br s, 1H), 1.72 (m, 1H), 1.81 (m, 1H), 1.97 (m, 1H), 2.08 (br s, 1H), 2.21 (m, 1H), 2.30 (br s, 1H), 2.66 (m, 3H), 2.97 (t, J = 4 Hz, 1H), 3.25 (m, 1H), 6.58 (m, 1H), 6.88 (m, 2H), 7.10 (t, J = 8 Hz, 1H), 7.16 (t, J = 8 Hz, 1H), 7.29 (t, J = 8 Hz, 2H), 7.51 (t, J = 8 Hz, 2H); LCMS (ESI) m/z 336 $[M + H]^+$; HRMS for $C_{23}H_{29}NO$ (M, 335.2249; $[M + H]$) calcd, 336.2322; found, 336.2320.

11: ^{1}H NMR (CD_3OD) δ 0.63 (d, J = 7 Hz, 3H), 1.32 (s, 3H), 1.37 (m, 1H), 1.48 (m, 1H), 1.62 (dq, J = 8 and 4 Hz, 1H), 1.98 (m, 2H), 2.08 (m, 1H), 2.18 (dt, J = 14 and 4 Hz, 2H), 2.37 (t, J

= 8 Hz, 1H), 2.62 (dt, *J* = 13 and 2 Hz, 1H), 2.74 (m, 1H), 2.92 (m, 2H), 6.61 (m, 1H), 6.89 (m, 1H), 6.92 (d, *J* = 8 Hz, 1H), 7.13 (t, *J* = 8 Hz, 1H), 7.19 (m, 1H), 7.28 (m, 4H); LCMS (ESI) *m*/*z* 336 $[M + H]^+$; HRMS for $C_{23}H_{29}NO$ (M, 335.2249; $[M + H]$) calcd, 336.2322; found, 336.2318.

1-((2*R*,4*R*,5*R*)-2-Allyl-4-(3-(benzyloxy)phenyl)-4,5-dimethylpiperidin-1-yl)prop-2-en-1-one (39). A solution of **18** (2.00 g, 5.97 mmol) and triethylamine (2.5 mL, 17.91 mmol) in dichloromethane (20 mL) was cooled to 0 °C. To this solution was added, dropwise, acryloyl chloride (0.75 mL, 8.96 mmol). The reaction mixture was stirred at room temperature for 2 h, then poured into a saturated ammonium chloride solution, and extracted with ethyl acetate. The combined organic extracts were washed with saturated brine, dried (Na_2SO_4), filtered, and evaporated. The crude material was purified by silica gel flash column chromatography, eluting with 0−40% ethyl acetate in hexanes to give **39** as a yellow oil (1.21 g, 52%). ^{1}H NMR ($CDCl_3$) δ 0.63 (d, *J* = 7 Hz, 3H), 1.49 (s, 3H), 1.85 (d, *J* = 14 Hz, 1H), 2.15 (br s, 1H), 2.29 (br s, 1H), 2.59 (t, *J* = 6 Hz, 1H), 3.68 (m, 1H), 5.09 (m, 3H), 5.66 (d, *J* = 9 Hz, 1H), 6.26 (m, 1H), 6.60 (m, 1H), 6.81 (m, 3H), 7.22 (d, *J* = 8 Hz, 1H), 7.33 (m, 1H), 7.39 (m, 2H), 7.44 (m, 2H); LCMS (ESI) *m*/*z* 390 $[M + H]^+$.

1-((2*S*,4*R*,5*R*)-2-Allyl-4-(3-(benzyloxy)phenyl)-4,5-dimethylpiperidin-1-yl)prop-2-en-1-one (40). Compound **40** was synthesized in a manner similar to compound **39**, using compound **19** as starting material: yield 45% (yellow oil).^{1}H NMR ($CDCl_3$) δ 0.40 (d, *J* = 7 Hz, 3H), 1.30 (s, 3H), 1.86 (m, 1H), 2.00 (m, 2H), 2.32 (m, 2H), 2.75 (br s, 1H), 4.29 (br s, 1H), 5.07 (m, 3H), 5.69 (dd, *J* = 10 and 2 Hz, 1H), 5.81 (m, 1H), 6.35 (dd, *J* = 16 and 2 Hz, 1H), 6.60 (dd, *J* = 16 and 10 Hz, 1H), 6.80 (dd, *J* = 8 and 2 Hz, 1H), 6.88 (m, 2H), 7.22 (t, *J* = 8 Hz, 1H), 7.32 (m, 1H), 7.37 (m, 2H), 7.42 (m, 2H); LCMS (ESI) *m*/*z* 390 $[M + H]^+$.

