JOC The Journal of Organic Chemistry

Article

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b01366 • Publication Date (Web): 27 Jul 2016

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Design, synthesis, and biological evaluation of structurally rigid analogues of 4-(3-hydroxyphenyl)piperidine opioid receptor antagonists

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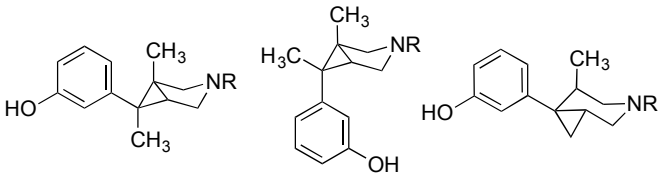


Abstract

In order to gain additional information concerning the active conformation of the *N*-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (**1**) class of opioid receptor antagonists, procedures were developed for the synthesis of structurally rigid *N*-substituted-6-(3-hydroxyphenyl)3-azabicyclo[3.1.0]hexane and 3-methyl-4-(3-hydroxyphenyl)-4-azabicyclo[4.1.0]heptanes. Evaluation of the conformationally constrained series in a [^{35}S]GTPγS assay showed that structural rigid compounds having the 3-hydroxyphenyl group locked in the piperidine equatorial orientation had potencies equal to or better than similar compounds having more flexible structures similar to **1**. The studies of the rigid compounds also suggested that the 3-methyl group present in compound **1** type antagonists may not be necessary for their pure opioid antagonist properties.

Keywords: azabicyclo[3.1.0]hexanes, azabicyclo[4.1.0]heptanes, opioid antagonist, x-ray structure

Introduction

N-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**1**) are a class of pure opioid receptor antagonists with a novel pharmacophore.[1] This pharmacophore has been used to design and develop several interesting opioid receptor antagonists. A few of the most studied compounds are LY255582 which was developed as a potential drug to treat obesity, LY246736 (alvimopan; ENTEREG®, a drug on the market that accelerates the time to upper and lower GI recovery following surgeries that include partial bowel resection with primary anastomosis) and

JDTic, a potent and selective kappa opioid receptor antagonist as a potential pharmacotherapy for treating depression, anxiety, and substance abuse that reached phase 1 clinical studies.[2] JDTic also proved highly useful for obtaining the x-ray structure of the human κ opioid receptor.[3]

The SAR studies that led to the discovery of LY255582, LY246736, and JDTic all involved changes in the *N*-substituent of **1** (Figure 1). We have previously reported the synthesis of **2**, **3**, **4**, and **5**, also in this class.[4] In this study we report the development of methods for the synthesis of *N*-substituted 6-(3-hydroxyphenyl)-3-azabicyclo[3.1.0]hexane analogues **6**, **7**, **8**, **9**, **10**, and **11,** and the *N*-substituted 3-methyl-4-(3-hydroxyphenyl)-4-azabicyclo[4.1.0]heptanes **12** and **13**, and compare their [^{35}S]GTPγS K_e values as opioid receptor antagonists to previously reported *N*-substituted *trans*-3,4-dimethyl-4-(3-hydrophenyl)-piperidines (**1-5**).

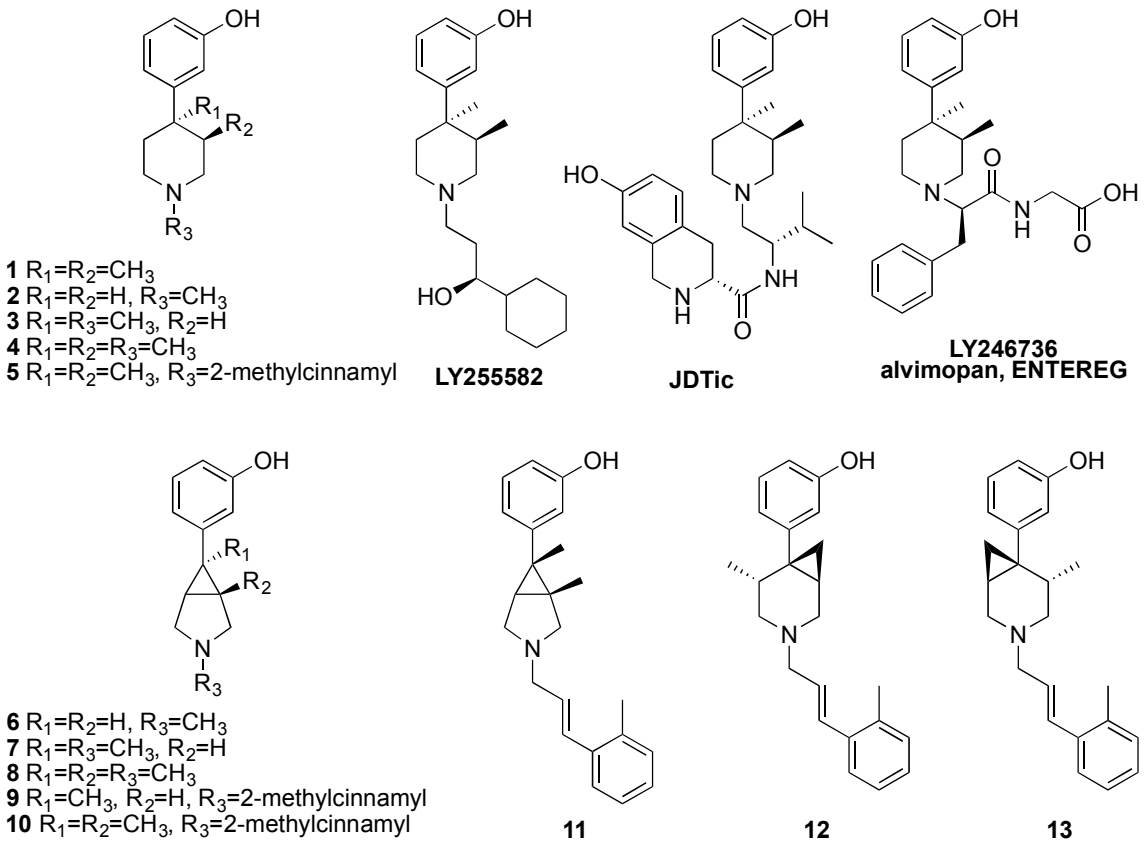
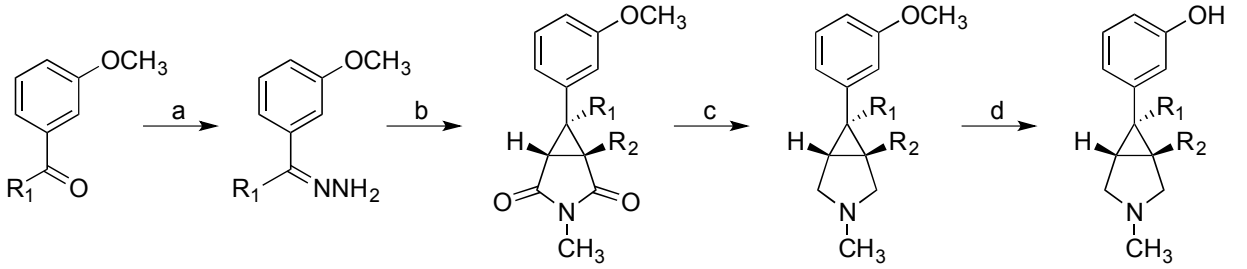


Figure 1. Structures of 1-5, LY255582, JDTic, alvimopan, and **6-13**.

Results

Compounds **6**, **7**, and **8** were synthesized as outlined in Scheme 1.[5] Compounds **14a** and **14b** were condensed with hydrazine hydrate to provide the hydrazones **15a** and **15b**, respectively. Oxidation of **15a** and **15b** with manganese dioxide in dioxane afforded the diazo compounds, which were reacted directly with the appropriate *N*-methylmaleimide to afford the imides **16a–c**. In the presence of boron trifluoride diethyl etherate, sodium borohydride reduced the imides to provide the amines **17a–c**. Demethylation of aryl methyl ethers **17a–c** was achieved using boron tribromide followed by the treatment of the resulting intermediate with refluxing piperazine to obtain target compounds **6**, **7**, and **8**.

Scheme 1. Synthesis of Compounds 6–8



14a R_1=H
14b R_1=CH_3

15a R_1=H
15b R_1=CH_3

16a R_1=R_2=H
16b R_1=CH_3, R_2=H
16c R_1=R_2=CH_3

17a R_1=R_2=H
17b R_1=CH_3, R_2=H
17c R_1=R_2=CH_3

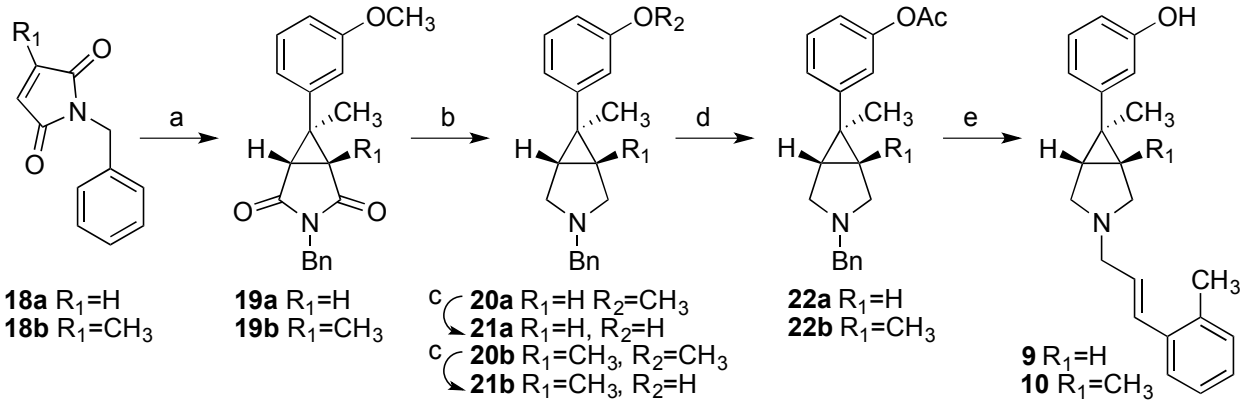
6 R_1=R_2=H
7 R_1=CH_3, R_2=H
8 R_1=R_2=CH_3

Reagents: a) NH_2NH_2•H_2O; b) (1) MnO_2, dioxane, (2) 1-methylmaleimide or 1,3-dimethylmaleimide, THF, reflux; c) $NaBH_4$, BF_3•$(OEt)_2$, THF; d) BBr_3, CH_2Cl_2.

