Dipolar Cycloaddition Route to Diverse Analogues of Cocaine: The 6- and 7-Substituted 3-Phenyltropanes

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In our quest for an antagonist or partial agonist of cocaine, access to certain 6- and 7-substituted 3-phenyltropanes of type I was required. Starting from 3-hydroxy-1-methyl-4-phenylpyridinium iodide, we disclose a pyridinium betaine-based dipolar cycloaddition route to tropenones of type II. In turn, we show how this intermediate can be transformed to type I products either through the copper-catalyzed conjugate addition reaction of Grignard reagents to the enones **7**−**9** or by the copper(I)-catalyzed cross coupling reaction of the allylic acetates **15a** and **16a** with Grignard reagents.

Introduction

(*R*)-Cocaine, a plant alkaloid purified from the leaves of *Erythroxylum coca*, has long been recognized to be a potent central nervous system stimulant.[1] Its abuse is one of the greatest concerns of the American public today, and it is clear that immediate therapies are needed for the treatment of individuals who have become addicted to this powerful reinforcing drug.[2] In order to discover agents for use in the treatment of cocaine abuse, we believe that it will be valuable to identify molecules that can act as cocaine antagonists and cocaine partial agonists. Previously, we have shown that cocaine's C-2 ester group can be replaced by alkyl and alkenyl groups with no loss in activity,[3] while other workers have shown that replacement of the C-3 benzoate by phenyl leads to compounds of higher potency (these phenyl-bearing structures are often referred to as the Win series compounds; see Figure 1).[4] In order to more quickly identify those structural changes that may lead to altered functional activity, we required a versatile chemical approach to diversely substituted 3-phenyltropanes of type I. While previous synthetic methodologies have been directed primarily to altering substituents about the three-carbon bridge, no general strategy that allowed for introduction of diverse functionality into the 6- and 7-positions of the 3-phenyltropane skeleton has been available.[5] We were particularly interested in gaining access to the Win series compounds of type I bearing substitution on the two-carbon bridge, for we had found previously that methoxylation of pseudococaine's 7-position led to a compound capable of acting as a weak antagonist.[6] Thus, in our quest for a cocaine antagonist or partial agonist, it was deemed logical to examine the structure−activity relationships of the higher potency Win series compounds bearing additional substitution on the two-carbon bridge.

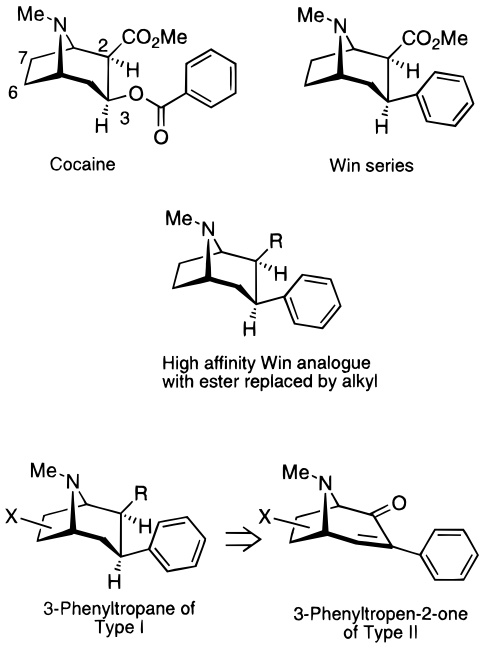

Figure 1. Structures of cocaine-related molecules.

Herein we disclose a pyridinium betaine-based dipolar cycloaddition route[7] to a tropenone of type II and show how this intermediate can be transformed to type I products.

Results and Discussion

To carry out the dipolar cycloaddition chemistry, we first required access to oxidopyridinium betaine **6**. This building block was, in fact, easily obtained as a crystalline, storable compound starting from 3-hydroxypyridine

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(2) (a) Woolverton, W. L.; Johnson, K. M. *Trends Pharmacol. Sci.* **1992**, *13*, 193. (b) Woolverton, W. L.; Kleven, M. S. *NIDA Res. Monogr.* **1988**, *88*, 160.
(3) Kozikowski, A. P.; Eddine Saiah, M. K.; Johnson, K. M.; Bergmann, J. S. *J. Med. Chem.* **1995**, *38*, 3086.
(4) (a) Clarke, R. L.; Daum, S. J.; Gambino, A. J.; Aceto, M. D.; Pearl, J.; Levitt, M.; Cumiskey, W. R.; Bogado, E. F. *J. Med. Chem.* **1973**, *16*, 1260. (b) Carroll, F. I.; Gao, Y.; Rahman, M. A.; Abraham, P.; Parham, K.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1991**, *34*, 2719. (c) Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. In *Drug Design for Neuroscience;* Kozikowski, A. P., Ed.; Raven Press: New York, 1993; pp 149−166.
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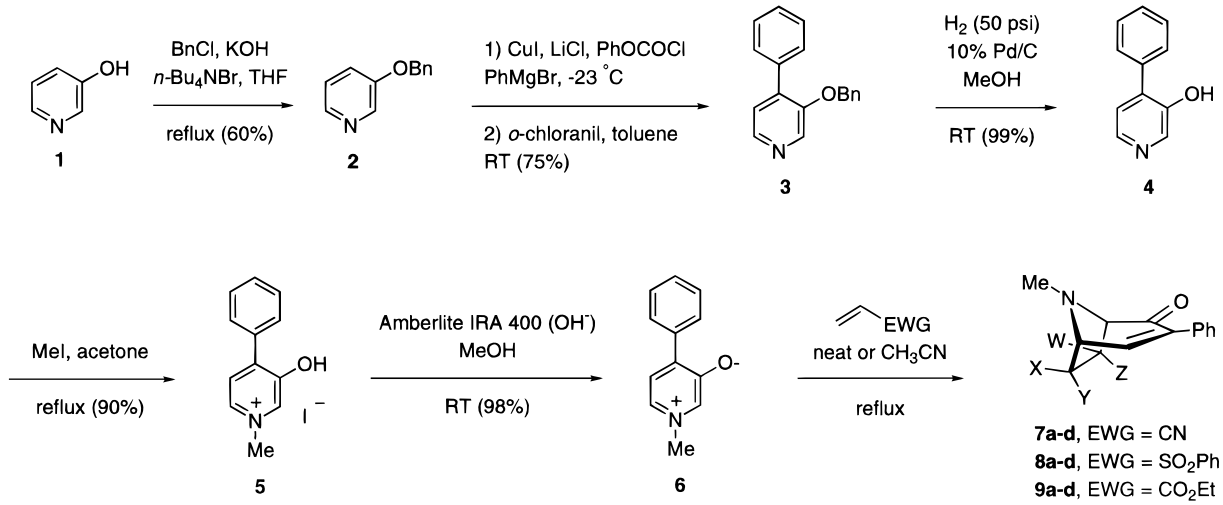
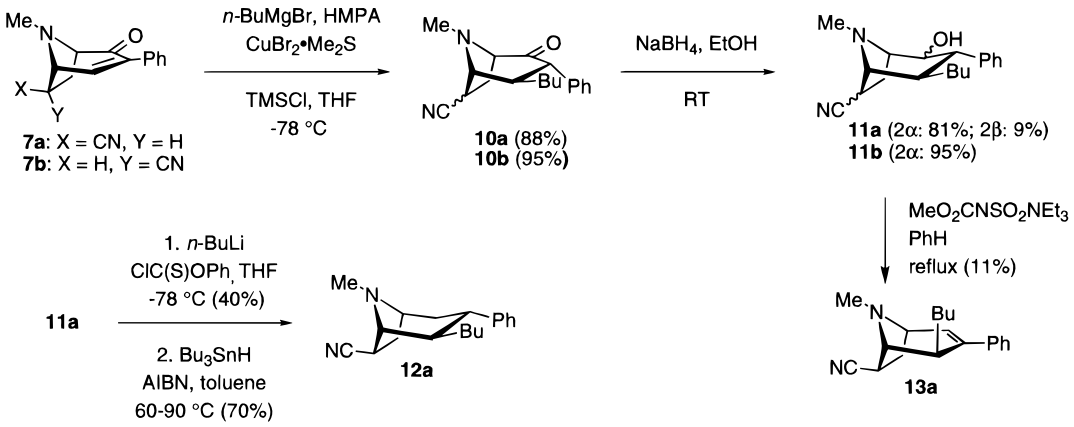
Scheme 1