(7*R*,8*R*,9α*R*)-8-(3-(Benzyloxy)phenyl)-7,8-dimethyl-7,8,9,9α-tetrahydro-1*H*-quinolizin-4(6*H*)-one (41). A solution of **39** (1.21 g, 3.11 mmol) in anhydrous methylene chloride (40 mL) was purged with nitrogen for 20 min. Grubbs' second-generation catalyst (0.13 g, 0.16 mmol) was then added to the reaction mixture, which was heated to reflux for 2 h. The solvents were removed under reduced pressure, and the residue was purified by silica gel column chromatography eluting with 0−40% ethyl acetate in hexanes: yield 74% (beige solid). ^{1}H NMR ($CDCl_3$) δ 1.09 (d, *J* = 7 Hz, 3H), 1.35 (s, 3H), 1.62 (dd, *J* = 14 Hz and 12 Hz, 1H), 1.89 (m, 1H), 2.16 (m, 2H), 2.34 (t, *J* = 6 Hz, 0.5H), 2.39 (t, *J* = 6 Hz, 0.5H), 2.72 (dd, *J* = 13 and 12 Hz, 1H), 3.70 (m, 1H), 4.12 (dd, *J* = 14 and 5 Hz, 1H), 5.89 (dd, *J* = 10 and 2 Hz, 1H), 6.47 (m, 1H), 6.83 (dd, *J* = 7 and 2 Hz, 1H), 6.98 (m, 2H), 7.22 (t, *J* = 8 Hz, 1H), 7.39 (m, 5H); LCMS (ESI) *m*/*z* 362 $[M + H]^+$.

(7*R*,8*R*,9α*S*)-8-(3-(Benzyloxy)phenyl)-7,8-dimethyl-7,8,9,9α-tetrahydro-1*H*-quinolizin-4(6*H*)-one (42). Compound **42** was synthesized in a manner similar to compound **41**, using compound **40** as starting material: yield 95% (yellow oil).^{1}H NMR ($CDCl_3$) δ 0.67 (d, *J* = 7 Hz, 3H), 1.36 (s, 3H), 1.76 (m, 1H), 2.12 (m, 2H), 2.32 (m, 1H), 2.44 (t, *J* = 6 Hz, 0.5H), 2.49 (t, *J* = 6 Hz, 0.5H), 3.22 (dd, *J* = 13 and 3 Hz, 1H), 3.76 (m, 1H), 4.21 (dd, *J* = 14 and 3 Hz, 1H), 5.93 (dd, *J* = 10 and 2 Hz, 1H), 6.52 (m, 1H), 6.82 (m, 1H), 6.89 (m, 1H), 7.25 (t, *J* = 8 Hz, 1H), 7.32 (m, 1H), 7.37 (t, *J* = 7 Hz, 2H), 7.43 (d, *J* = 7 Hz, 2H); LCMS (ESI) *m*/*z* 362 $[M + H]^+$.

(7*R*,8*R*,9α*R*)-8-(3-Hydroxyphenyl)-7,8-dimethyl-hexahydro-1*H*-quinolizin-4(6*H*)-one (43). To a solution of **41** (0.20 g, 0.55 mmol) in ethanol (30 mL) was added 10% palladium on charcoal (catalytic), and the mixture was stirred at room temperature under a hydrogen atmosphere for 3 h. The mixture was then filtered through Celite. The Celite was washed with warm ethanol, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography on silica, eluting with 0−50% ethyl acetate in hexanes to give **43** as a white solid (0.15 g, 100%). ^{1}H NMR ($CDCl_3$) δ 1.23 (d, *J* = 7 Hz, 3H), 1.35 (s, 3H), 1.48 (m, 3H), 1.81 (m, 3H), 2.11 (dd, *J* = 14 and 2 Hz, 1H), 2.38 (m, 2H), 3.01 (t, *J* = 13 Hz, 1H), 3.35 (m, 1H), 4.55 (dd, *J* = 14 and 5 Hz, 1H), 6.71 (dd, *J* = 8 and 1 Hz, 1H), 6.83 (dd, *J* = 8 and 1 Hz, 1H), 7.17 (m, 2H), 8.95 (br s, 1H); LCMS (ESI) *m*/*z* 274 $[M + H]^+$.