The synthesis of **9** and **10** is outlined in Scheme 2. The diazo intermediate from **15b** (Scheme 1) was reacted with *N*-benzylmaleimide **18** to afford the 3-aza-[3.1.0]-bicyclo compounds **19a** and **19b**. Diborane reduction of the imides in tetrahydrofuran yielded **20a** and **20b**. Demethylation of the aryl methyl ethers was effected with boron trichloride and tetrabutylammonium iodide[6] in dichloromethane to afford the phenols **21a** and **21b**, which were converted to the phenyl acetates **22a** and **22b** for ease of handling. Catalytic hydrogenation

afforded the secondary amines, which were alkylated with *trans*-2-methylcinnamaldehyde and sodium cyanoborohydride. Finally, acetate hydrolysis afforded **9** and **10**.

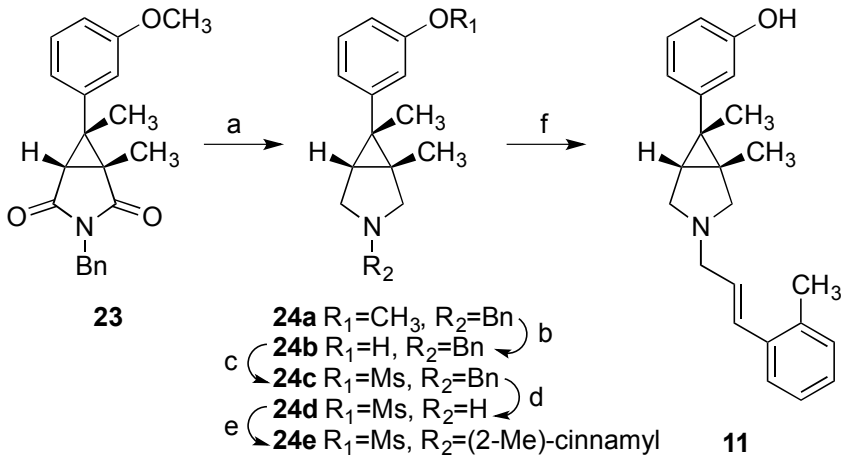
Scheme 2. Synthesis of Compounds 9 and 10



Reagents: a) 1-(3-Methoxyphenyl)-diazoethane, dioxane, reflux; b) $NaBH_4$, BF_3•$(OEt)_2$, THF; c) BCl_3, TBAI, CH_2Cl_2; d) (1) NaOH, $(NBu_4)_2SO_4$, dioxane or NaH, THF, (2) AcCl; e) (1) Pd/C, H_2, HCl, EtOH, (2) *trans*-2-methylcinnamaldehyde, $NaBH(OAc)_3$, 1,2-dichloroethane; (3) K_2CO_3, CH_3OH (aq).

The cyclopropanation reaction, which afforded **19b**, was found to produce a small yield of a competing product **23**. The diastereomer **23** was separated by chromatography and carried forward as shown in Scheme 3. The aryl methyl ether **24a** was converted to the phenol **24b**, which was masked as the phenyl mesylate **24c**. Hydrogenation afforded the secondary amine **24d**, which was reductively alkylated with 2-methylcinnamaldehyde to afford the penultimate intermediate **24e**. Mesylate hydrolysis afforded the final product **11**.

Scheme 3. **Synthesis of Compound 11**



Reagents: a) $NaBH_4$, BF_3•$(OEt)_2$, THF; b) BCl_3, TBAI, CH_2Cl_2; c) MsCl, pyridine; d) Pd/C, EtOH, HCl, H_2; e) *trans*-2-methylcinnamaldehyde, $NaBH(OAc)_3$, 1,2-dichloroethane; f) NaOH, CH_3OH.

A review of the literature confirms cyclopropanation of alternately substituted maleimides proceeds with high selectivity for the 6-*exo*-product where the largest group from the diazo compound is oriented away from the formed [3.1.0] ring system.[7-9] The groups at the 5- and 6-positions of **16a–c** and **19a–b** are stereospecifically fixed upon the same face via the 1,3-dipolar cycloaddition forming the pyrazoline prior to denitrogenation. X-ray analysis of **6** (See Figure S1 in Supporting Information) confirms the *exo* configuration was exclusively obtained in **16a**. Depending on the size of groups involved, a small amount of the competing *endo*-product (such as **23**) may also be formed. In the case of **19b** and **23**, ROESY analysis of the major product **19b** revealed a through space correlation between the δ 1.23 6-*endo* methyl (assigned by HMBC correlation with the δ 142.4 aromatic carbon) and the δ 4.61 *N*-benzyl methylene. Importantly, no correlation between the *N*-benzyl methylene and the electron-rich aromatic protons of the 6-*exo*-(3-methoxyphenyl) was observed. These observations support the assignment of **19b** as the *exo*-product and **23** as the minor, *endo*-product.

The major products **7**, **8**, **9** and **10** were therefore assigned analogous (1α,5α,6α) stereochemistry. The relative stereochemistry of the minor product **11** (arising from **23**) has been assigned (1α,5α,6β). As can be seen in Figure 2, this results in the 6-(3-hydroxyphenyl) occupying the opposite (β) face of the cyclopropane relative to the 1-methyl and 3-hydro substituents on the primary (α) face of the ring. The (1α,5α,6α) geometry of **6**, **7**, **8**, **9, 10** compares favorably to the natural conformation of *N*-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**1**) such as **4**, **5**, LY255582 and JDTic (Figure 1).

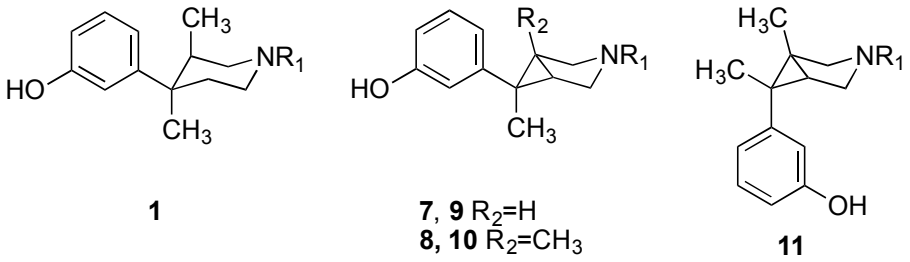
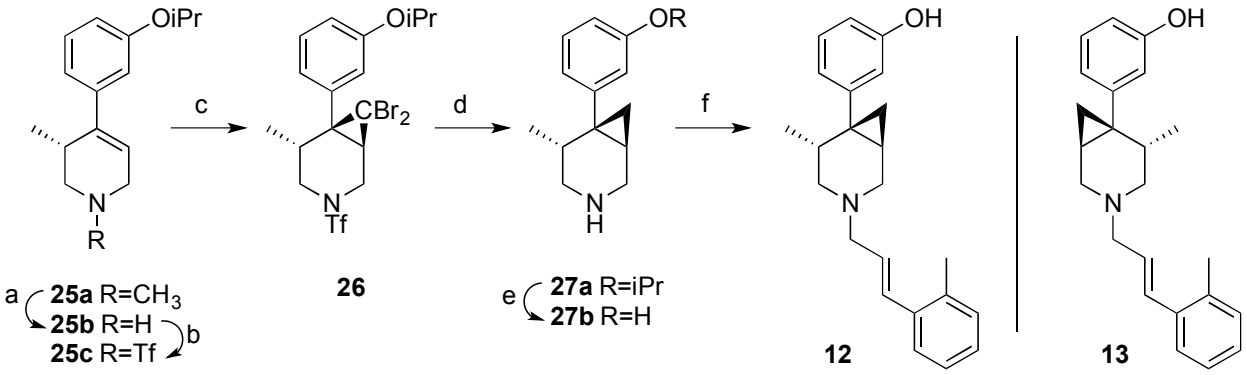


Figure 2. Conformational representation of general structure **1** and the (1α,5α,6α)-compounds **7-10** as compared to the (1α,5α,6β)-11.

Compounds **12** and **13** were prepared from the corresponding pure enantiomers as shown in Scheme 4. Demethylation of *N*-methyl-1,2,3,6-tetrahydropyridine **25a** afforded the secondary amine **25b**.[10] The amine was converted to the trifluoromethylsulfonamide **25c**. Cyclopropanation with dibromocarbene proceeded stereoselectively on the face opposite the 3-methyl of **25c** to afford the intermediate **26**.[11] Reduction of the dibromide proceeded concomitant to the triflamide hydrolysis yielding the piperidine **27a**,[12] which was subjected to x-ray analysis to confirm the structure and relative stereochemistry (See Figure S2 in Supporting Information). Deprotection to the phenol **27b** and reductive amination with 2-cinnamylaldehyde afforded to final product **12**.

Scheme 4. Synthesis of Compounds 12 and 13



Reagents: a) (1) 1-Chloroethyl chloroformate, 1,2-dichloroethane, (2) CH_3OH; b) Tf_2O, NEt_3, CH_2Cl_2; c) (1) NaOH, $CHBr_3$, $BnNMe_3Cl$, EtOH, CH_2Cl_2, (2) O_3, CH_2Cl_2, (3) $S(CH_3)_2$; d) Na, tBuOH, THF, NH_3; e) BCl_3, CH_2Cl_2; f) *trans*-2-methylcinnamaldehyde, $NaBH(OAc)_3$, 1,2-dichloroethane.