Scheme 2



as outlined in Scheme 1. Comins[8] has previously described the synthesis of 3-benzyloxypyridine (**2**) by reaction of 3-chloropyridine with the sodium salt of benzyl alcohol in DMSO at 125 °C. In our hands, this reaction proceeded in good yield (70%); however, the pyridine derivative was apparently contaminated with some sulfur-containing byproducts, for difficulty was experienced in the subsequent hydrogenolysis step. Therefore, the synthesis of the protected pyridine **2** was performed using 3-hydroxypyridine and benzyl chloride under phase-transfer conditions. The addition of phenylmagnesium bromide to the pyridine **2** was performed following the Comins protocol but using soluble CuI·2LiCl[9] in place of CuI/Me_2S. The dihydropyridine intermediate was directly aromatized using *o*-chloranil to afford 3-(benzyloxy)-4-phenylpyridine (**3**) in 75% yield. Hydrogenation of compound **3** gave in quantitative yield the hydroxypyridine **4**, which was treated with MeI in acetone at reflux. Finally, the resulting hydroxypyridinium salt **5** was stirred with Amberlite IRA 400 (OH^-) ion-exchange resin in methanol to afford the desired betaine **6** in quantitative yield.

The 1,3-dipolar cycloaddition of betaine **6** with acrylonitrile proceeded readily at reflux temperature within 3 h. Two major adducts **7a** and **7b** were isolated. These compounds are of a single regiochemistry and of either 6β (**7a**, 37% isolated yield) or 6α (**7b**, 42%) stereochemistry. In addition, small amounts of the other two regioisomeric products were isolated (**7c**, 7β-isomer, 5%, and **7d**, 7α-isomer, 16%, see Scheme 1 and Table 1). Similar results were achieved upon using phenyl vinyl sulfone as the dipolarophile and acetonitrile as solvent. After 3 h at reflux, the resulting mixture contained **8a** as the major reaction product together with small amounts of the isomers **8b** and **8c**. In this particular case, the isomer **8d** could not be detected (Table 1). The results obtained using ethyl acrylate are also provided in Table 1. NMR assignments of all of the pure isomers were

Table 1. Products and Isolated Yields Obtained for the Reaction of Betaine 6 with Three Representative Dipolarophiles

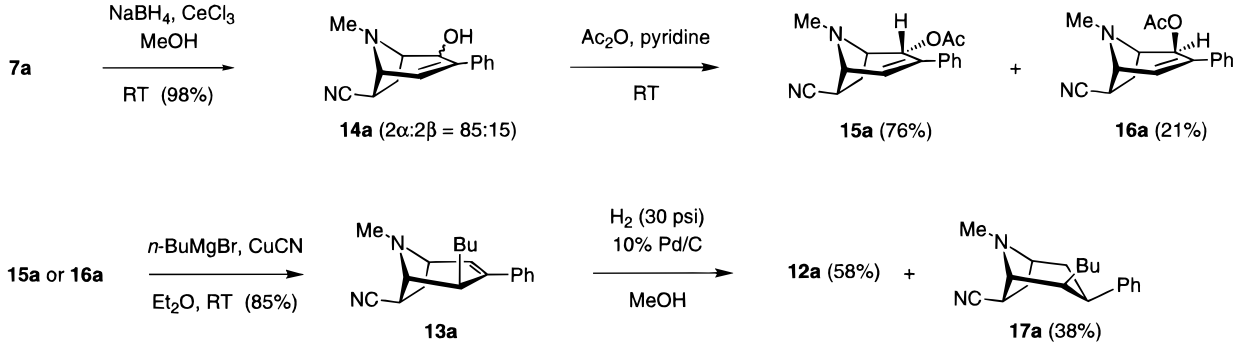
compd[a]	X	Y	W	Z	yield (%)
7a	CN	H	H	H	37
7b	H	CN	H	H	42
7c	H	H	CN	H	5
7d	H	H	H	CN	16
8a	SO_2Ph	H	H	H	60
8b	H	SO_2Ph	H	H	16
8c	H	H	SO_2Ph	H	15
8d	H	H	H	SO_2Ph	0
9a	CO_2Et	H	H	H	33
9b	H	CO_2Et	H	H	26
9c	H	H	CO_2Et	H	20
9d	H	H	H	CO_2Et	12

[a] See Scheme 1 for the structures of compounds **7**−**9**.

(8) Commins, D. L.; Stroud, E. D. *J. Heterocycl. Chem.* **1985**, *22*, 1419.

(9) Reetz, M. T.; Kindler, A. *J. Organomet. Chem.* **1995**, *502*, C5.

Scheme 3



made through the use of COSY, DEPT, and HETCOR experiments.

To investigate the general utility of these tropenone intermediates to afford access to a wide variety of 3-phenyltropanes, we carried out further chemistry on **7a**. For example, reaction of **7a** with *n*-BuMgBr in the presence of CuBr and Me_3SiCl[10] at −78 °C furnished the conjugate addition product **10a** in 88% yield (Scheme 2). Attempts to effect this same reaction by use of higher order organocuprates were unsuccessful. The ketone **10a** was reduced in turn with $NaBH_4$ to afford predominantly the 2α-alcohol **11a** in 81% yield. Next, we treated this alcohol with *n*-BuLi followed by phenyl thionochloroformate in THF[11] at −78 °C to provide the thionocarbonate, which was deoxygenated with *n*-Bu_3SnH to the tropane **12a**. Alternatively, the alcohol **11a** could be dehydrated with the Burgess reagent[12] to provide the olefin **13a** in poor yield. Subsequent hydrogenation provided a readily separable 6:4 mixture of **12a** and **17a**.

In the case of **7b**, conjugate addition followed by $NaBH_4$ reduction provided **11b** as a crystalline solid. Unequivocal structure proof was obtained from X-ray crystallography. The ORTEP drawing of **11b** is shown in Figure 2.[13] This X-ray structure revealed the α stereochemistry of the hydroxyl, phenyl, and cyano groups and the *β* stereochemistry of the *n*-butyl group. Additionally, the six-membered ring was found to adopt the boat conformation.

While the sequence of reactions shown in Scheme 2 provides ready access to a new series of tropane derivatives possessing substitution at the 6- or 7-positions, together with α-stereochemistry at C-2 and C-3, we still desired efficient access to those analogues possessing cocaine-like, i.e., 2*β*,3*β*, stereochemistry. Thus, efforts were made to epimerize ketone **10b** so as to locate the phenyl ring on the *β* face. Unfortunately, we were unsuccessful in carrying out this transformation under a number of conditions such as the use of DBU in refluxing methanol. Quantum mechanical calculations using the semiempirical AM1 method in the MOPAC 6.0 molecular-modeling package offered some rationale for this result. The heat of formation of **10b** was found to be 20.33 kcal/mol, while the heat of formation of its C-3 epimer is 16.15 kcal/mol. Thus, the α-phenyl isomer **10b** is more stable than its epimer by 4.18 kcal/mol based upon this gas phase calculation. Further attempts to effect the epimerization reaction were therefore abandoned.

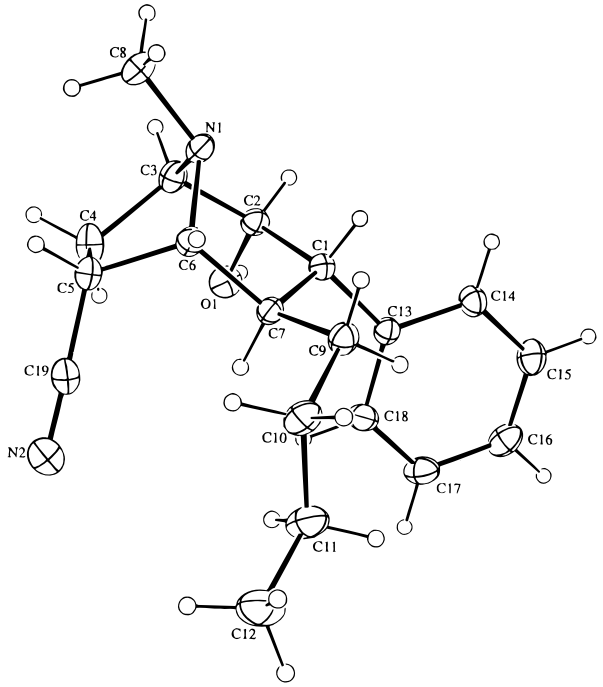


Figure 2.