(7*R*,8*R*,9α*S*)-8-(3-Hydroxyphenyl)-7,8-dimethyl-hexahydro-1H-quinolizin-4(6*H*)-one (44). Compound **44** was synthesized in a manner similar to compound **43**, using compound **42** as starting material: yield 100% (yellow foam).^{1}H NMR ($CDCl_3$) δ 0.61 (br s, 3H), 1.41 (br s, 3H), 1.66 (m, 1H), 1.74 (m, 2H), 1.92 (m, 1H), 2.14 (m, 3H), 2.55 (m, 1H), 2.71 (m, 1H), 3.18 (m, 1H), 3.73 (m, 1H), 4.53 (m, 1H), 6.70 (d, *J* = 8 Hz, 1H), 6.77 (d, *J* = 6 Hz, 2H), 7.18 (t, *J* = 8 Hz, 1H); LCMS (ESI) *m*/*z* 274 $[M + H]^+$.

3-((2*R*,3*R*,9α*R*)-2,3-Dimethyl-octahydro-1*H*-quinolizin-2-yl)-phenol (12). To a solution of **43** (0.15 g, 0.55 mmol) in anhydrous THF (10 mL) was added borane−dimethyl sulfide complex (2 M anhydrous solution in THF, 0.55 mL, 1.10 mmol), and the reaction mixture was heated to reflux under a nitrogen atmosphere for 16 h. The mixture was then cooled to 0 °C. Methanol (10 mL) was then added to the reaction, which was stirred at 0 °C for 1 h. A 2 M anhydrous solution of HCl in diethyl ether was then added to the reaction mixture, which was heated to reflux for 1 h. Solvents were removed under reduced pressure. The residue was taken up in methanol and stripped of solvent under reduced pressure (this process was repeated five times). The residue was then basified with a 1 M aqueous solution of NaOH (5 mL), and the mixture was extracted with a 10% solution of methanol in methylene chloride. The organic extracts were washed with saturated brine, dried (Na_2SO_4), filtered and evaporated. The crude product was purified by silica gel flash column chromatography, eluting with 0−100% ethyl acetate in hexanes to give **12** as a white solid (0.058 g, 41%). ^{1}H NMR (CD_3OD), δ 1.09 (d, *J* = 7 Hz, 3H), 1.31 (m, 5H), 1.49 (dd, *J* = 15 and 12 Hz, 1H), 1.67 (m, 3H), 1.75 (m, 1H), 2.04 (m, 2H), 2.22 (m, 1H), 2.37 (m, 2H), 2.61 (m, 1H), 2.90 (d, *J* = 12 Hz, 1H), 6.61 (dd, *J* = 8 and 2 Hz, 1H), 6.91 (m, 2H), 7.10 (t, *J* = 8 Hz, 1H); LCMS (ESI): *m*/*z* 260$[M + H]^+$. Anal. ($C_{17}H_{25}NO\bullet0.25H_2O$) C, H, N.

3-((2*R*,3*R*,9α*S*)-2,3-Dimethyl-octahydro-1*H*-quinolizin-2-yl)-phenol (13). Compound **13** was synthesized in a manner similar to compound **12**, using compound **44** as starting material: yield 26% (white solid).^{1}H NMR (CD_3OD) δ 0.75 (d, *J* = 7 Hz, 3H), 1.33 (s, 4H), 1.37 (m, 2H), 1.52 (d, *J* = 14 Hz, 1H), 1.66 (m, 3H), 1.78 (m, 1H), 1.92 (t, *J* = 13 Hz, 1H), 2.03 (m, 1H), 2.10 (m, 0.5H), 2.19 (m, 0.5H), 2.56 (d, *J* = 12 Hz, 1H), 2.75 (m, 2H), 6.57 (dd, *J* = 8 and 3 Hz, 1H), 6.70 (t, *J* = 2 Hz, 1H), 6.74 (d, *J* = 8 Hz, 1H), 7.09 (t, *J* = 8 Hz 1H); LCMS (ESI) *m*/*z* 260 $[M + H]^+$. Anal. ($C_{17}H_{25}NO\cdot0.1H_2O$) C, H, N.