In this study, we compared the opioid receptor properties of structurally rigid **6**, **7**, **8**, **10**, **11**, **13**, and **12** to the corresponding *N*-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine analogs **2**, **3**, **4**, and **5** (Table 1).[4] Compound **8** has K_e = 18, 244, and 42 nM at the μ, δ, and κ opioid receptors compared to K_e = 29.3, 681, and 134 nM at the μ, δ, and κ receptors for **4**. Thus, the in vitro antagonist activity for **8** is a little bit better than that for **4** at all three opioid receptors. Compound **7** has K_e = 241 and 479 nM at the μ and κ opioid receptors, compared to K_e = 974 and 479 nM at the μ, and δ receptors for **3**. Thus, **7** is also slightly better than **3** at the μ and κ opioid receptors. Compound **3** was an agonist at the δ receptor, whereas **7** is an antagonist with K_e = 2390 nM. Both **6** and **2** lack antagonist activity at the μ and δ opioid receptors and have very little antagonist activity at the κ opioid receptor. The *N*-2-methylcinnamyl analog **10** has K_e = 0.02, 0.74, and 0.39 nM at the μ, δ, and κ opioid receptors, respectively, compared to K_e = 0.08, 1.21, and 0.44 nM at the μ, δ, and κ receptors, respectively, for **5** and thus, has slightly better antagonist activity than **5** at the μ and δ opioid

receptors (K_e = 0.08 and 1.21 nM) and almost identical antagonism at the κ opioid receptor (K_e = 0.44 nM). In contrast **11** (K_e = 54.6, 85 and IA at the μ, δ, and κ receptors, respectively), which has the 3,4-dimethyl groups in a *cis* relationship, is much less potent than **10** and **5**, which have the 3,4-dimethyl groups in a *trans* relationship. The *N*-2-methylcinnamyl analog **9** which does not have a 3-methyl group remains a pure opioid receptor antagonist with K_e = 0.48, 8.8, and 2.9 nM at the μ, δ, and κ opioid receptors, respectively, and thus has a little less antagonist potency than **5** at all three opioid receptors.

Table 1. Inhibition of Agonist-stimulated [35S]GTPγS Binding in Cloned Human μ, δ, κ Opioid Receptors

Compound	μ, DAMGO K_e (nM)	δ, DPDPE K_e (nM)	κ, U69,593 K_e (nM)
7	241 ± 65	2390 ± 440	479 ± 130
6	IA[a]	IA[a]	>8000
8	18 ± 6	244 ± 75	42 ± 10
9	0.48 ± 0.02	8.8 ± 3	2.9 ± 1
10	0.02 ± 0.01	0.74 ± 0.3	0.39 ± 0.2
11	54.6 ± 17	85 ± 26	IA[a]
13	3.5 ± 1	156 ± 90	50.2 ± 14
12	0.42 ± 0.02	89 ± 46	40.8 ± 15
2[b]	IA[a]	IA[a]	2700 ± 1300
3[b]	974 ± 230	[c]	479 ± 150
4[b]	29.3 ± 3	681 ± 240	134 ± 27
5	0.08 ± 0.03	1.21 ± 0.4	0.44 ± 0.2

[a] IA = inactive. [b] Data taken from Ref 4. [c] **3** was an agonist, ED_{50} = 8300 ± 2500 with E_{max} = 6490 ± 590 of DPDPE max.

Discussion

Synthetic procedures were developed for the synthesis of structurally rigid *N*-substituted 6-(3-hydrophenyl)-3-azabicyclo[3.10]hexane and 3-methyl-4-(3-hydroxyphenyl)-4-

azabicyclo[4.1.0]heptanes of the 3,4-dimethyl-4-(3-hydroxyphenyl)piperidine class of opioid receptor antagonists and were used to synthesize analogs **6**, **7**, **8**, **10**, **11**, **13**, and **12**.

Results from early NMR studies of trimethyl-substituted 4-(3-hydroxyphenyl)-piperidines suggested that a 3-hydroxyphenyl equatorial piperidine chair conformation mediated the opioid antagonist properties of the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine class of opioid antagonist.[13, 14] At this point in time it was also thought that the presence of the 3-methyl group on the piperidine ring was necessary for the opioid receptor antagonists' properties. Evaluation of the compounds in this study for their opioid properties using an [^{35}S]GTPγS assay showed that each of the analogs which have the 3-hydroxyphenyl group locked in an equatorial orientation were opioid receptor antagonist with efficacy at least as good as the corresponding *trans*-1,3-dimethyl-4-(3-hydroxyphenyl)piperidine compound and in the case of **10**, its antagonist activity was slightly better than that of the corresponding **5**.

In order to determine the importance of the 1-methyl group (equivalent to the 3-methyl in the 3,4-dimethylpiperidine class of antagonist) of the 1,6-dimethyl-3-azabicyclo[3.1.0]hexane ring system of **10**, we synthesized and evaluated the 1-desmethyl analog **9**. We found that **9**, which also has the 3-hydroxyphenyl group in a locked equatorial-like orientation, was a pure opioid receptor antagonist with K_es of 0.48, 8.6, and 2.9 nM at the μ, δ, and κ opioid receptors suggesting that the 3-position methyl group on **1** may not be needed for its opioid antagonist receptor of **10**. Although functional antagonism was not affected by the lack of a 1-position methyl group in the azabicyclo[3.1.0]hexanes series, the absence of a methyl group in this position did result in a small decrease in potency.

Experimental

Melting points were determined using a capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were obtained on a 500 MHz NMR spectrometer or a 300 MHz NMR spectrometer. Chemical shifts are reported in parts per million (ppm) with reference to internal solvent. Mass spectra (MS) were conducted on a mass spectrometer equipped with ESI (turbospray) source. Elemental analyses were performed by an external laboratory. The purity of the compounds (>95%) was established by elemental analysis. Optical rotations were measured on an automatic polarimeter. Analytical thin-layer chromatography (TLC) was carried out using silica gel 60 F_{254} TLC plates. TLC visualization was achieved with a UV lamp or in an iodine chamber. Flash column chromatography was done on a system using prepacked silica gel columns or using silica gel 60A (230–400 mesh). Solvent system: CMA80 80:18:2 $CHCl_3$:MeOH:conc. NH_4OH. Unless otherwise stated, reagent-grade chemicals were obtained from commercial sources and were used without further purification. All moisture- and air-sensitive reactions and reagent transfers were carried out under dry nitrogen.

3-[(1*α*,5*α*,6*α*)-3-Methyl-3-azabicyclo[3.1.0]hex-6-yl]phenol (6). Boron tribromide (1M solution in CH_2Cl_2, 5.4 mL) was added dropwise to a solution of **17a** (500 mg, 2.5 mmol) in dichloromethane (25 mL) at –78 °C under N_2. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was cooled to –78 °C, treated with MeOH (20 mL), warmed to r.t and stirred 10 min. The methanol was evaporated. The residue was partitioned between EtOAc and aq. piperazine. The resulting biphasic mixture was heated to reflux. Upon cooling, the organic layer was separated and concentrated. The residue was subjected to chromatography on silica gel eluting with a gradient of CMA80 in CH_2Cl_2 to afford

6 (59.6 mg, 13%) as white solid. mp 131–132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (t, J = 7 Hz, 1H), 6.59 (m, 2H), 6.49 (m, 1H), 3.13 (d, J = 10 Hz, 2H), 2.48 (d, J = 10 Hz, 2H), 2.37 (s, 3H), 2.20 (m, 1H), 1.70 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 144.4, 129.4, 112.9, 64.9, 57.7, 41.5, 27.9, 24.9; LRMS (ESI-quadrupole) m/z 190.3 ($M + H^+$); Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found C, 75.74; H, 7.71; N, 7.39.

***rac*-3-[(1*α*,5*α*,6*α*)-1,3-Dimethyl-3-azabicyclo[3.1.0]hex-6-yl]phenol (7)**. Boron tribromide (1M solution in CH_2Cl_2, 4.8 mL) was added dropwise to a solution of **17b** (500 mg, 2.3 mmol) in dichloromethane (25 mL) at –78 °C under N_2. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was cooled to –78 °C, treated with MeOH (20 mL), warmed to room temperature and stirred for 10 min. The methanol was evaporated. The residue was partitioned between EtOAc and aq. piperazine. The resulting biphasic mixture was heated to reflux. Upon cooling, the organic layer was separated and concentrated. The residue was subjected to chromatography on silica gel eluting with a gradient of CMA80 in CH_2Cl_2 to afford **7** (95.1 mg, 19%) as a white crystalline solid. m.p. 150–152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (t, J = 8 Hz, 1H), 6.95 (d, J = 8 Hz, 1H), 6.70 (d, J = 7 Hz, 1H), 6.46 (s, 1H), 3.42 (m 2H), 2.63 (d, J = 10 Hz, 2H), 2.38 (s, 3H), 2.08 (s, 2H), 1.39 (s, 3H); LRMS (ESI-quadrupole) m/z 204.6 ($M + H^+$). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found C, 76.69; H, 8.27; N, 6.95.

***rac*-3-[(1*α*,5*α*,6*α*)-1,3,6-Trimethyl-3-azabicyclo[3.1.0]hex-6-yl]phenol (8).** Boron tribromide (1M solution in CH_2Cl_2, 1.82 mL) was added dropwise to a solution of **17c** (200 mg, 0.86 mmol) in dichloromethane (20 mL) at –78 °C under N_2. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was cooled to –78 °C, treated with MeOH (20 mL), warmed to r.t and stirred for 10 min. The methanol was evaporated. The residue

was partitioned between EtOAc and aq. piperazine. The resulting biphasic mixture was heated to reflux. Upon cooling, the organic layer was separated and concentrated. The residue was subjected to chromatography on silica gel eluting with a gradient of CMA80 in CH_2Cl_2 to afford **8** as a white solid (68.2 mg, 36%). m.p. 119–121 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (t, J = 8 Hz, 1H), 6.72 (d, J = 7 Hz, 1H), 6.65 (m, 2H), 3.12 (m, 1H), 2.87 (d, J = 10 Hz, 1H), 2.78 (d, J = 11 Hz, 2H), 2.34 (s, 3H), 1.67 (m, 1H), 1.40 (s, 3H), 0.94 (s, 3H); LRMS (ESI-quadrupole) m/z 218.5 ($M + H^+$). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found C, 77.12; H, 8.75; N, 6.42.