After some experimentation, we were able to realize our goal in another way. As shown in Scheme 3, the ketone **7a** undergoes exclusive 1,2-reduction using sodium borohydride/cerium chloride in methanol[14] to provide the allylic alcohol **14** as a mixture of α- and *β*-stereoisomers in a GC ratio of 85:15. These alcohols were converted to their acetates **15a** and **16a**, and the mixture was then separated by flash chromatography. Both isomerically pure acetates were found to undergo a copper(I)-catalyzed cross-coupling reaction[15] using *n*-BuMgBr as the nucleophile to afford the same olefin **13a** derived by an S_N2'-type mechanism and having the *n*-butyl group in the *β* orientation. Although S_N2' displacement reactions by organocuprates generally proceed with anti selectivity, reaction through a syn mechanism has been observed in sterically hindered cases.[15]

The olefin **13a** was subjected in turn to hydrogenation over Pd/C to yield the desired 2*β*,3*β* isomer **17a** together

(10) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025.

(11) Berkowitz, D. B.; Eggen, M. J.; Shen, Q.; Shoemaker, R. K. *J. Org. Chem.* **1996**, *61*, 4666.

(12) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

(13) The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

(14) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(15) Tseng, C. C.; Paisley, S. D.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2884.

with the product **12a** derived from β-face hydrogenation. The GC ratio of **17a** to **12a** was 4:6, and these isomers were separable by preparative layer chromatography. This cuprate chemistry thus affords a higher yielding route to olefin **13a** than the dehydration method shown in Scheme 2.

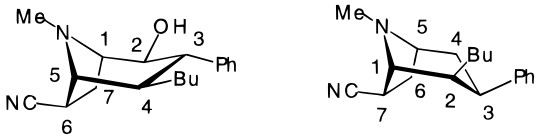
Conclusion

In conclusion, we have demonstrated a convenient route for the synthesis of Win-type compounds by way of a 3-phenyltropen-2-one using a pyridinium betaine-based dipolar cycloaddition. The foregoing chemistry is expected to be applicable to a range of other tropenones derived from any of a number of other reactive dipolarophiles. In particular, in view of the encouraging results achieved previously regarding the weak antagonist activity found for a 7-methoxylated analogue of pseudococaine, we are now in an excellent position to rapidly explore the effect of 6- and 7-substitution on the activity of the higher potency Win-type compounds. The dipolar cycloaddition strategy can thus be used to create a stereodefined library of tropane structures for biological assay. Further modifications to the current chemical process include the use of dipolarophiles bearing chiral auxiliary groups to permit access to optically pure tropanes as well as the attachment of the betaine to resin supports for use in combinatorial chemistry approaches. These modifications as well as results from biological assays will be reported separately.[16]

Experimental Section

General Methods. Starting materials were obtained from Aldrich Chemicals or from other commercial suppliers. Solvents were purified as follows: diethyl ether was distilled from phosphorus pentoxide; THF was freshly distilled under nitrogen from sodium benzophenone.

^{1}H and ^{13}C NMR spectra were obtained at 300 and 75.46 MHz, respectively. ^{1}H chemical shifts (δ) are reported in ppm downfield from internal TMS. ^{13}C chemical shifts are referred to $CDCl_3$ (central peak, δ = 77.0 ppm), benzene-d_6 (central peak, δ = 128.0 ppm), or DMSO-d_6 (central peak, δ = 39.7 ppm). NMR assignments were made with the help of COSY, DEPT, and HETCOR experiments. The subscript numbers used to identify the tropane protons are defined according to the following numbering scheme:



Melting points were determined in Pyrex capillaries with a Thomas Hoover Unimelt apparatus and are uncorrected. Mass spectra were measured in the EI mode at an ionization potential of 70 eV. TLC was performed on Merck silica gel 60F_{254} glass plates; column chromatography was performed using Merck silica gel (60−200 mesh).

3-(Benzyloxy)pyridine (2). A mixture of 3-hydroxypyridine (5.0 g, 0.053 mol), pulverized KOH (5.9 g, 0.11 mol), *n*-Bu_4NBr (0.85 g, 0.0026 mol), and benzyl chloride (9.7 mL, 0.084 mol) in THF (150 mL) was stirred at reflux for 6 h. Water (200 mL) was added and the organic phase extracted with 10% HCl (2 × 100 mL). The combined aqueous phases were basified with 25% NaOH and extracted with CH_2Cl_2 (2 × 150 mL). The combined organic phases were washed with brine (100 mL), dried, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel using EtOAc/hexane as eluent to afford the title compound (5.8 g, 60%) as a yellow oil: R_f 0.6 (EtOAc/hexane 3/4); ^{1}H NMR ($CDCl_3$) δ 5.11 (s, 2H), 7.18−7.29 (m, 2H), 7.30−7.47 (m, 5H), 8.23 (dd, 1H, J = 1.5, 4.5 Hz), 8.39 (d, 1H, J = 2.7 Hz); ^{13}C NMR ($CDCl_3$) δ 70.26, 121.50, 123.81, 126.96, 127.49, 128.28, 128.70, 136.11, 138.31, 142.35, 154.85.

3-(Benzyloxy)-4-phenylpyridine (3). To a solution of **2** (7.7 g, 42.0 mmol) in dry THF (200 mL) under N_2 was added CuI (0.80 g, 4.2 mmol) and LiCl (0.35 g, 8.3 mmol). The mixture was cooled to −23 °C, and then PhOCOCl (5.74 mL, 46.0 mmol) was added dropwise and the mixture stirred at −23 °C for 10 min. A 1 M solution of PhMgBr in THF (46 mL) was added dropwise. The mixture was stirred at −23 °C for 15 min, allowed to warm to rt, and quenched with 20% NH_4Cl solution (120 mL). Ether (120 mL) was added, and the organic layer was washed with 120-mL portions each of 20% NH_4Cl/NH_4OH (1/1), water, 10% HCl, water, and brine. After drying, the solution was concentrated to give the crude dihydropyridine (18.0 g) as a viscous oil, which was used directly in the next step.

To the crude dihydropyridine in toluene (180 mL) was added dropwise *o*-chloranil (11.0 g, 46.2 mmol) in toluene (70 mL). The mixture was stirred at rt for 15 h. An aqueous solution of 10% NaOH (150 mL) was added, and the mixture was stirred for 10 min at 25 °C. After ether (150 mL) was added the organic layer was washed with 150-mL portions of 10% NaOH and water and then extracted with 10% HCl. The combined acid extracts were cooled, made basic with 25% NaOH, and extracted with DCM (4 × 100 mL). The combined organic layers were washed with brine (200 mL), dried, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using EtOAc/hexane as eluent to afford the title compound (8.1 g, 75%) as a white solid: mp 75 °C; R_f 0.4 (EtOAc/hexane 1/1); ^{1}H NMR ($CDCl_3$) δ 5.16 (s, 2H), 7.29 (d, 1H, J = 4.8 Hz), 7.30−7.36 (m, 5H), 7.40−7.49 (m, 3H), 7.60−7.66 (m, 2H), 8.33 (d, 1H, J = 4.8 Hz), 8.41 (s, 1H).

4-Phenyl-3-pyridinol (4). A mixture of **3** (4.5 g, 17.2 mmol) and 10% Pd/C (0.7 g) in MeOH (40 mL) was hydrogenated at 50 psi and rt for 3 h. After filtration through a pad of Celite, the clear solution was concentrated under reduced pressure to afford the title compound (2.98 g, 99%) as a white solid: mp 168−170 °C (lit.[8] mp 125−126 °C); R_f = 0.35 (EtOAc/*n*-hexane 1/1); ^{1}H NMR ($CDCl_3$) δ 5.33 (s, 1 H), 7.33 (d, 1H, J = 4.8 Hz), 7.38−7.52 (m, 3H), 7.66−7.72 (m, 2H), 8.15 (d, 1H, J = 4.8 Hz), 8.48 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 125.07, 128.57, 128.63, 128.98, 135.406, 137.06, 137.22, 139.86, 152.04.