1-((2*S*,3*R*,4*R*)-2-Allyl-4-(3-(benzyloxy)phenyl)-3,4-dimethylpiperidin-1-yl)prop-2-en-1-one (45a) and 1-((2*R*,3*R*,4*R*)-2-Allyl-4-(3-(benzyloxy)phenyl)-3,4-dimethylpiperidin-1-yl)prop-2-en-1-one (45b). Compounds **45a** and **45b** were synthesized in a manner similar to compound **39**, using compound **33a**,**b** as starting material: yield 65% (white solid). ^{1}H NMR ($CDCl_3$) δ 0.51 (d, *J* = 7 Hz, 3H), 0.84 (m, 3H), 1.03 (br s, 3H), 1.37 (m, 3H), 1.52 (t, *J* = 12 Hz, 1H), 1.69 (m, 1H), 2.03 (m, 4H), 2.24 (br s, 1H), 2.50 (m, 2H), 2.94 (dt, *J* = 16 and 3 Hz, 1H), 3.38 (dt, *J* = 16 and 3 Hz, 1H), 3.73 (m, 1H), 3.86 (d, *J* = 14 Hz, 1H), 4.57 (m, 0.5H), 4.74 (m, 1.5H), 4.86 (m, 1H), 4.96 (m, 3H), 5.03 (m, 2H), 5.55 (m, 2H), 5.70 (m, 1H), 6.20 (m, 2H), 6.46 (m, 2H), 6.73 (m, 3H), 6.87 (m, 2H), 7.15 (m, 2H), 7.30 (m, 3H), 7.34 (m, 3H); LCMS (ESI) *m*/*z* 390 $[M + H]^+$.

(8*R*,9*R*,9α*S*)-8-(3-(Benzyloxy)phenyl)-8,9-dimethyl-7,8,9,9α-tetrahydro-1*H*-quinolizin-4(6*H*)-one (46a) and (8*R*,9*R*,9α*R*)-8-(3-(Benzyloxy)phenyl)-8,9-dimethyl-7,8,9,9α-tetrahydro-1*H*-quinolizin-4(6*H*)-one (46b). Compounds **46a**,**b** were synthesized in a manner similar to compound **41**, using **45a**,**b** as starting material: yield 100% (brown oil). ^{1}H NMR ($CDCl_3$) δ 0.62 (d, *J* = 6 Hz, 3H), 0.77 (d, *J* = 6 Hz, 3H), 1.32 (s, 3H), 1.40 (s, 3H), 1.58 (t, *J* = 3 Hz, 0.5H), 1.61 (t, *J* = 3 Hz, 0.5H), 1.73 (m, 2H), 1.89 (br s, 1H), 2.05 (m, 3H), 2.19 (m, 2H), 2.39 (t, *J* = 5 Hz, 0.5H), 2.43 (t, *J* = 5 Hz, 0.5H), 2.55 (t, *J* = 5 Hz, 0.5H), 2.59 (t, *J* = 5 Hz, 0.5H), 2.97 (dt, *J* = 15 and 3 Hz, 1H), 3.45 (m, 2H), 3.67 (m, 0.5H), 3.76 (m, 0.5H), 4.36 (m, 1H), 5.95 (d, *J* = 10 Hz,

2H), 6.52 (m, 2H), 6.83 (d, $J = 9$ Hz, 2H), 6.98 (m, 4H), 7.26 (m, 2H), 7.29−7.48 (m, 10H); LCMS (ESI) *m*/*z* 362 $[M + H]^+$.

(8*R*,9*R*,9α*S*)-8-(3-Hydroxyphenyl)-8,9-dimethyl-hexahydro-1*H*-quinolizin-4(6*H*)-one (47a) and (8*R*,9*R*,9α*R*)-8-(3-Hydroxyphenyl)-8,9-dimethyl-hexahydro-1*H*-quinolizin-4(6*H*)-one (47b). Compounds **47a** and **47b** were synthesized in a manner similar to compound **43**, using **46a**,**b** as starting material: yield 85% (white foam). ^{1}H NMR ($CDCl_3$) δ 0.62 (d, $J = 6$ Hz, 3H), 0.93 (d, $J = 7$ Hz, 3H), 1.33 (s, 6H), 1.43 (m, 1H), 1.52 (m, 1H), 1.61 (m, 4H), 1.86 (m, 4H), 2.13 (m, 3H), 2.34 (m, 3H), 2.49 (m, 2H), 2.79 (t, $J = 14$ Hz, 1H), 3.04 (t, $J = 14$ Hz, 1H), 3.30 (m, 1H), 3.56 (m, 1H), 4.35 (m, 1H), 4.74 (m, 1H), 6.74 (d, $J = 8$ Hz, 2H), 6.87 (t, $J = 8$ Hz, 2H), 6.92 (s, 1H), 7.01 (s, 1H), 7.14 (m, 2H), 8.30 (br s, 1H), 8.61 (br s, 1H); LCMS (ESI) *m*/*z* 274 $[M + H]^+$.