3-{(1*α*,5*α*,6*α*)-6-Methyl-3-[(2*E*)-3-(2-methylphenyl)prop-2-en-1-yl]-3-azabicyclo[3.1.0]hex-6-yl}phenol oxalate (9). A solution of **22a** (860 mg, 2.68 mmol) in EtOH (35 mL) was added to a Parr hydrogenation bottle under N_2. Solid 10% Pd/C (1.0 g) was added and a 1.0 M solution of HCl in Et_2O (2.68 mL, 2.68 mmol) was then added and the solution was hydrogenated at 40 psi for 8 h. The solution was then filtered through a pad of Celite and concentrated under reduced pressure to afford 3-[(1*α*,5*α*,6*α*)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl acetate as the HCl salt (0.92 g, 88%). A solution of *trans*-2-methylcinnamaldehyde (80.0 mg, 0.51 mmol) in 1,2-dichloroethane (10 mL) was then added to a suspension of 3-[(1*α*,5*α*,6*α*)-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl acetate (100 mg, 0.43 mmol) and sodium triacetoxyborohydride (130 mg, 0.65 mmol) in 1,2-dichloroethane (30 mL). The suspension was allowed to stir at room temperature for 4 h and was diluted with a saturated solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The resulting extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford an oil that was purified using silica gel chromatography ($CHCl_3$, MeOH, NH_4OH; 90:9:1) to provide 3-{(1*α*,5*α*,6*α*)-6-methyl-3-[(2*E*)-3-(2-methylphenyl)prop-2-en-1-yl]-3-azabicyclo[3.1.0]hex-6-

yl}phenyl acetate (0.065 g, 42 %) as a colorless oil. Solid K_2CO_3 (120 mg, 0.90 mmol) was added to a solution of 3-{(1*α*,5*α*,6*α*)-6-methyl-3-[(2*E*)-3-(2-methylphenyl)prop-2-en-1-yl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl acetate in MeOH (5 mL) and H_2O (2 mL). The solution was allowed to stir at room temperature for 2 h and was acidified with 1.0 M HCl, made basic with $NaHCO_3$ and extracted with EtOAc (3 × 25 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oil was purified on silica gel chromatography ($CHCl_3$, MeOH, NH_4OH; 80:18:2) to afford pure 3-{(1*α*,5*α*,6*α*)-6-methyl-3-[(2*E*)-3-(2-methylphenyl)prop-2-en-1-yl]-3-azabicyclo[3.1.0]hex-6-yl}phenol (0.05 g, 83 %) as the free base: ^{1}H NMR (300 MHz, MeOD) δ 7.42 (td, *J* = 2.3, 4.5 Hz, 1H), 7.24–6.96 (m, 4H), 6.82 (d, *J* = 15.4 Hz, 1H), 6.75–6.64 (m, 2H), 6.56 (dd, *J* = 2.4, 8.1 Hz, 1H), 6.12 (td, *J* = 6.5, 15.5 Hz, 1H), 3.38–3.25 (m, 3H), 3.13–3.00 (m, 2H), 2.87 (d, *J* = 10.5 Hz, 2H), 2.33 (s, 3H), 1.86 (br. s., 2H), 1.44 (s, 3H). The salt was formed by dissolving the free base and 1.1 eq. oxalic acid in acetone (10 mL) followed by gentle heating and cooling to induce precipitation. The collected solids were then recrystallized from acetone and EtOAc to afford **9** as a white solid. m.p. 161–162 °C; Anal. Calcd for $C_{22}H_{25}NO•C_2H_2O_4$: C, 70.40; H, 6.65; N, 3.42. Found C, 70.18; H, 6.61; N, 3.41.

***rac*-3-{(1α,5α,6α)-1,6-Dimethyl-3-[(2*E*)-3-(2-methylphenyl)prop-2-en-1-yl]-3-azabicyclo[3.1.0]hex-6-yl}phenol resorcylate (10).** A solution of **22b** (1.12 g, 0.0033 mol in EtOH (30 mL) was added to a Parr hydrogenation bottle under N_2. Solid 10% Pd/C (0.20 g) was added and a 1.0 M solution of HCl in Et_2O (3.34 mL, 3.34 mmol) was then added and the solution was hydrogenated at 40 psi for 8 h. The solution was then filtered through a pad of Celite and concentrated under reduced pressure to afford *rac*-3-[(1*α*,5*α*,6*α*)-1,6-dimethyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl acetate as the HCl salt (0.92 g, 88%). A solution of *trans*-2-

methylcinnamaldehyde (0.66 g, 4.5 mmol) in 1,2-dichloroethane (10 mL) was then added to a suspension of *rac*-3-[(1*α*,5*α*,6*α*)-1,6-dimethyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl acetate (920 mg, 3.75 mmol) and sodium triacetoxyborohydride (1.19 g, 0.0057 mol) in 1,2-dichloroethane (30 mL). The suspension was allowed to stir at room temperature for 4 h and was diluted with a saturated solution of $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The resulting extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford an oil that was purified using silica gel chromatography ($CHCl_3$, MeOH, NH_4OH; 90:9:1) to provide *rac*-3-{(1*α*,5*α*,6*α*)-1,6-dimethyl-3-[(2*E*)-3-(2-methylphenyl)prop-2-en-1-yl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl acetate (0.30 g, 21%) as a colorless oil. Solid K_2CO_3 (0.64 g, 4.63 mmol) was added to a solution of *rac*-3-{(1*α*,5*α*,6*α*)-1,6-dimethyl-3-[(2*E*)-3-(2-methylphenyl)prop-2-en-1-yl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl acetate in MeOH (9.5 mL) and H_2O (6.5 mL). The solution was allowed to stir at room temperature for 2 h and was acidified with 1.0 M HCl, made basic with $NaHCO_3$ and extracted with EtOAc (3 × 25 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oil was purified on silica gel chromatography ($CHCl_3$, MeOH, NH_4OH; 80:18:2) to afford pure *rac*-3-{(1α,5α,6α)-1,6-dimethyl-3-[(2*E*)-3-(2-methylphenyl)prop-2-en-1-yl]-3-azabicyclo[3.1.0]hex-6-yl}phenol (0.14 g, 50%) as the free base: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.48–7.21 (m, 2H), 7.20–7.04 (m, 4H), 6.82–6.56 (m, 4H), 6.14 (td, *J* = 6.6, 15.4 Hz, 1H), 3.33 (d, *J* = 6.4 Hz, 2H), 3.21 (dd, *J* = 5.7, 10.2 Hz, 1H), 2.99–2.85 (m, 2H), 2.82 (d, *J* = 10.2 Hz, 1H), 2.32 (s, 3H), 1.67 (d, *J* = 4.9 Hz, 1H), 1.46–1.36 (m, 3H), 0.92 (s, 3H). The salt was formed by dissolving 1.1 eq. 3,5-dihydroxybenzoic acid in MeOH (1 mL) and adding it to the free base in MeOH (3 mL) followed by Et_2O (10 mL) to induce precipitation. The collected solids were then recrystallized from MeOH and EtOAc to afford **10** as a white solid. m.p. 136–138 °C; Anal.

Calcd for $C_{23}H_{27}NO•C_7H_6O_4•1.25H_2O$: C, 70.64; H, 7.01; N, 2.74. Found C, 70.38; H, 6.75; N, 2.63.

***rac*-3-{(1*α*,5*α*,6β)-1,6-Dimethyl-3-[(2*E*)-3-(2-methylphenyl)prop-2-en-1-yl]-3-azabicyclo[3.1.0]hex-6-yl}phenol resorcylate (11).** A 1.0 M solution of NaOH (10 mL) was added to a solution of **24e** (110 mg, 0.27 mmol) in MeOH (25 mL) at 0 °C. The solution was allowed to warm to room temperature over 4 hours and was made acidic with 1.0 M HCl, made basic with $NaHCO_3$ and extracted with EtOAc (3 × 25 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting oil was purified on silica gel chromatography ($CHCl_3$, MeOH, NH_4OH; 80:18:2) to afford *rac*-3-{(1*α*,5*α*,6β)-1,6-dimethyl-3-[(2*E*)-3-(2-methylphenyl)prop-2-en-1-yl]-3-azabicyclo[3.1.0]hex-6-yl}phenol (0.054 g, 60%) as a colorless oil: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.24 (d, *J* = 3.8 Hz, 1H), 7.20–7.02 (m, 4H), 6.67 (d, *J* = 7.5 Hz, 1H), 6.62–6.51 (m, 2H), 6.37 (d, *J* = 15.8 Hz, 1H), 5.62 (td, *J* = 6.4, 15.8 Hz, 1H), 5.30 (br. s, 1H), 2.92 (dd, *J* = 3.4, 9.4 Hz, 2H), 2.84 (d, *J* = 6.0 Hz, 2H), 2.73 (dd, *J* = 4.3, 9.6 Hz, 1H), 2.51 (d, *J* = 9.4 Hz, 1H), 2.25 (s, 3H), 1.39 (s, 3H), 1.24 (s, 3H), 1.18 (d, *J* = 4.5 Hz, 1H). The salt was formed by adding a solution of 1.1 eq. 3,5-dihydroxybenzoic acid in MeOH (1 mL) to the free base in MeOH (3 mL) followed by Et_2O (10 mL) to induce precipitation. The collected solids were then recrystallized from MeOH and EtOAc to afford **11** as a white solid. m.p. 126–128 °C; Anal. Calcd for $C_{23}H_{27}NO•C_7H_6O_4•H_2O$: C, 71.26; H, 6.97; N, 2.77. Found C, 71.17; H, 6.71; N, 2.74.

3-{(1*R*,5*R*,6*S*)-5-Methyl-3-[(2*E*)-3-(2-methylphenyl)prop-2-en-1-yl]-3-azabicyclo[4.1.0]hept-6-yl}phenol resorcylate (12). A solution of *trans*-2-methylcinnamaldehyde (150 mg, 0.98 mmol) in 1,2-dichloroethane (5 mL) was then added to a suspension of **27b** (200 mg, 1.06 mmol) and sodium triacetoxyborohydride (250 mg, 1.18 mmol)

in 1,2-dichloroethane (15 mL). The suspension was allowed to stir at room temperature for 4 h and was diluted with a saturated solution of $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The resulting extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford an oil that was purified using silica gel chromatography using petroleum ether, Et_2O, TEA (10:9:1) as eluents to provide 3-{(1*R*,5*R*,6*S*)-5-methyl-3-[(2*E*)-3-(2-methylphenyl)prop-2-en-1-yl]-3-azabicyclo[4.1.0]hept-6-yl}phenol (0.16 g, 56 %) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.27 (m, 1H), 7.05–7.01 (m, 4H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.70–6.61 (m, 3H), 6.53 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.03 (dt, *J* = 9.0, Hz Hz, 1H) 3.08 (d, *J* = 6.6 Hz, 2H), 2.97 (d, *J* = 11.1 Hz, 1H), 2.66 (dd, *J* = 11.3, 5.0 Hz, 1H), 2.53 (dd, *J* = 11.4, 4.5 Hz, 1H), 2.21 (s, 3H), 2.18 – 2.07 (m, 1H), 1.77 (t, *J* = 10.4 Hz, 1H), 1.32–1.24 (m, 1H), 0.85–0.76 (m, 2H), 0.58 (d, *J* = 15.9, 6.6 Hz, 3H). The resorcylate salt was formed by adding a solution of 1.1 eq. 3,5-dihydroxybenzoic acid in MeOH (1 mL) to the free base in MeOH (3 mL) followed by Et_2O (10 mL) to induce precipitation. The collected solids were then recrystallized from MeOH and EtOAc to afford **12** as a white solid. m.p. 155–157 °C; $[\alpha]_D^{22}$ –14.6 (c 0.11, MeOH; Anal. Calcd for $C_{23}H_{27}NO•C_7H_6O_4•1.25H_2O$: C, 70.63; H, 7.01; N, 2.75. Found C, 70.74; H, 6.79; N, 2.79.