3-Hydroxy-1-methyl-4-phenylpyridinium Iodide (5). To a solution of **4** (4.1 g, 24.0 mmol) in acetone (100 mL) was added MeI (3.0 mL, 48.0 mmol). The mixture was refluxed for 3 h and stirred at rt for 20 h. Ether (100 mL) was added, and the precipitate was filtered off and washed with ether to afford the title compound (6.8 g, 90%) as a pale yellow solid: mp 175 °C; ^{1}H NMR (DMSO-d_6) δ 4.31 (s, 3 H), 7.53−7.61 (m, 3 H), 7.76−7.84 (m, 2 H), 8.07 (d, 1 H, J = 6.0 Hz), 8.35 (s, 1 H), 8.53 (d, 1 H, J = 6.0 Hz), 12.1 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 47.46, 127.40, 128.81, 129.42, 130.20, 133.34, 133.55, 135.24, 142.27, 155.00.

1-Methyl-4-phenyl-3-pyridiniumolate (6). A mixture of **5** (4.03 g, 12.9 mmol) and Amberlite IRA-400 (OH^-) resin (20 mL) in MeOH (70 mL) was stirred at rt for 1 h, and then the resin was filtered off and washed several times with MeOH. The resulting clear solution was concentrated under reduced pressure to afford the crude title compound (2.21 g, 92%) as a pale yellow solid that was used in the next step without further purification: mp 154−157 °C; ^{1}H NMR (DMSO-d_6) δ 3.97 (s, 3 H), 7.30−7.52 (m, 5 H), 7.38 (d, 1 H, J = 7.5 Hz), 8.04 (d, 1 H, J = 8.1 Hz), 8.05 (s, 1 H).

8-Methyl-2-oxo-3-phenyl-8-azabicyclo[3.2.1]oct-3-ene-6-carbonitrile and 8-Methyl-2-oxo-3-phenyl-8-azabicyclo-[3.2.1]oct-3-ene-7-carbonitrile (7a−d). To a solution of **6** (2.21 g, 11.9 mmol) in acrylonitrile (20 mL) was added a small amount of hydroquinone. The mixture was refluxed under nitrogen for 1 h and then concentrated under reduced pressure.

(16) For other recent synthetic work in the cocaine area, see: Keverline, K. L.; Abraham, P.; Lewin, A. H.; Carroll, F. I. *Tetrahedron Lett.* **1995**, *36*, 3099.

The four isomers **7a**−**d** present in the crude mixture were separated by flash chromatography on silica gel using EtOAc/hexane as eluent. **7a** (1.07 g, 37%): pale yellow solid; mp 129−130 °C; R_f 0.6 (EtOAc/hexane 2/3); ^{1}H NMR ($CDCl_3$) δ 2.19 (dd, $H_{7\alpha}$, $J_{7\alpha-7\beta}$ = 13.8 Hz, $J_{7\alpha-6}$ = 9.3 Hz), 2.62 (s, 3 H), 2.78 (ddd, $H_{7\beta}$, $J_{7\beta-6}$ = 3.3 Hz, $J_{7\beta-1}$ = 7.5 Hz, $J_{7\beta-7\alpha}$ = 13.8 Hz), 3.06 (dd, H_6, $J_{6-7\beta}$ = 3.6 Hz, $J_{6-7\alpha}$ = 9.0 Hz), 3.84 (d, H_1, $J_{1-7\beta}$ = 7.5 Hz), 4.18 (d, H_5, J_{5-4} = 5.4 Hz), 6.97 (d, H_4, J_{4-5} = 5.4 Hz), 7.36 (br s, 5 H); ^{13}C NMR ($CDCl_3$) δ 30.37, 31.63, 36.03, 64.72, 70.16, 121.34, 128.15, 128.29, 128.69, 133.08, 138.771, 141.12, 196.40. **7b** (1.23 g, 42%): pale yellow solid; mp 110−112 °C; R_f 0.42 (EtOAc/*n*-hexane 4/1); ^{1}H NMR ($CDCl_3$) δ 2.00 (dd, $H_{7\alpha}$, $J_{7\alpha-7\beta}$ = 13.8 Hz, $J_{7\alpha-6}$ = 5.7 Hz), 2.48 (s, 3 H), 2.88 (ddd, $H_{7\beta}$, $J_{7\beta-6}$ = 10.2 Hz, $J_{7\beta-7\alpha}$ = 13.8 Hz, $J_{7\beta-1}$ = 7.8 Hz), 3.45 (dt, H_6, J_{6-5} = $J_{6-7\alpha}$ = 5.7 Hz, $J_{6-7\beta}$ = 10.5 Hz), 3.75 (d, H_1, $J_{1-7\beta}$ = 7.5 Hz), 4.18 (t, H_5, J_{5-4} = J_{5-6} = 5.4 Hz), 7.14 (d, H_4, J_{4-5} = 5.4 Hz), 7.3−7.5 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 29.93, 30.72, 36.83, 62.45, 70.67, 119.62, 128.26, 128.46, 128.66, 133.33, 139.84, 142.08, 195.99. **7c** (0.15 g, 5%): pale yellow wax; R_f 0.4 (EtOAc/*n*-hexane 2/3); ^{1}H NMR (benzene-d_6) δ 1.22 (dd, $H_{6\alpha}$, $J_{6\alpha-6\beta}$ = 12.3 Hz, $J_{6\alpha-7}$ = 9.3 Hz), 1.84 (dt, $H_{6\beta}$, $J_{6\beta-5}$ = $J_{6\beta-7}$ = 6.3 Hz, $J_{6\beta-6\alpha}$ = 12.3 Hz), 1.96 (s, 3 H), 1.9−2.0 (m, H_7), 2.88 (dd, H_5, J_{5-4} = 5.4 Hz, $J_{5-6\beta}$ = 6.0 Hz), 3.75 (s, H_1), 6.12 (d, H_4, J_{4-5} = 5.4 Hz), 7.1−7.2 (m, 3 H), 7.3−7.4 (m, 2 H); ^{13}C NMR (benzene-d_6) δ 27.91, 34.59, 37.13, 61.43, 76.07, 116.64, 121.55, 128.91, 128.94, 134.57, 137.05, 146.21, 193.20. **7d** (0.47 g, 16%): pale yellow solid; mp 117 °C, R_f 0.26 (EtOAc/*n*-hexane 4/1); ^{1}H NMR (benzene-d_6) δ 1.42 (dd, $H_{6\alpha}$, $J_{6\alpha-7}$ = 3.3 Hz, $J_{6\alpha-6\beta}$ = 12.3 Hz), 1.64 (ddd, $H_{6\beta}$, $J_{6\beta-6\alpha}$ = 12.3 Hz, $J_{6\beta-7}$ = 10.5 Hz, $J_{6\beta-5}$ = 5.7 Hz), 1.75 (s, 3 H), 2.52 (ddd, H_7, J_{7-1} = 7.2 Hz, $J_{7-6\beta}$ = 10.8 Hz, $J_{7-6\alpha}$ = 3.3 Hz), 2.81 (t, H_5, J_{5-4} = $J_{5-6\beta}$ = 5.7 Hz), 3.44 (d, H_1, J_{1-7} = 7.5 Hz), 6.28 (d, H_4, J_{4-5} = 5.4 Hz), 7.05−7.20 (m, 3 H), 7.43−7.58 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 26.04, 33.91, 37.31, 61.35, 73.44, 119.13, 128.29, 128.31, 128.53, 133.59, 138.44, 146.08, 193.57.