3-((1*R*,2*R*,9α*S*)-1,2-Dimethyl-octahydro-1*H*-quinolizin-2-yl)phenol (14) and 3-((1*R*,2*R*,9α*R*)-1,2-Dimethyl-octahydro-1*H*-quinolizin-2-yl)phenol (15). To a solution of **47a**,**b** (0.09 g, 0.33 mmol) in anhydrous THF (10 mL) was added borane−dimethyl sulfide complex (2 M anhydrous solution in THF, 0.33 mL, 0.66 mmol), and the reaction mixture was heated to reflux under a nitrogen atmosphere for 16 h. The mixture was then cooled to 0 °C. Methanol (10 mL) was then added to the reaction, which was stirred at 0 °C for 1 h. A 2 M anhydrous solution of HCl in diethyl ether was then added to the reaction mixture, which was heated to reflux for 1 h. Solvents were removed under reduced pressure. The residue was taken up in methanol and stripped of solvent under reduced pressure (this process was repeated five times). The residue was then basified with a 1 M aqueous solution of NaOH (5 mL), and the mixture was extracted with a 10% solution of methanol in methylene chloride. The organic extracts were washed with saturated brine, dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel flash column chromatography, eluting with 0−100% ethyl acetate in hexanes to give a mixture of **14** and **15**. LC separation of that mixture gave **14** as a white solid (0.005 g, 6%) and **15** as a white solid (0.012 g, 15%).

14: ^{1}H NMR (CD_3OD) δ 1.08 (d, $J = 7$ Hz, 4H), 1.33 (s, 4H), 1.61 (m, 3H), 1.86 (m, 2H), 2.01 (m, 2H), 2.15 (m, 1H), 2.36 (m, 2H), 2.61 (m, 1H), 2.81 (m, 1H), 6.58 (m, 1H), 6.92 (m, 2H), 7.08 (t, $J = 8$ Hz, 1H); LCMS (ESI) *m*/*z* 260 $[M + H]^+$. HRMS for $C_{17}H_{25}NO$ (M, 259.1936; [M + H]) calcd, 260.2009; found, 260.2002.

15: ^{1}H NMR (CD_3OD) δ 0.57 (d, $J = 6$ Hz, 3H), 1.15 (m, 1.5H), 1.29 (s, 3H), 1.45 (m, 1H), 1.65 (m, 2H), 1.80 (m, 1H), 1.92 (m, 2.5H), 2.05 (m, 1H), 2.15 (dt, $J = 13$ and 9 Hz, 1H), 2.24 (dt, $J = 11$ and 4 Hz, 1H), 2.55 (dt, $J = 13$ and 3 Hz, 1H), 2.70 (m, 1H), 2.88 (d, $J = 12$ Hz, 1H), 6.59 (dd, $J = 8$ and 2 Hz, 1H), 6.86 (d, $J = 2$ Hz, 1H), 6.89 (d, $J = 8$ Hz, 1H), 7.11 (t, $J = 8$ Hz, 1H); LCMS (ESI) *m*/*z* 260 $[M + H]^+$. Anal. ($C_{17}H_{25}NO \cdot 0.8H_2O$) C, H, N.