3-{(1*S*,5*S*,6*R*)-5-Methyl-3-[(2*E*)-3-(2-methylphenyl)prop-2-en-1-yl]-3-azabicyclo[4.1.0]hept-6-yl}phenol resorcylate (13). Compound **13** was prepared in manner analogous to **12**. The free base: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.27 (m, 1H), 7.05–7.01 (m, 4H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.70–6.61 (m, 3H), 6.53 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.03 (dt, *J* = 9.0, Hz Hz, 1H) 3.08 (d, *J* = 6.6 Hz, 2H), 2.97 (d, *J* = 11.1 Hz, 1H), 2.66 (dd, *J* = 11.3, 5.0 Hz, 1H), 2.53 (dd, *J* = 11.4, 4.5 Hz, 1H), 2.21 (s, 3H), 2.18–2.07 (m, 1H), 1.77 (t, *J* = 10.4 Hz, 1H), 1.32–1.24 (m, 1H), 0.85–0.76 (m, 2H), 0.58 (d, *J* = 15.9, 6.6 Hz, 3H). The resorcylate salt: m.p. 152–

155 °C $[\alpha]_D^{22}$ +14.75 (c 0.19, MeOH). Anal. Calcd for $C_{23}H_{27}NO•C_7H_6O_4•H_2O$: C, 71.26; H, 6.97; N, 2.77. Found C, 71.08; H, 6.75; N, 2.73.

[(3-Methoxyphenyl)methylidene]hydrazine (15a). Hydrazine hydrate (36.7 g, 0.734 mol) was added dropwise to cooled *m*-anisaldehyde (**14a**) (10 g, 0.073 mol). Ethanol (5 mL) was rinsed through the addition funnel and added to the reaction. The reaction mixture was allowed to warm to room temperature and stirred overnight. Water (100 mL) was added and the product extracted with CH_2Cl_2 (3 × 150 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated to afford a quantitative yield of **15a** as oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.23 (t, *J* = 7 Hz, 1H), 7.16 (s, 1H), 7.08 (d, *J* = 8 Hz, 1H), 6.85 (d, *J* = 8 Hz, 1H), 5.53 (s, 2H), 3.82 (s, 3H).

[1-(3-Methoxyphenyl)ethylidene]hydrazine (15b). 3-Methoxyacetophenone (**14b**) (10 g, 0.067 mol) was slowly added to hydrazine hydrate (33.3 g, 0.67 mol) at room temperature then the solution was heated to reflux for 30 min. Upon cooling, water (100 mL) was added to the reaction mixture and the product extracted with CH_2Cl_2 (3 × 150 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to obtain a quantitative yield of **15b** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 3H), 6.86 (m, 1H), 5.36 (s, 2H), 3.83 (s, 3H), 2.12 (s, 3H).

(1*α*,5*α*,6*α*)-6-(3-methoxyphenyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione (16a). Manganese dioxide (15.2 g, 0.17 mol) was added to a solution of **15a** (11.0 g, 0.074 mol) in dioxane (100 mL). The reaction mixture was stirred for 45 min then filtered through Celite and washed through with dioxane (250 mL). The resulting red solution was treated with 1-methyl-1*H*-pyrrole-2,5-dione (9.34 g, 74 mmol). The reaction mixture was stirred at room temperature for 1 h then heated to reflux overnight. The reaction mixture was cooled, then concentrated. The residue was subjected to chromatography on silica gel eluting with petroleum ether/acetone

(90:10) to afford 5.29 g (31%) of **16a** as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (t, J = 8 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 6.63 (m, 2H), 3.80 (s, 3H), 2.92 (s, 3H), 2.76 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 159.9, 137.3, 130.1, 118.4, 113.2, 112.4, 55.4, 38.1, 28.9, 24.5.

***rac*-(1*α*,5*α*,6*α*)-6-(3-methoxyphenyl)-1,3-dimethyl-3-azabicyclo[3.1.0]hexane-2,4-dione (16b).** Manganese dioxide (14.5 g, 0.17 mol) was added to a solution of **15b** (10.9 g, 0.067 mol) in dioxane (100 mL). The reaction mixture was stirred for 45 min then filtered through Celite and washed through with dioxane (250 mL). The resulting red solution was treated with 1-methyl-1*H*-pyrrole-2,5-dione (7.33 g, 0.067 mol). The reaction mixture was stirred at room temperature for 1 h then heated to reflux overnight. The reaction mixture was cooled, then concentrated. The residue was subjected to chromatography on silica gel eluting with petroleum ether/acetone (90:10) to afford 3.52 g, (22%) of **16b** as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (t, J = 8 Hz, 1H), 6.90 (d, J = 8 Hz, 1H), 6.86 (m, 2H), 3.81 (s, 3H), 2.95 (s, 3H), 2.80 (s, 2H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 159.9, 144.1, 134.2, 130.1, 119.5, 113.3, 55.4, 42.6, 32.7, 24.1, 17.6.

***rac*-(1α,5α,6α)-6-(3-methoxyphenyl)-1,3,6-trimethyl-3-azabicyclo[3.1.0]hexane-2,4-dione (16c).** Manganese dioxide (14.5 g, 0.166 mol) was added to a solution of **15b** (10.9 g, 0.067 mol) in dioxane (100 mL). The reaction mixture was stirred for 45 min then filtered through Celite and washed through with dioxane (250 mL). The resulting red solution was treated with 1,3-dimethyl-1*H*-pyrrole-2,5-dione (8.41 g, 0.067 mol). The reaction mixture was stirred at room temperature for 1 h then heated to reflux overnight. The reaction mixture was cooled, then concentrated. The residue was subjected to chromatography on silica gel eluting with petroleum ether/acetone (90:10) to afford 6.3 g (37%) of **16c** as colorless oil. ^{1}H NMR (300

MHz, $CDCl_3$) δ 7.28 (m, 1H), 6.81 (m, 3H), 3.82 (s, 3H), 2.95 (s, 3H), 2.68 (s,H), 1.42 (s, 3H), 1.19 (s, 3H); LRMS (ESI, quadrupole) *m*/*z* 260.4 ($M + H^+$).

(1*α*,5*α*,6*α*)-6-(3-Methoxyphenyl)-3-methyl-3-azabicyclo[3.1.0]hexane (17a). Sodium borohydride (1.19 g, 31.6 mmol) was added in portions to a solution of **16a** (3.52 g, 0.014 mol) in THF at –5 °C. Boron trifluoride diethyl etherate (5.70 g, 40.1 mmol) was added dropwise to the mixture leading to the formation of a white precipitate. The reaction mixture was allowed to warm to room temperature, stirred for 2 h, and then heated at reflux for 3 h. The reaction mixture was cooled, treated with saturated $NaHCO_3$ (150 mL) then extracted with EtOAc (3 × 150 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to obtain a white solid which was subjected to chromatography on silica gel eluting with CH_2Cl_2 to obtain 2.27 g (78%) of **17a** as a white solid. ^1H NMR (300MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.9 Hz, 1 H), 6.68 (ddd, *J* = 0.9, 2.5, 8.2 Hz, 1 H), 6.65–6.60 (m, 1 H), 6.60–6.56 (m, 1 H), 3.81–3.74 (m, 3 H), 3.16 (d, *J* = 9.0 Hz, 2 H), 2.42 (td, *J* = 1.1, 9.0 Hz, 2 H), 2.36 (s, 3 H), 2.24 (t, *J* = 3.3 Hz, 1 H), 1.67 (dt, *J* = 1.1, 2.6 Hz, 2 H); ^{13}C NMR (75MHz, $CDCl_3$) δ 159.6, 144.5, 129.2, 118.1, 111.6, 110.6, 57.6, 55.1, 41.3, 28.0, 24.2; LRMS (ESI-quadrupole) *m*/*z* 204.6 ($M + H^+$).

***rac*-(1*α*,5*α*,6*α*)-6-(3-Methoxyphenyl)-1,3-dimethyl-3-azabicyclo[3.1.0]hexane (17b).** Sodium borohydride (1.19 g, 31.6 mmol) was added in portions to a solution of **16b** (3.52 g, 0.014 mol) in THF at –5 °C. Boron trifluoride diethyl etherate (5.70 g, 0.040 mol) was added dropwise to the mixture leading to the formation of a white precipitate. The reaction mixture was allowed to warm to room temperature, stirred for 2 h, and then heated at reflux for 3 h. The reaction mixture was cooled, treated with saturated $NaHCO_3$ (150 mL) then extracted with EtOAc (3 × 150 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to obtain a white solid which was subjected to chromatography on silica gel eluting with CH_2Cl_2 to obtain

2.27 g (78%) of **17b** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (t, J = 6 Hz, 1H), 6.78 (m, 3H), 3.81 (s, 3H), 3.59 (m, 1H), 3.12 (m, 2H), 2.73 (m, 3H), 2.65 (m, 1H), 2.30 (m, 1H), 2.23 (m, 1H), 1.46 (s, 2H), 1.37 (s, 1H); LRMS (ESI-quadrupole) 217.0 ($M + H^+$).