8-Methyl-2-oxo-3-phenyl-8-azabicyclo[3.2.1]oct-3-en-6-yl Phenyl Sulfone and 8-Methyl-2-oxo-3-phenyl-8-azabicyclo[3.2.1]oct-3-en-7-yl Phenyl Sulfone (8a−c). To a solution of **6** (0.59 g, 3.17 mmol) in acetonitrile (20 mL) was added phenyl vinyl sulfone (1.07 g, 6.34 mmol). The resulting solution was refluxed under N_2 for 1 h and then concentrated under reduced pressure. The three isomers **8a**−**c** present in the crude mixture were separated by flash chromatography on silica gel using EtOAc/hexane as eluent. **8a** (0.64 g, 60%): pale yellow solid; R_f = 0.8 (EtOAc/hexane 1/1); ^{1}H NMR ($CDCl_3$) δ 2.01 (dd, $H_{7\alpha}$, $J_{7\alpha-7\beta}$ = 14.1 Hz, $J_{7\alpha-6}$ = 9.0 Hz), 2.49 (s, 3 H), 2.82 (ddd, $H_{7\beta}$, $J_{7\beta-6}$ = 4.5 Hz, $J_{7\beta-1}$ = 7.5 Hz, $J_{7\beta-7\alpha}$ = 14.1 Hz), 3.67 (dd, H_6, $J_{6-7\beta}$ = 4.5 Hz, $J_{6-7\alpha}$ = 9.0 Hz), 3.71 (d, H_1, $J_{1-7\beta}$ = 7.5 Hz), 4.41 (d, H_5, J_{5-4} = 5.4 Hz), 6.99 (d, H_4, J_{4-5} = 5.4 Hz), 7.34 (br s, 5 H), 7.55−7.63 (m, 2 H), 7.64−7.72 (m, 1 H), 7.91−7.98 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 27.76, 34.74, 61.00, 67.70, 70.29, 128.16, 128.29, 128.62, 128.66, 129.28, 133.28, 133.95, 138.29, 138.92, 141.08, 196.85. **8b** (0.18 g, 16%): pale yellow foam; R_f 0.4 (EtOAc/*n*-hexane 4/1); ^{1}H NMR ($CDCl_3$) δ 2.15 (dd, $H_{7\alpha}$, $J_{7\alpha-7\beta}$ = 14.1 Hz, $J_{7\alpha-6}$ = 6.9 Hz), 2.46 (s, 3 H), 2.56 (ddd, $H_{7\beta}$, $J_{7\beta-6}$ = 9.6 Hz, $J_{7\beta-7\alpha}$ = 13.8 Hz, $J_{7\beta-1}$ = 8.1 Hz), 3.73 (d, H_1, $J_{1-7\beta}$ = 7.8 Hz), 4.15 (m, H_6), 4.22 (t, H_5, J_{5-4} = J_{5-6} = 5.1 Hz), 7.20 (d, H_4, J_{4-5} = 5.1 Hz), 7.32−7.43 (m, 3 H), 7.47−7.53 (m, 2 H), 7.54−7.62 (m, 2 H), 7.64−7.72 (m, 1 H), 7.87−7.94 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 27.16, 36.65, 62.07, 67.13, 71.10, 127.90, 128.13, 128.25, 128.62, 129.5, 134.01, 139.23, 139.77, 141.60, 196.38. **8c** (0.16 g, 16%): pale yellow foam; R_f 0.2 (EtOAc/hexane 1/1); ^{1}H NMR ($CDCl_3$) δ 2.20 (dd, $H_{6\alpha}$, $J_{6\alpha-6\beta}$ = 13.2 Hz, $J_{6\alpha-7}$ = 9.0 Hz), 2.56 (s, 3 H), 2.80 (dt, $H_{6\beta}$, $J_{6\beta-5}$ = $J_{6\beta-7}$ = 6.6 Hz, $J_{6\beta-6\alpha}$ = 12.9 Hz), 3.53 (t, H_7, $J_{7-6\beta}$ = $J_{7-6\alpha}$ = 8.1 Hz), 3.9−4.2 (m, H_5 and H_1), 7.03 (d, H_4, J_{4-5} = 5.4 Hz), 7.32 (br s, 5 H), 7.55−7.63 (m, 2 H), 7.64−7.72 (m, 1 H), 7.92−7.99 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 30.88, 36.60, 61.35, 64.40, 71.89, 128.15, 128.23, 128.33, 128.46, 129.46, 133.37, 134.05, 137.05, 138.63, 145.29, 193.61.

Ethyl 8-Methyl-2-oxo-3-phenyl-8-azabicyclo[3.2.1]oct-3-ene-6-carboxylate and Ethyl 8-Methyl-2-oxo-3-phenyl-8-azabicyclo[3.2.1]oct-3-ene-7-carboxylate (9a−d). Using a procedure similar to that for **7**, **9** was obtained as a mixture of four isomers separated by silica gel column chromatography using EtOAc/hexane as eluent. **9a** (33%): dark yellow oil; R_f 0.70 (EtOAc/*n*-hexane 1/1); ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3 H, J = 6.9 Hz), 1.99 (dd, $H_{7\alpha}$, $J_{7\alpha-6}$ = 9.9 Hz, $J_{7\alpha-7\beta}$ = 14.1 Hz), 2.52 (s, 3 H), 2.90 (ddd, $H_{7\beta}$, $J_{7\beta-6}$ = 3.6 Hz, $J_{7\beta-1}$ = 7.8 Hz, $J_{7\beta-7\alpha}$ = 13.8 Hz), 3.02 (dd, H_6, $J_{6-7\beta}$ = 3.6 Hz, $J_{6-7\alpha}$ = 9.3 Hz), 3.74 (d, H_1, $J_{1-7\beta}$ = 7.5 Hz), 4.23 (q, 2 H, J = 7.2 Hz), 4.25 (d, H_5, J_{5-4} = 5.4 Hz), 7.07 (d, H_4, J_{4-5} = 5.4 Hz), 7.3−7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.20, 27.84, 35.83, 47.52, 61.44, 63.61, 70.72, 128.23, 128.28, 133.95, 137.93, 143.61, 172.83, 197.86. **9b** (26%): yellow oil; R_f 0.4 (EtOAc/hexane 1/1); ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3 H, J = 7.2 Hz), 2.11 (dd, $H_{7\alpha}$, $J_{7\alpha-6}$ = 6.0 Hz, $J_{7\alpha-7\beta}$ = 14.4 Hz), 2.48 (s, 3 H), 2.64 (ddd, $H_{7\beta}$, $J_{7\beta-1}$ = 7.8 Hz, $J_{7\beta-6}$ = 10.2 Hz, $J_{7\beta-7\alpha}$ = 13.8 Hz), 3.60 (dt, H_6, J_{6-5} = $J_{6-7\alpha}$ = 5.7 Hz, $J_{6-7\beta}$ = 10.5 Hz), 3.70 (d, H_1, $J_{1-7\beta}$ = 8.1 Hz), 4.20 (t, H_5, J_{5-4} = J_{5-6} = 5.4 Hz), 6.98 (d, H_4, J_{4-5} = 5.1 Hz), 7.34 (br s, 5 H). **9c** (20%): pale yellow oil; R_f 0.6 (EtOAc/hexane 1/1); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3 H, J = 7.2 Hz), 2.22 (dd, $H_{6\alpha}$, $J_{6\alpha-7}$ = 9.6 Hz, $J_{6\alpha-6\beta}$ = 12.6 Hz), 2.80 (dt, $H_{6\beta}$, $J_{6\beta-5}$ = $J_{6\beta-7}$ = 6.3 Hz, $J_{6\beta-6\alpha}$ = 12.6 Hz), 3.53 (dd, H_7, $J_{7-6\beta}$ = 6.6 Hz, $J_{7-6\alpha}$ = 9.3 Hz), 3.97 (t, H_5, J_{5-4} = $J_{5-6\beta}$ = 5.7 Hz), 4.01 (s, H_1), 7.08 (d, H_4, J_{4-5} = 5.4 Hz), 7.36 (br s, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.18, 32.45, 37.10, 43.39, 61.49, 61.65, 74.17, 128.20, 128.26, 129.87, 132.90, 134.03, 136.83, 146.61, 173.43, 195.92. **9d** (12%): pale yellow oil; R_f 0.35 (EtOAc/hexane 1/1); ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3 H, J = 7.2 Hz), 2.30 (dd, $H_{6\alpha}$, $J_{6\alpha-7}$ = 3.9 Hz, $J_{6\alpha-6\beta}$ = 12.3 Hz), 2.47 (s, 3 H), 2.52 (ddd, $H_{6\beta}$, $J_{6\beta-5}$ = 6.6 Hz, $J_{6\beta-7}$ = 10.5 Hz, $J_{6\beta-6\alpha}$ = 12.4 Hz), 3.64 (m, H_7), 3.87 (t, H_5, J_{5-4} = $J_{5-6\beta}$ = 6.0 Hz), 3.95 (d, H_1, J_{1-7} = 7.2 Hz), 4.07 (q, 2 H, J = 7.2 Hz), 7.11 (d, H_4, J_{4-5} = 5.7 Hz), 7.33 (br s, 5 H).