B. Biological Methods. Radioligand Binding Assays. Membrane preparations from Chinese hamster ovary (CHO) cells stably expressing human κ-, μ-, or δ-opioid receptors were prepared as described previously.[24] The assay buffer used is composed of 50 mM tris(hydroxymethyl) aminomethane HCl, pH 7.8, 1.0 mM ethylene glycol bis(β-aminoethyl ether)-*N*,*N*,*N*′,*N*′-tetraacetic acid (EGTA-free acid), 5.0 mM $MgCl_2$, 10 mg/L leupeptin, 10 mg/L pepstatin A, 200 mg/L bacitracin, and 0.5 mg/L aprotinin. After dilution in assay buffer and homogenization in a Polytron homogenizer (Brinkmann, Westbury, NY) for 30 s at a setting of 1, membrane proteins (10−80 μg) in 250 μL of assay buffer were added to mixtures containing test compound and [^{3}H]diprenorphine (0.5−1.0 nM, 25 000−50 000 dpm) in 250 μL of assay buffer in 96-well deep-well polystyrene titer plates (Beckman) and incubated at room temperature for 60 min. Reactions were terminated by vacuum filtration with a Brandel MPXR-96T harvester through GF/B filters that had been pretreated with a solution of 0.5% polyethylenimine and 0.1% bovine serum albumin for at least 1 h. The filters were washed four times with 1.0 mL each of ice-cold 50 mM Tris-HCl, pH 7.8, and 30 μL of Microscint-20 (Packard Instrument Company, Meriden, CT) was added to each filter. Radioactivity on the filters was determined by scintillation spectrometry in a Packard TopCount.

[^{3}H]Diprenorphine with a specific activity of 50 Ci/mmol was purchased from Perkin-Elmer Life Sciences, Inc. (Boston, MA). The K_D values for [^{3}H]diprenorphine binding were 0.33 nM for the κ and μ receptors and 0.26 nM for the δ receptor. Receptor expression levels, determined as B_{max} values from Scatchard analyses, were 4400, 4700, and 2100 fmol/mg of protein for the κ, μ, and δ receptors, respectively. Preliminary experiments were performed to show that no specific binding was lost during the wash of the filters, that binding achieved equilibrium within the incubation time and remained at equilibrium for at least an additional 60 min and that binding was linear with regard to protein concentration. Nonspecific binding, determined in the presence of 10 μM unlabeled naloxone, was less than 10% of total binding. Protein was quantified by the method of Bradford.[25]

The data from competition experiments were fit by nonlinear regression analysis with the program Prism (GraphPad Software, Inc., San Diego, CA) using the four-parameter equation for one-site competition, and K_i values were subsequently calculated from EC_{50} values by the Cheng−Prusoff equation.

Receptor-Mediated [^{35}S]GTPγS Binding. Receptor-mediated [^{35}S]GTPγS binding was performed by modifications of the methods of Selley and collaborators[26] and Traynor and Nahorski.[27] Assays were carried out in 96-well FlashPlates (Perkin-Elmer Life Sciences, Inc, Boston, MA). Membranes prepared from CHO cells expressing the appropriate receptor (50−100 μg of protein) were added to assay mixtures containing agonist with or without antagonists, approximately 100 000 dpm (100 pM) [^{35}S]GTPγS, 3.0 μM GDP, 75 mM NaCl, 15 mM $MgCl_2$, 1.0 mM EGTA, 1.1 mM dithiothreitol, 10 mg/L leupeptin, 10 mg/L pepstatin A, 200 mg/L bacitracin, and 0.5 mg/L aprotinin in 50 mM Tris-HCl buffer, pH 7.8. After incubation at room temperature for 1 h, the plates were sealed and centrifuged at 800 *g* in a swinging bucket rotor for 5 min, and bound radioactivity was determined with a TopCount microplate scintillation counter (Packard Instrument Co., Meriden, CT).

Agonist potency and efficacy were assessed by measuring stimulation of [^{35}S]GTPγS binding by a series of concentrations of agonist. The concentration to give half-maximal stimulation (EC_{50}) was determined by nonlinear regression using Prism relative to the maximal stimulation achieved by loperamide.

Antagonist activities were obtained by titration in the presence of a concentration of loperamide (50 nM) that yielded 80% of its maximal stimulation (EC_{80}), and the data were analyzed by nonlinear regression fit using Prism. Efficacy was expressed as the maximum percent inhibition of the agonist-stimulated [^{35}S]GTPγS binding, and potency was expressed as the concentration of antagonist that achieved 50% of the maximum inhibition of that antagonist. Loperamide was used as μ agonist.

Supporting Information Available: Tables of crystallographic data for compounds **31** and **8**. Table of elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Crystallographic data for compound **8** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 604293. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Rd., Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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