***rac*-(1*α*,5*α*,6*α*)-6-(3-methoxyphenyl)-1,3,6-trimethyl-3-azabicyclo[3.1.0]hexane (17c).** Sodium borohydride (885 mg, 23.4 mmol) was added in portions to a solution of **16c** (2.76 g, 0.011 mol) in THF at –5 °C. Boron trifluoride diethyl etherate (4.22 g, 0.03 mol) was added dropwise to the mixture leading to the formation of a white precipitate. The reaction mixture was allowed to warm to room temperature, stirred for 2 h, and then heated at reflux for 2 h. The reaction mixture was cooled, treated with saturated $NaHCO_3$ (150 mL) then extracted with CH_2Cl_2 (3 × 150 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to obtain a yellow oil which was subjected to chromatography on silica gel eluting with petroleum ether/acetone (90:10) to obtain the 1.5 g (76%) of **17c** as a white solid. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.23 (t, J = 7.9 Hz, 1 H), 6.82–6.68 (m, 3 H), 3.80 (s, 3 H), 3.37 (d, J = 13.4 Hz, 1 H), 3.28–3.13 (m, 2 H), 2.88 (dd, J = 1.1, 13.4 Hz, 1 H), 2.80 (s, 3 H), 2.11–2.03 (m, 1 H), 1.45 (s, 3 H), 1.12 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 145.6, 129.5, 121.2, 114.9, 111.6, 68.6, 63.4, 55.2, 53.0, 40.2, 36.3, 34.2, 21.0, 18.1; LRMS (ESI-quadrupole) 232.6 ($M + H^+$).

(1*α*,5*α*,6*α*)-3-Benzyl-6-(3-methoxyphenyl)-6-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione (19a). Manganese dioxide (7.17 g, 82.5 mmol) was added to a solution of **15b** (4.95 g, 0.033 mol) in dioxane (80 mL). The reaction mixture was stirred for 45 min then filtered through Celite and washed through with dioxane (50 mL). The resulting red solution was treated with *N*-benzylmaleimide (**18a**) (6.17 g, 0.033 mol). The reaction mixture was stirred at room temperature for 1 h then heated to reflux overnight. The reaction mixture was cooled, then concentrated. The residue was subjected to chromatography on silica gel eluting with petroleum

ether/acetone (90:10) to afford 4.15 g (39%) of **19a** as a white solid mp. 110–112 °C ^{1}H NMR (300MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.31–7.22 (m, 4H), 6.86 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.81 (s, 1H), 6.81 (d, *J* = 2.1 Hz, 1H), 4.60 (s, 2H), 3.78 (s, 3H), 2.76 (s, 2H), 1.26 (s, 3H).

***rac*-(1*α*,5*α*,6*α*)-3-Benzyl-6-(3-methoxyphenyl)-1,6-dimethyl-3-azabicyclo[3.1.0]hexane-2,4-dione (19b).** Manganese dioxide (17.36 g, 0.2 mol) was added to a solution of **15b** (10.94 g, 0.067 mol) in dioxane (160 mL). The reaction mixture was stirred for 1 h then filtered through Celite and washed through with dioxane (150 mL). The resulting red solution was treated with 1-benzyl-3-methyl-2,5-dihydropyrrole-2,5-dione (13.39 g, 0.067 mol). The reaction mixture was stirred at room temperature for 2 h then heated at reflux for 2 h. The reaction mixture was cooled, then concentrated under reduced pressure. The residue was subjected to chromatography on silica gel eluting with petroleum ether/acetone (90:10) to afford a 7:1 mixture of **19b** (2.28 g, 10 %) and **23** (1.82 g, 8 %) as white semisolids. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.29 Hz, 2H), 7.20–7.35 (m, 4H), 6.79 (t, *J* = 7.55 Hz, 2H), 6.73 (br. s., 1H), 4.54–4.68 (m, 2H), 3.79 (s, 3H), 2.65 (s, 1H), 1.23 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 177.0, 174.3, 160.3, 142.4, 136.1, 130.4, 129.7, 129.0, 128.4, 120.8, 114.3, 113.3, 55.7, 46.1, 42.5, 37.0, 35.3, 19.0, 12.5.

(1*α*,5*α*,6*α*)-3-Benzyl-6-(3-methoxyphenyl)-6-methyl-3-azabicyclo[3.1.0]hexane (20a). Sodium borohydride (0.26 g, 6.9 mmol) was added in portions to a solution of **19a** (1.05 g, 0.0033 mol) in THF at –10 °C. Boron trifluoride diethyl etherate (1.30 g, 0.0092 mol) was added dropwise and the reaction mixture was allowed to warm to room temperature, stirred for 2 h, and then heated at reflux for 3 h. The reaction mixture was cooled, treated with an aqueous solution of piperazine hydrate (1.7 g, 19.6 mmol) in H_2O (12 mL) then heated at reflux for 18 h. The solution was cooled to room temperature and extracted with EtOAc (3 × 50 mL). The organic

extracts were combined, dried (Na_2SO_4), and concentrated under reduced pressure to obtain a pale yellow oil which was subjected to chromatography on silica gel eluting with petroleum ether/acetone (95:5) to obtain the 0.69 g (72%) of **20a** as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.33–7.08 (m, 6H), 6.82–6.79 (m, 2H), 6.68–6.64 (m, 1H), 3.73 (s, 3H), 3.63 (s, 2H), 3.02 (d, J = 9.3 Hz, 2H), 2.82–2.73 (m, 2H), 1.72 (s, 2H), 1.61 (s, 3H).

***rac*-(1*α*,5*α*,6*α*)-3-Benzyl-6-(3-methoxyphenyl)-1,6-dimethyl-3-azabicyclo[3.1.0]hexane (20b).** Sodium borohydride (0.54 g, 14.3 mmol) was added in portions to a solution of **19b** (2.28 g, 0.0068 mol) in THF (150 mL) at –10 °C. Boron trifluoride diethyl etherate (2.70 g, 19.04 mmol) was added dropwise and reaction mixture was allowed to warm to room temperature, stirred for 2 h, and then heated at reflux for 3 h. The reaction mixture was cooled, treated with an aqueous solution of piperazine hydrate (3.4 g, 0.039 mol) in H_2O (25 mL) then heated at reflux for 12 h. The solution was cooled to room temperature, diluted with H_2O (200 mL) and extracted with EtOAc (3 × 150 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to obtain a pale yellow oil which was subjected to chromatography on silica gel eluting with petroleum ether/acetone (95:5) to obtain the 1.51 g (72%) of **20b** as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.35–7.12 (m, 6H), 6.82–6.65 (m, 3H), 3.78 (s, 3H), 3.73–3.59 (m, 2H), 3.07 (dd, J = 3.0, 9.4 Hz, 2H), 2.91 (dd, J = 4.9, 9.4 Hz, 1H), 2.60 (d, J = 9.4 Hz, 1H), 1.61 (s, 3H), 1.57 (d, J = 4.9 Hz, 1H), 0.91 (s, 3H).

3-[(1*α*,5*α*,6*α*)-3-Benzyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenol (21a). A 1.0 M solution of boron trichloride in CH_2Cl_2 (10.57 mL, 10.57 mmol) was added dropwise to a solution of tetrabutylammonium iodide (2.17 g, 0.0059 mol), **20a** (690 mg, 2.35 mmol) in CH_2Cl_2 (15 mL). The mixture was allowed to warm to room temperature and stirred for 2 h. Ice and water (50 mL) were added to quench the reaction and the biphasic mixture was allowed to

stir for 30 min and was extracted with CH_2Cl_2 (3 × 50 mL). The extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford an oil. The oil was purified using silica gel chromatography with petroleum ether and acetone (9:1) as eluents to afford **21a** (0.62 g, 94%) as a colorless semisolid. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.86 (br. s, 1H), 7.35–7.20 (m 5H), 7.04 (t, *J* = 7.8 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 6.64–6.57 (m, 2H), 3.66 (s, 2H), 3.03–2.91 (m, 2H), 2.78 (d, *J* = 10.2 Hz, 2H), 1.75 (s, 2H), 1.41 (s, 3H); ^{13}C-DEPT135 NMR (75 MHz, $CDCl_3$) δ 129.8 (CH), 129.3 (CH), 128.8 (CH), 127.5 (CH), 119.1 (CH), 114.8 (CH), 113.7 (CH), 59.5 (CH_2), 53.5 (CH_2), 31.0 (CH), 15.18 (CH_3).

***rac*-3-[(1*α*,5*α*,6*α*)-3-benzyl-1,6-dimethyl-3-azabicyclo[3.1.0]hex-6-yl]phenol (21b).** A 1.0 M solution of boron trichloride in CH_2Cl_2 (22 mL, 22 mmol) was added dropwise to a solution of tetrabutylammonium iodide (4.53 g, 0.0123 mol), **20b** (1.51 g, 0.0049 mol) in CH_2Cl_2 (30 mL). The mixture was allowed to warm to room temperature and stirred for 2 h. Ice and water (75 mL) were added to quench the reaction and the biphasic mixture was allowed to stir for 30 min and was extracted with CH_2Cl_2 (3 × 75 mL). The extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford an oil. The oil was purified using silica gel chromatography with petroleum ether and acetone (9:1) as eluents to afford **21b** (1.36 g, 94 %) as a colorless semisolid. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.33–7.21 (m, 5H), 7.06 (t, *J* = 8.1 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 6.60 (s, 1H), 6.59 (d, *J* = 6.3 Hz, 1H), 3.72–3.62 (m, 2H), 3.09–3.03 (m, 1H), 2.88 (d, *J* = 9.9 Hz, 1H), 2.84 (d, *J* = 9.9 Hz, 1H), 2.73 (d, *J* = 9.9 Hz, 1H), 1.56 (d, *J* = 4.8 Hz, 1H), 1.31 (s, 3H), 0.85 (s, 3H).

3-[(1*α*,5*α*,6*α*)-3-benzyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl acetate (22a). Sodium hydroxide (180 mg, 4.47 mmol) was added to a solution of **21a** (1.25 g, 0.0045 mol) and tetrabutylammonium sulfate (0.015 g) in dioxane at 0 °C and allowed to stir for 1 h. Acetyl

chloride (0.42 g, 5.36 mmol) was then added dropwise and the reaction was allowed to warm to room temperature over 4 h. The solution was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford an oil. The oil was purified using silica gel chromatography eluting with petroleum ether/acetone (90:10) to obtain **22a** (0.86 g, 60%) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.29–7.18 (m 6H), 7.05 (d, *J* = 7.8 Hz, 1H), 6.86 (s, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 3.63 (s, 2H), 3.02 (d *J* = 9.9 Hz, 2H), 2.82–2.72 (m, 2H), 2.21 (s, 3H), 1.75–1.67 (m, 2H), 1.61 (s, 3H).