4β-Butyl-8-methyl-2-oxo-3α-phenyl-8-azabicyclo[3.2.1]-octane-6-*exo*-carbonitrile (10a). To a cooled (−78 °C) mixture of *n*-BuMgBr (1.05 mL, 1.01 mmol, 0.96 M in ether), HMPA (0.35 mL, 2.01 mmol), and CuBr·Me_2S (8.6 mg, 0.04 mmol) was added dropwise a mixture of **7a** (200 mg, 0.84 mmol) and Me_3SiCl (0.21 mL, 1.68 mmol) in dry THF (10 mL). After 1 h, the reaction was quenched with a 20% solution of NH_4OH (20 mL), and the mixture was extracted with EtOAc (30 mL). The organic phase was washed with brine (30 mL), dried, and concentrated under reduced pressure. The crude mixture containing the silyl enol ether intermediate was diluted with MeOH (5 mL), and potassium fluoride was added (24 mg, 0.84 mmol). The resulting solution was stirred at rt for 5 min and then concentrated under reduced pressure, and the crude mixture was purified by flash chromatography on silica gel using EtOAc/hexane as eluent to afford the title compound (220 mg, 88%) as a wax: R_f 0.8 (EtOAc/hexane 1/1); ^{1}H NMR (CD_3OD) δ 0.82 (t, 3 H, J = 7.2 Hz), 1.1−1.35 (m, 3 H), 1.37−1.1.5 (m, 4 H), 1.5−1.7 (m, H_4), 2.31 (dd, $H_{7\alpha}$, $J_{7\alpha-7ex}$ = 13.5 Hz, $J_{7\alpha-6}$ = 9.9 Hz), 2.57 (s, 3 H), 2.66 (dt, $H_{7\beta}$, $J_{7\beta-7\alpha}$ = 13.8 Hz, $J_{7\beta-6}$ = $J_{7\beta-1}$ = 7.2 Hz), 3.06 (dd, H_6, $J_{6-7\beta}$ = 6.9 Hz, $J_{6-7\alpha}$ = 9.6 Hz), 3.55 (d, H_3, J_{3-4} = 8.7 Hz), 3.67 (s, H_5), 3.76 (d, H_1, $J_{1-7\beta}$ = 7.2 Hz), 6.95−7.10 (m, 2 H), 7.2−7.4 (m, 3 H); ^{13}C NMR (benzene-d_6) δ 14.35, 23.25, 29.16, 33.47, 33.50, 34.73, 40.74, 48.82, 56.82, 72.53, 73.08, 123.03, 127.64, 128.90, 130.42, 131.24, 138.19, 209.46; IR (film) 2955, 2234, 1723, 1453 cm^{-1}.

4β-Butyl-8-methyl-2-oxo-3α-phenyl-8-azabicyclo[3.2.1]-octane-6-*endo*-carbonitrile (10b). Using a procedure similar to that for **10a**, **10b** was obtained (95%) as a colorless oil: R_f 0.6 (EtOAc/hexane 1/1); ^{1}H NMR (benzene-d_6) δ 0.72 (t, 3 H, J = 6.9 Hz), 1.0−1.43 (m, 6 H), 1.55 (s, 3 H), 1.68−1.88 (m, $H_{7\alpha}$ and $H_{7\beta}$), 2.23 (td, H_4, J_{4-3} = $J_{4-1'}$ = 9.3 Hz, $J_{4-1''}$ = 3.0 Hz), 2.35 (dt, H_6, J_{6-5} = $J_{6-7\alpha}$ = 6.3 Hz, $J_{6-7\beta}$ = 11.7 Hz), 2.85 (d, H_5, J_{5-6} = 6.3 Hz), 2.97 (d, H_1, $J_{1-7\beta}$ = 7.2 Hz), 3.44 (d, H_3, J_{3-4} = 9.6 Hz), 7.0−7.2 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.87, 22.42, 28.66, 29.45, 32.08, 33.95, 40.16, 40.54, 56.06, 68.30, 71.65, 120.29, 127.25, 128.58, 129.74, 136.78, 210.82; IR (film) 2956, 2930, 2235, 1724, 1462, 1105 cm^{-1}.

4β-Butyl-2-hydroxy-8-methyl-3α-phenyl-8-azabicyclo-[3.2.1]octane-6-*exo*-carbonitrile (11a). To a solution of **10a** (0.55 g, 1.86 mmol) in EtOH (20 mL) was added portionwise $NaBH_4$ (0.21 g, 5.57 mmol). The resulting solution was stirred at rt for 1 h and then concentrated, and the residue was diluted with water (60 mL) and extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with brine (80 mL), dried, and concentrated under reduced pressure. The crude mixture containing the two hydroxy isomers was purified by

flash chromatography on silica gel using EtOAc/hexane as eluent. 2α-Isomer (0.45 g, 81%): white solid; R_f 0.8 (EtOAc/hexane 1/1); ^{1}H NMR (benzene-d_6) δ 0.63 (d, OH, $J_{OH-2} = 3.0$ Hz,), 0.72 (t, 3 H, $J = 6.9$ Hz), 0.9−1.15 (m, 5 H), 1.16−1.30 (m, 1 H), 1.36 (dt, H_4, $J_{4-3} = 11.1$ Hz, $J_{4-1'} = J_{4-1''} = 6.0$ Hz), 1.84 (dt, $H_{7\beta}$, $J_{7\beta-1} = J_{7\beta-6} = 6.5$ Hz, $J_{7\beta-7\alpha} = 11.1$ Hz), 2.27 (s, 3 H), 2.37 (dd, H_6, $J_{6-7\alpha} = 9.0$ Hz, $J_{6-7\beta} = 7.1$ Hz), 2.69 (dd, $H_{7\alpha}$, $J_{7\alpha-7\beta} = 12.9$ Hz, $J_{7\alpha-6} = 9.6$ Hz), 2.74 (dd, H_3, $J_{3-2} = 4.5$ Hz, $J_{3-4} = 11.4$ Hz), 3.11 (dd, H_1, $J_{1-2} = 8.4$ Hz, $J_{1-7\beta} = 6.9$ Hz), 3.29 (s, H_5), 3.70 (ddd, H_2, $J_{2-OH} = 3.0$ Hz, $J_{2-1} = 8.6$ Hz, $J_{2-3} = 4.8$ Hz), 6.85−6.98 (m, 2 H), 7.0−7.1 (m, 3 H); ^{13}C NMR (benzene-d_6) δ 14.10, 22.99, 26.73, 28.89, 34.40, 34.56, 42.03, 45.47, 47.19, 66.08, 70.57, 71.91, 123.95, 127.00, 128.89, 129.80, 140.40; MS m/z 298 (M^+, 16), 255 (34), 245 (10), 177 (39), 135 (30), 107 (71), 42 (100); IR (film) 3466, 2932, 2231, 1451 cm^{-1}. 2β-Isomer (0.05 g, 9%): colorless oil; R_f 0.6 (EtOAc/hexane 1/1); ^{1}H NMR ($CDCl_3$) δ 0.74 (t, 3 H, $J = 7.2$ Hz), 0.70−0.95 (m, 1 H), 1.00−1.35 (m, 4 H), 1.37−1.70 (m, 3 H), 2.38 (dd, $H_{7\alpha}$, $J_{7\alpha-6} = 6.0$ Hz, $J_{7\alpha-7\beta} = 12.6$ Hz), 2.44−2.60 (m, H_3 and $H_{7\beta}$), 2.59 (s, 3 H), 2.89 (dd, H_6, $J_{6-7\alpha} = 6.0$ Hz, $J_{6-7\beta} = 9.6$ Hz), 3.46 (br t, H_1, $J = 4.8$ Hz), 3.63 (s, H_5), 4.27 (dd, H_2, $J_{2-OH} = 3.0$ Hz, J_2−3 = 10.5 Hz), 7.1−7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.93, 22.53, 27.57, 27.86, 29.75, 30.49, 42.56, 46.45, 46.67, 67.78, 68.65, 70.82, 124.03, 127.02, 128.61, 128.82, 138.12; MS m/z 298 (M^+, 14), 255 (43), 245 (4), 241 (52), 177 (12), 135 (27), 107 (24), 42 (100).