***rac*-3-[(1*α*,5*α*,6*α*)-3-benzyl-1,6-dimethyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl acetate (22b).** A solution of **21b** (1.36 g, 0.0046 mol) in THF (20 mL) was added to a solution of NaH (60%, 210 mg, 5.34 mmol) in THF (50 mL) at 0 °C under N_2. The suspension was allowed to stir at 0 °C for 1 h. Acetyl chloride (420 mg, 5.34 mmol) was then added dropwise and the solution was allowed to warm to room temperature. The solution was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure to afford an oil that was purified on silica gel eluting with petroleum ether/acetone (95:5) to obtain **22b** (1.12 g, 72%) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.31–7.17 (m, 6H), 7.05 (d, *J* = 7.8 Hz, 1H), 6.91–6.84 (m, 2H), 3.79–3.60 (m, 2H), 3.06 (dd, *J* = 9.5, 3.2 Hz, 2H), 2.90 (dd, *J* = 9.5, 5.0 Hz, 1H), 2.60 (d, *J* = 9.6 Hz, 1H), 2.27 (s, 3H), 1.62 (s, 3H), 1.56 (d, *J* = 4.8 Hz, 1H), 0.91 (s, 3H).

***rac*-3-[(1*α*,5*α*,6β)-3-Benzyl-6-(3-methoxyphenyl)-1,6-dimethyl-3-azabicyclo[3.1.0]hexane-2,4-dione (23)**. Manganese dioxide (17.36 g, 0.2 mol) was added to a solution of **15b** (10.94 g, 0.067 mol) in dioxane (160 mL). The reaction mixture was stirred for 1 h then filtered through Celite and washed through with dioxane (150 mL). The resulting red

solution was treated with 1-benzyl-3-methyl-2,5-dihydropyrrole-2,5-dione (13.39 g, 0.067 mol). The reaction mixture was stirred at room temperature for 2 h then heated at reflux for 2 h. The reaction mixture was cooled, then concentrated under reduced pressure. The residue was subjected to chromatography on silica gel eluting with petroleum ether/acetone (90:10) to afford a 7:1 mixture of **19b** (2.28 g, 10 %) and **23** (1.82 g, 8 %) as white semisolids. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.12–7.05 (m, 3H), 7.01 (t, J = 7.9 Hz, 1H), 6.94–6.84 (m, 2H), 6.74 (d, J = 7.5 Hz, 1H), 6.64 (s, 1H), 6.61–6.54 (m, 1H), 4.04 (s, 2H), 3.64 (s, 3H), 2.32 (s, 1H), 1.64 (s, 3H), 1.43 (s, 3H)

***rac*-3-[(1*α*,5*α*,6β)-3-Benzyl-6-(3-methoxyphenyl)-1,6-dimethyl-3-azabicyclo[3.1.0]hexane (24a)**. Sodium borohydride (430 mg, 11.4 mmol) was added in portions to a solution of **23** (1.82 g, 0.0054 mol) in THF (100 mL) at –10 °C. Boron trifluoride diethyl etherate (2.15 g, 0.015 mol) was added dropwise and reaction mixture was allowed to warm to room temperature, stirred for 2 h, and then heated at reflux for 3 h. The reaction mixture was cooled, treated with an aqueous solution of piperazine hydrate (2.68 g, 0.031 mol) in H_2O (20 mL) then heated at reflux for 12 h. The solution was cooled to room temperature, diluted with H_20 (200 mL) and extracted with EtOAc (3 × 100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to obtain a pale yellow oil which was subjected to chromatography on silica gel eluting with petroleum ether/acetone (95:5) to obtain **24a** (0.91 g, 55 %) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.23 (t, J = 7.7 Hz, 1H), 7.09–7.00 (m, 3H), 6.81 (dd, J = 2.6, 8.3 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 6.67 (d, J = 1.9 Hz, 1H), 6.51–6.40 (m, 2H), 3.77 (s, 3H), 3.24 (q, J = 13.6 Hz, 2H), 2.95–2.77 (m, 2H), 2.50 (dd, J = 4.0, 8.9 Hz, 1H), 2.26 (d, J = 9.0 Hz, 1H), 1.36 (s, 3H), 1.26 (s, 3H), 1.12 (d, J = 3.8 Hz, 1H)

***rac*-3-[(1*α*,5*α*,6β)-3-Benzyl-1,6-dimethyl-3-azabicyclo[3.1.0]hex-6-yl]phenol (24b)**. A 1.0 M solution of boron trichloride in CH_2Cl_2 (12 mL, 12 mmol) was added dropwise to a solution of tetrabutylammonium iodide (2.47 g, 0.0067 mol) and **24a** (820 mg, 2.68 mmol) in CH_2Cl_2 (20 mL). The mixture was allowed to warm to room temperature and stirred for 2 h. Ice and water (50 mL) were added to quench the reaction and the biphasic mixture was allowed to stir for 30 min and was extracted with CH_2Cl_2 (3 × 50 mL). The extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford an oil. The oil was purified using silica gel chromatography with petroleum ether and acetone (9:1) as eluents to afford **24b** (0.23 g, 30 %) as a colorless semisolid. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.7 Hz, 1H), 7.10–7.01 (m, 3H), 6.73 (dd, *J* = 1.9, 7.9 Hz, 1H), 6.68 (d, *J* = 7.5 Hz, 1H), 6.60 (br. s., 1H), 6.53 (d, *J* = 3.0 Hz, 2H), 3.33–3.12 (m, 2H), 2.93–2.73 (m, 2H), 2.61 (s, 1H), 2.54 (dd, *J* = 3.8, 9.0 Hz, 1H), 2.29 (d, *J* = 9.0 Hz, 1H), 1.38–1.29 (m, 3H), 1.26 (s, 3H), 1.10 (d, *J* = 3.8 Hz, 1H).

***rac*-3-[(1*α*,5*α*,6β)-3-Benzyl-1,6-dimethyl-3-azabicyclo[3.1.0]hex-6-yl]phenol methane sulfonate (24c)**. Methanesulfonyl chloride (110 mg, 0.94 mmol) was added to a solution of **24b** (230 mg, 0.78 mmol) in pyridine (10 mL) at 0 °C. The solution was allowed to warm to room temperature over 2 h and H_2O (10 mL) was added. The biphasic mixture was extracted with CH_2Cl_2 (3 × 25 mL) and the organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure to afford an oil. The oil was purified on silica gel eluting with petroleum ether/acetone (95:5) to obtain **24c** (0.18 g, 60 %) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.42–7.28 (m, 1H), 7.22–7.14 (m, 1H), 7.13–7.00 (m, 5H), 6.46–6.35 (m, 2H), 3.28 (d, *J* = 13.6 Hz, 1H), 3.17 (d, *J* = 13.6 Hz, 1H), 2.98 (s, 3H), 2.89 (d, *J* = 9.4 Hz, 1H), 2.76 (d, *J* = 9.0 Hz, 1H), 2.53 (dd, *J* = 3.8, 9.4 Hz, 1H), 2.27 (d, *J* = 9.4 Hz, 1H), 1.37 (s, 3H), 1.26 (s, 3H), 1.17 (d, *J* = 3.4 Hz, 1H).

***rac*-3-[(1*α*,5*α*,6β)-1,6-Dimethyl-3-azabicyclo[3.1.0]hex-6-yl]phenyl methanesulfonate (24d).** A solution of **24c** (170 mg, 0.47 mmol) in EtOH (20 mL) was added to a Parr hydrogenation bottle under N_2. Solid 10% Pd/C (0.15 g) was added and then a 1.0 M solution of HCl in Et_2O (0.47 mL, 0.47 mmol) was then added and the solution was hydrogenated at 40 psi for 8 h. The solution was then filtered through a pad of Celite and concentrated under reduced pressure to afford **24d** (0.18 g, 88%) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.38 (t, J = 6.0 Hz, 1H), 7.23–7.06 (m, 3H), 3.13 (s, 3H), 3.02 (d, J = 12 Hz, 1H), 2.91–2.76 (m, 3H), 1.41 (s, 3H), 1.26 (s, 3H), 1.22 (d, J = 3 Hz, 1H).

***rac*-3-[(1*α*,5*α*,6β)-1,6-Dimethyl-3-[(2*E*)-3-(2-methylphenyl)prop-2-en-1-yl]-3-azabicyclo[3.1.0]hex-6-yl}phenyl methanesulfonate (24e)**. A solution of *trans*-2-methylcinnamaldehyde (70 mg, 0.50 mmol) in 1,2-dichloroethane (10 mL) was then added to a suspension of **24d** (120 mg, 0.42 mmol) and sodium triacetoxyborohydride (140 mg, 0.63 mmol) in 1,2-dichloroethane (10 mL). The suspension was allowed to stir at room temperature for 4 h and was diluted with a saturated solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The resulting extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford an oil that was purified using silica gel chromatography ($CHCl_3$, MeOH, NH_4OH; 90:9:1) to provide **24e** (0.11 g, 65%) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.36–6.99 (m, 8H), 6.32 (d, J = 15.8 Hz, 1H), 5.36 (td, J = 6.4, 15.4 Hz, 1H), 2.97–2.76 (m, 7H), 2.53 (dd, J = 3.6, 9.2 Hz, 1H), 2.33 (d, J = 9.4 Hz, 1H), 2.24 (s, 3H), 1.39 (s, 3H), 1.31–1.22 (m, 3H), 1.19–1.12 (m, 1H).