4β-Butyl-2α-hydroxy-8-methyl-3α-phenyl-8-azabicyclo-[3.2.1]octane-6-*endo*-carbonitrile (11b). Using a procedure similar to that for **11a**, **11b** was obtained (95%) as a white solid: R_f 0.4 (EtOAc/hexane 1/1); ^{1}H NMR (benzene-d_6) δ 0.80 (t, 3 H, $J = 7.2$ Hz), 0.90 (br s, OH), 1.0−1.4 (m, 6 H), 1.63 (ddd, $H_{7\beta}$, $J_{7\beta-1} = 7.5$ Hz, $J_{7\beta-6} = 12.0$ Hz, $J_{7\beta-7\alpha} = 13.5$ Hz), 1.74 (s, 3 H), 2.32−2.44 (m, H_4), 2.54 (dt, H_6, $J_{6-5} = J_{6-7\alpha} = 6.3$ Hz, $J_{6-7\beta} = 12.0$ Hz), 2.76 (dd, $H_{7\alpha}$, $J_{7\alpha-7\beta} = 13.5$ Hz, $J_{7\alpha-6} = 6.3$ Hz), 2.81 (d, H_5, $J_{5-6} = 6.0$ Hz), 2.90 (dd, H_3, $J_{3-2} = 5.4$ Hz, $J_{3-4} = 12.0$ Hz), 2.97 (dd, H_1, $J_{1-2} = 8.2$ Hz, $J_{1-7\beta} = 7.3$ Hz), 3.89 (ddd, H_2, $J_{2-OH} = 2.1$ Hz, $J_{2-1} = 8.1$ Hz, $J_{2-3} = 5.1$ Hz), 6.98−7.20 (m, 5 H); ^{13}C NMR (benzene-d_6) δ 14.18, 23.0, 24.55, 28.6, 30.06, 34.57, 38.68, 41.03, 47.37, 65.31, 68.27, 70.16, 121.73, 127.0, 128.92, 130.19, 139.79; MS m/z 298 (M^+, 14), 255 (30), 241 (8), 177 (10), 137 (29), 82 (52), 42 (100).

2β-Butyl-8-methyl-3α-phenyl-8-azabicyclo[3.2.1]octane-6-*exo*-carbonitrile (12a). To a solution of alcohol **11a** (54 mg, 0.18 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (0.072 mL, 0.18 mmol, 2.5 M in hexane), followed immediately by phenyl thionochloroformate (0.038 mL, 0.27 mmol). After 1 h, the reaction was quenched with a saturated solution of $NaHCO_3$ (20 mL), and the mixture was extracted with ether (2 × 20 mL). The collected organic phases were dried and concentrated under reduced pressure, and the crude mixture was purified by flash chromatography on silica gel using EtOAc/hexane as eluent to afford the phenoxy(thiocarbonyl)-oxy derivative (30 mg, 40%) as a colorless oil: R_f 0.8 (EtOAc/hexane 1/4); ^{1}H NMR ($CDCl_3$) δ 0.83 (t, 3 H, $J = 6.6$ Hz), 1.2−1.5 (m, 6 H), 1.62−1.80 (m, H_4), 2.25−2.50 (m, $H_{7\alpha}$ and $H_{7\beta}$), 2.57 (s, 3 H), 2.77 (br t, H_6, $J = 8.1$ Hz), 3.07 (dd, H_3, $J_{3-2} = 4.8$ Hz, $J_{3-4} = 10.8$ Hz), 3.50 (br s, H_5), 3.98 (br t, H_1, $J = 6.6$ Hz), 5.75 (dd, H_2, $J_{2-3} = 5.1$ Hz, $J_{2-1} = 8.7$ Hz), 6.84 (d, 2 H, $J = 7.8$ Hz), 7.1−7.4 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 13.95, 22.62, 28.34, 28.64, 33.79, 34.12, 41.95, 44.55, 46.07, 64.15, 71.60, 76.58, 77.00, 77.42, 83.32, 121.67, 123.51, 126.62, 126.91, 128.29, 129.46, 129.76, 138.00, 153.05, 194.33.

A solution of the above derivative (20 mg, 0.046 mmol), Bu_3-SnH (0.02 mL, 0.069 mmol), and AIBN (1.5 mg, 0.01 mmol) in toluene (2 mL) was purged with argon. The reaction flask was placed in a preheated oil bath at 60 °C and then heated from 60 to 90 °C over 15 min. After concentration under reduced pressure, the crude residue was purified by flash chromatography on silica gel using EtOAc/hexane as eluent to afford the title compound (9 mg, 70%) as a colorless oil: R_f 0.80 (EtOAc/hexane 7/3); ^{1}H NMR ($CDCl_3$) δ 0.82 (t, 3 H, $J = 6.6$ Hz), 1.1−1.5 (m, 8 H), 2.03 (dd, $H_{6\alpha}$, $J_{6\alpha-7} = 9.3$ Hz, $J_{6\alpha-6\beta} = 12.9$ Hz), 2.3−2.6 (m, 3 H), 2.49 (s, 3 H), 2.75 (t, H_7, $J = 8.1$ Hz), 3.41 (s, H_1), 3.47 (br t, H_5, $J_{5-4} = 7.8$ Hz), 7.1−7.3 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.93, 22.71, 28.94, 33.00, 34.02, 36.23, 39.08, 40.09, 42.05, 51.47, 60.82, 71.52, 123.99, 126.21, 127.89, 128.35, 144.45; MS m/z 282 (M^+, 12), 239 (13), 225 (64), 172 (12), 107 (32), 42 (100). Anal. Calcd for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 80.58; H, 9.49; N, 9.54.

2-Hydroxy-8-methyl-3-phenyl-8-azabicyclo[3.2.1]oct-3-ene-6-*exo*-carbonitrile (14a). Enone **7a** (200 mg, 0.84 mmol) was dissolved in a solution of $CeCl_3 \cdot 7H_2O$ (340 mg, 0.92 mmol) in MeOH (2.3 mL), and then $NaBH_4$ (32 mg, 0.84 mmol) was added portionwise. This mixture was stirred at rt for 5 min and then diluted with water (30 mL) and extracted with EtOAc (2 × 30 mL). The combined organic phases were dried and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel using EtOAc/hexane as eluent to obtain a mixture of the two alcohols (200 mg, 98%) as a white foam: R_f 0.8 (EtOAc/hexane 4/1). 2α-Isomer: ^{1}H NMR ($CDCl_3$) δ 1.83 (br s, OH), 2.32 (ddd, $H_{7\beta}$, $J_{7\beta-6} = 3.3$ Hz, $J_{7\beta-1} = 7.2$ Hz, $J_{7\beta-7\alpha} = 14.1$ Hz), 2.66 (s, 3 H), 2.77 (dd, $H_{7\alpha}$, $J_{7\alpha-6} = 9.6$ Hz, $J_{7\alpha-7\beta} = 13.8$ Hz), 3.02 (dd, H_6, $J_{6-7\beta} = 3.3$ Hz, $J_{6-7\alpha} = 9.6$ Hz), 3.68 (br t, H_1, $J = 6.0$ Hz), 3.78 (d, H_5, $J_{5-4} = 5.4$ Hz), 5.15 (d, H_2, $J_{2-1} = 5.1$ Hz), 6.11 (d, H_4, $J_{4-5} = 5.4$ Hz), 7.24−7.40 (m, 5 H); MS m/z 240 (M^+, 4), 186 (2), 170 (28), 154 (3), 128 (30), 85 (4), 57 (100). 2β-Isomer: ^{1}H NMR ($CDCl_3$) δ 1.70 (br s, OH), 1.95 (dd, $H_{7\alpha}$, $J_{7\alpha-6} = 9.9$ Hz, $J_{7\alpha-7\beta} = 14.1$ Hz), 2.55 (ddd, $H_{7\beta}$, $J_{7\beta-6} = 3.9$ Hz, $J_{7\beta-1} = 8.1$ Hz, $J_{7\beta-7\alpha} = 14.1$ Hz), 2.90 (dd, H_6, $J_{6-7\beta} = 3.6$ Hz, $J_{6-7\alpha} = 9.9$ Hz), 3.68 (d, H_1, $J_{1-7\beta} = 8.1$ Hz), 3.91 (d, H_5, $J_{5-4} = 6.0$ Hz), 4.13 (s, H_2), 6.33 (d, H_4, $J_{4-5} = 6.0$ Hz), 7.24−7.45 (m, 5 H); MS m/z 240 (M^+, 2), 186 (4), 170 (30), 115 (2), 85 (3), 57 (100).