(3*R*)-3-Methyl-4-[3-(1-methylethoxy)phenyl]-1,2,3,6-tetrahydropyridine (25b). 1-Chloroethyl chloroformate (29.13 g, 0.2 mol) was added to a solution of **25a**[15] (10 g, 0.041 mol) in 1,2-dichloroethane (150 mL) and heated at reflux for 48 h. The solution was allowed to cool to

room temperature and MeOH (150 mL) was added and the mixture was again heated at reflux for 48 h. The solution was cooled, made basic with saturated $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 75 mL). The extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford an oil that was purified using silica gel chromatography ($CHCl_3$, MeOH, NH_4OH; 80:18:2) to provide **25b** (7.92 g, 84%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (t, *J* = 8.0 Hz, 1H), 6.89–6.84 (m, 2H), 6.77 (dd, *J* = 8.1, 2.4 Hz, 1H), 5.92 (t, *J* = 3.3 Hz, 1H), 4.55 (sept., *J* = 6.0 Hz, 1H), 3.52–3.38 (m, 2H), 3.13 (dd, *J* = 12.5, 4.7 Hz, 1H), 2.83 (dd, *J* = 12.3, 4.2 Hz, 1H), 2.72 (br. s, 1H), 1.59 (br. s, 1H), 1.34 (dd, *J* = 6.0, 2.1 Hz, 6H), 0.99 (d, *J* = 6.9 Hz, 3H).

(3*R*)-3-Methyl-4-[3-(1-methylethoxy)phenyl]-1-[(trifluoromethyl)sulfonyl]-1,2,3,6-tetrahydropyridine (25c). Trifluoromethanesulfonic acid anhydride (11.60 g, 0.041 mol) was added dropwise to a solution of **25b** (7.92 g, 0.034 mol) and TEA (4.16 g, 41.07 mmol) in CH_2Cl_2 (150 mL) at –78 °C under N_2. The solution was allowed to stir at –78 °C for 2 h and then allowed to warm to room temperature. The solution was then made acidic with 1 M HCl and extracted with CH_2Cl_2 (3 × 100 mL). The extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to provide an oil. The oil was purified on silica gel using petroleum ether and acetone (9.5:0.5) as eluents to afford **25c** (9.08 g, 73 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (t, *J* = 8.4 Hz, 1H), 6.88–6.82 (m, 3H), 5.83 (t, *J* = 3.2 Hz, 1H), 4.57 (sept., *J* = 6.2 Hz, 1H), 4.24 (d, *J* = 17.1 Hz, 1H), 4.02 (d, *J* = 17.4 Hz, 1H), 3.69–3.42 (m, 2H), 2.94 (br. s, 1H), 1.34 (dd, *J* = 6.0, 2.1 Hz, 6H), 1.09 (d, *J* = 6.9 Hz, 3H).

(1*R*,5*R*,6*R*)-7,7-Dibromo-5-methyl-6-[3-(1-methylethoxy)phenyl]-3-[(trifluoromethyl)sulfonyl]-3-azabicyclo[4.1.0]heptane (26). Sodium hydroxide (50% aqueous, 12.5 mL) was added dropwise to a solution of **25c** (9.08 g, 0.025 mol), $CHBr_3$ (13.54 g,

0.05 mol), benzyltrimethylammonium chloride (125 mg, 0.55 mmol), EtOH (0.10 mL), in CH_2Cl_2 (10 mL) at –10 °C. The solution was allowed to warm to room temperature and stir for 24 h. The solution was diluted with H_2O (150 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The extracts were combined, dried, and concentrated under reduced pressure to provide an oil. The resulting oil was purified on silica gel chromatography using petroleum ether and acetone (9.5:0.5) as eluents to provide an inseparable mixture of product and starting alkene. This mixture was then dissolved in CH_2Cl_2 (150 mL) and cooled to –78 °C. Ozone (g) was bubbled through the solution until a blue green color persisted and dimethyl sulfide was added to quench the reaction. The reaction was allowed to warm to room temperature and was concentrated under reduced pressure. The resulting oil was purified on silica gel using petroleum ether and acetone (9.5:0.5) as eluents to afford **26** as a colorless oil (5.44 g, 41 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (br. s, 1H), 6.79 (br. d, 2H), 6.51 (br. s, 1H), 4.49 (br. s, 1H), 4.15 (br. s, 1H), 3.41 (br. d, *J* = 7.8 Hz, 2H), 2.92 (br. s, 1H), 2.33 (sept., *J* = 4.8 Hz, 1H), 2.17 (t, *J* = 7.1 Hz, 1H), 1.28 (d, *J* = 5.7 Hz, 6H), 0.73 (d, *J* = 6.9 Hz, 3H).

(1*R*,5*R*,6*S*)-5-Methyl-6-[3-(1-methylethoxy)phenyl]-3-azabicyclo[4.1.0]heptane (27a). Sodium wire was added in small pieces to **26** (5.44 g, 0.010 mol) in a solution of t-butanol (135 mL), THF (135 mL), and liquid NH_3 (270 mL) at –78 °C until a blue color persisted for 10 min. Solid NH_4Cl (10 g) was added and the resulting suspension was allowed to warm to room temperature over 8 h. Water (100 mL) was added and the biphasic mixture was extracted with CH_2Cl_2 (3 × 75 mL). The extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford an oil. The oil was purified using silica gel chromatography ($CHCl_3$, MeOH, NH_4OH; 95:4.5:0.5) to provide **27a** (1.58 g, 64%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (t, *J* = 9.0 Hz, 1H), 6.81 (d, *J* = 9.0 Hz, 1H), 6.79 (s, 1H), 6.68 (d, *J* = 9.0

Hz, 1H), 4.51 (sept., J = 6.0 Hz, 1H), 4.24 (dd, J = 12.0, 6.0 Hz, 1H), 3.11 (d, J = 12.0 Hz, 1H), 2.78 (dd, J = 12.0, 6.0 Hz, 1H), 2.24 (dd, J = 12.0, 9.0 Hz, 1H), 2.03 (q, J = 6.0 Hz, 1H), 1.31–1.29 (m, 2H), 1.30 (d, J = 6.0 Hz, 6H), 0.89–0.79 (m, 2H), 0.65 (d, J = 9.0 Hz, 3H); ^{13}C-DEPT135 NMR (75 MHz, $CDCl_3$) δ 129.1 (CH), 122.9 (CH), 118.6 (CH), 113.5 (CH), 70.1 (CH), 51.2 (CH_2), 45.1 (CH_2), 33.6 (CH), 22.5 (CH_3), 19.0 (CH), 18.8 (CH_2), 18.3 (CH_3).

3-[(1*R*,5*R*,6*S*)-5-Methyl-3-azabicyclo[4.1.0]hept-6-yl]phenol (27b). A 1.0 M solution of BCl_3 in CH_2Cl_2 (38.64 mL, 38.64 mmol) was added dropwise to a solution of **27a** (1.58 g, 0.064 mol) in CH_2Cl_2 (45 mL) at –78 °C under N_2. The solution was allowed to stir for 2 h and then allowed to warm to room temperature. The reaction was quenched with saturated $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The resulting extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford an oil. The oil was purified using Brockman III neutral alumina chromatography with CH_2Cl_2 and MeOH (9.5:0.5) as eluents to afford **27b** (0.20 g, 15 %) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (t, J = 9.0 Hz, 1H), 6.78 (d, J = 7.5 Hz, 1H), 6.72 (t, J = 1.8 Hz, 1H), 6.63 (ddd, J = 7.8, 2.4, 0.6 Hz, 1H), 4.35 (br. s, 2H), 3.40 (dd, J = 13.3, 5.4 Hz, 1H), 3.16 (d, J = 13.2 Hz, 1H), 2.84 (dd, J = 13.1, 4.7 Hz, 1H), 2.36 (dd, J = 12.9, 8.1 Hz, 1H), 2.09–1.98 (m, 1H), 1.37–1.32 (m, 1H), 0.96 (dd, J = 9.0, 4.5 Hz, 1H), 0.79 (t, J = 5.3 Hz, 1H), 0.70 (d, J = 6.9 Hz, 3H).

X-ray Crystal Structure of 6 and 27a. Single-crystal X-ray diffraction data on compounds **6** and **27a** were collected using MoKα radiation and a APEX 2 CCD area detector and CuKα radiation and a Bruker Platimun-135 CCD area detector respectively. The structures was solved by direct methods and refined by full-matrix least squares on F^2 values using the programs found in the SHELXTL suite (SHELXTL v6.10, 2000). Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen

atoms on carbons were included using a riding model [coordinate shifts of C applied to H atoms] with C-H distance set at 0.96 Å. Atomic coordinates for these compounds have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers 1480747 and 1480746 for compounds **6** and **27a**, respectively). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk

6 (X1). A 0.205 x 0.143 x 0.025 mm^3 crystal of **X1** was prepared for data collection coating with high viscosity microscope oil. The oil-coated crystal was mounted on a glass rod and transferred immediately to the cold stream (218°K) on the diffractometer. The crystal was monoclinic in space group $P2_1$ with unit cell dimensions a = 7.5585(2) Å, b = 7.1426(2) Å, c = 19.8369(5) Å, and β= 97.549(2)°. Corrections were applied for Lorentz, polarization, and absorption effects. Data were 99.6% complete to 29.01° θ (approximately 0.73 Å) with an average redundancy of 4.0. The reference molecule ((R,R)-tartaric acid) was disordered over two positions with and occupancy ratio of 8:2. The lower occupancy position was modeled using constraints in SHELX to fix the bond lengths and angles while allowing the atom positions and torsion angles to refine.

27a (X2). A 0.196 x 0.063 x 0.024 mm^3 crystal of **X2** was prepared for data collection coating with high viscosity microscope oil. The oil-coated crystal was mounted on a glass rod and transferred immediately to the diffractometer and data collected at room temperature (296°K). The crystal was monoclinic in space group $P2_1/c$ with unit cell dimensions a = 7.9239(3) Å, b = 16.0550(7) Å, c = 8.1077(4) Å, and β= 100.693(2)°. Corrections were applied for Lorentz, polarization, and absorption effects. Data were 89.2% complete to 67.71° θ (approximately 0.83 Å) with an average redundancy of 4.7.

[^{35}S]GTPγS Assays. The [^{35}S] GTPγS assays were conducted using the methods previously reported.[16]

Acknowledgements

This research was supported by the National Institute on Drug Abuse Grant DA12001. X-ray crystallographic work was supported by NIDA through Interagency Agreement number ADA 12003-005 with the Naval Research Laboratory (NRL).

Supporting Information

The Support Information is available free of charge on the ACS Publications website at DOI: 10.1021//acs/joc.

NMR spectra for isolated compounds (PDF)

X-ray data for compound **6** (CIF)

X-ray data for compound **27a** (CIF)

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