2-Acetoxy-8-methyl-3-phenyl-8-azabicyclo[3.2.1]oct-3-ene-6-*exo*-carbonitrile (15a and 16a). To a solution of **14a** (200 mg, 0.83 mmol) in pyridine (2 mL) was added Ac_2O (0.31 mL, 3.33 mmol). The resulting solution was stirred at rt for 15 h and then concentrated under reduced pressure, diluted with EtOAc (30 mL), and washed with NH_4Cl (2 × 20 mL). Drying and concentration under reduced pressure afforded a crude mixture of the two isomers, which were separated by flash chromatography on silica gel using EtOAc/hexane as eluent. Compound **15a** (180 mg, 76%): white solid; mp 107−109 °C; R_f 0.6 (EtOAc/hexane 1/1); ^{1}H NMR ($CDCl_3$) δ 1.91 (s, 3 H), 2.34 (ddd, $H_{7\beta}$, $J_{7\beta-6} = 3.0$ Hz, $J_{7\beta-1} = 6.9$ Hz, $J_{7\beta-7\alpha} = 13.8$ Hz), 2.64 (dd, $H_{7\alpha}$, $J_{7\alpha-6} = 9.6$ Hz, $J_{7\alpha-7\beta} = 13.8$ Hz), 2.70 (s, 3 H), 3.08 (dd, H_6, $J_{6-7\beta} = 3.3$ Hz, $J_{6-7\alpha} = 9.6$ Hz), 3.76 (t, H_1, $J_{1-2} = J_{1-7\beta} = 6.0$ Hz), 3.81 (d, H_5, $J_{5-4} = 5.4$ Hz), 6.25 (d, H_4, $J_{4-5} = 5.4$ Hz), 6.30 (d, H_2, $J_{2-1} = 5.1$ Hz), 7.15−7.22 (m, 2 H), 7.27−7.36 (m, 3 H), ^{13}C NMR ($CDCl_3$) δ 20.86, 28.92, 33.61, 37.23, 60.73, 63.60, 69.37, 122.37, 125.62, 128.03, 128.32, 128.43, 136.41, 136.62, 170.49; MS m/z 282 (M^+, 5), 223 (10), 182 (7), 170 (100), 128 (9), 115 (9). Compound **16a** (50 mg, 21%): white solid; mp 134−137 °C; R_f 0.55 (EtOAc/hexane 1/1); ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 3 H), 2.03 (dd, $H_{7\alpha}$, $J_{7\alpha-6} = 9.3$ Hz, $J_{7\alpha-7\beta} = 13.8$ Hz), 2.56 (ddd, $H_{7\beta}$, $J_{7\beta-6} = 3.3$ Hz, $J_{7\beta-1} = 7.5$ Hz, $J_{7\beta-7\alpha} = 13.8$ Hz), 2.61 (s, 3 H), 2.88 (dd, H_6, $J_{6-7\beta} = 3.3$ Hz, $J_{6-7\alpha} = 9.3$ Hz), 3.65 (d, H_1, $J_{1-7\beta} = 7.5$ Hz), 4.0 (d, H_5, $J_{5-4} = 5.4$Hz), 5.42 (s, H_2), 6.40 (d, H_4, $J_{4-5} = 5.7$ Hz), 7.24−7.57 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 20.93, 31.13, 32.30, 38.37, 62.84, 64.03, 68.86, 122.25, 125.56, 128.36, 128.62, 128.84, 134.23, 136.32, 170.53; MS m/z 282 (M^+, 3), 223 (4), 186 (3), 170 (100), 154 (5), 128 (40), 127 (3), 115 (3), 57 (76).

2β-Butyl-8-methyl-3-phenyl-8-azabicyclo[3.2.1]oct-3-ene-6-*exo*-carbonitrile (13a). To a suspension of CuCN (4.0 mg, 0.045 mmol) in dry ether (2 mL) at −7 °C was added *n*-BuMgBr (0.45 mL, 1.0 M in ether). After 10 min, a solution of **15a** (60 mg, 0.22 mmol) in dry ether (3 mL) was added dropwise. The resulting mixture was stirred at rt for 1.5 h and diluted with ether (20 mL), and the organic phase was washed with a saturated solution of NH_4Cl (2 × 20 mL), dried, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel using EtOAc/hexane as eluent to afford the title compound (48 mg, 80%) as a colorless oil: R_f 0.7 (EtOAc/hexane 3/7); ^{1}H NMR (benzene-d_6) δ 0.76 (t, 3 H, $J = 6.6$ Hz), 1.0−1.4 (m, 5 H), 1.6−1.7 (m, H_2), 1.71 (dd, $H_{6\alpha}$, $J_{6\alpha-7} = 9.0$ Hz, $J_{6\alpha-6\beta} = 12.0$ Hz), 2.0−2.12 (m, $H_{6\beta}$), 2.21 (s, 3 H), 2.12−2.30 (m, H_7), 2.90 (t, H_5, $J_{5-4} = J_{5-6\beta} = 5.4$ Hz), 3.51 (s, H_1), 5.58 (d, H_4, $J_{4-5} = 5.4$ Hz), 7.04−7.20 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.94, 22.61, 30.17,

30.70, 31.85, 37.22, 41.94, 47.52, 62.16, 70.10, 123.62, 125.83, 127.52, 128.32, 128.47, 138.17, 139.39; MS *m/z* 280 (M^+, 3), 237 (2), 170 (9), 119 (100), 107 (17), 91 (14).

2*β*-Butyl-8-methyl-3-phenyl-8-azabicyclo[3.2.1]octane-6-*exo*-carbonitrile (12a and 17a). A mixture of **13a** (80 mg, 0.30 mmol) and a catalytic amount of 10% Pd/C in MeOH (7 mL) was hydrogenated under 30 psi of H_2 at 25 °C for 24 h. Filtration through a pad of Celite and concentration under reduced pressure afforded a mixture containing the two isomers, which were separated by preparative thin-layer chromatography on silica gel using EtOAc/hexane as eluent to afford the title compounds. **12a** (46 mg, 58%): colorless oil. **17a** (30 mg, 38%): colorless oil; R_f 0.85 (EtOAc/hexane 7/3); ^{1}H NMR ($CDCl_3$) δ 0.75 (t, 3 H, J = 7.2 Hz), 0.70−0.95 (m, 2 H), 1.04−1.30 (m, 3 H), 1.36−1.56 (m, 2 H), 1.66−1.76 (m, 1 H), 2.18 (dd, $H_{6\alpha}$, $J_{6\alpha-7}$ = 9.6 Hz, $J_{6\alpha-6\beta}$ = 13.2 Hz), 2.12−2.24 (m, 1 H), 2.48−2.59 (m, 1 H), 2.53 (s, 3 H), 2.82 (dt, $H_{6\beta}$, $J_{6\beta-5} = J_{6\beta-7}$ = 5.1 Hz, $J_{6\beta-6\alpha}$ = 13.2 Hz), 2.99 (dd, H_7, $J_{7-6\beta}$ = 5.7 Hz, $J_{7-6\alpha}$ = 9.6 Hz), 3.44−3.54 (m, H_5), 3.66 (s, H_1), 7.05−7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.98, 22.60, 26.42, 29.60, 30.58, 32.21, 32.55, 36.53, 42.68, 45.91, 63.02, 71.28, 124.25, 126.21, 127.58, 127.91, 128.26, 141.95; MS *m/z* 282 (M^+, 12), 239 (13), 225 (11), 172 (20), 107 (57), 42 (100). Anal. Calcd for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 80.48; H, 9.03; N, 9.56.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for the compounds **7b**−**d**, **10b**, **11b**, **12a**, **13a**, **15a**, **16a**, and **17a** and ^{1}H NMR spectra for the compounds **5**, **6**, **7a**, and **11a** are provided (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microform version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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