Diastereoselective Kinetic Protonation of Exocyclic Enolates Derived from Bicyclic Ketones: Control of Stereochemistry Mediated by Bridging Heteroatoms

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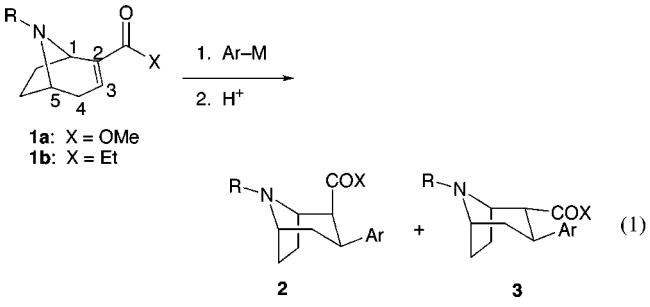
Introduction

3β-Aryltropane-2β-carboxylates **2** represent an important class of biologically active compounds as they are known to bind strongly to both the dopamine and serotonin transport proteins in the brain.[1] Furthermore, these compounds are being actively pursued toward use as possible medications to treat cocaine addiction.[2−5] The crucial step for most of the synthetic routes to these compounds is the 1,4-addition of aryl nucleophiles to anhydroecgonine derivatives (**1**) (eq 1). While the initial attack of the nucleophile (usually a Grignard or a cuprate reagent) occurs stereoselectively from the top, or exo face, the stereospecificity of the enolate quench at C2 is highly dependent on the reaction conditions. It is generally observed that use of both low temperatures and nonaqueous proton sources results in higher selectivity in favor of endo protonation giving the nonthermodynamic 2β-isomer, **2**. For example, the reaction between anhydroecgonine methyl ester (**1a**) and phenylmagnesium bromide followed by quenching with TFA at −78 °C[6] or with ethereal HCl at −20 °C[7] results in a 1.7:1 ratio of **2a** to **3a**. Use of ethereal HCl in quenching of the reaction between **1b** and *p*-tolylmagnesium bromide/Cu(I) results in an 88:12 ratio of **2b** to **3b**.[4]



(1)

Despite the generality of this trend, it is unclear why quenching under kinetic conditions results in protonation from the endo face to give product **2**, since this face is disfavored for reagent approach to bicyclo[3.2.1]octane systems. It is hypothesized that the heteroatom attached β to the carbonyl mediates an increased steric and or electronic barrier to the transition state for protonation of the enolate from the top or exo face. Accordingly, substrates lacking the bridging heteroatom β to the carbonyl would give primarily the exo protonation product even were strictly kinetic quenching conditions maintained. Additionally, if quenching were carried out at higher temperatures or in aqueous media, equilibration could occur to give the more stable exo-protonated products (**3**). Evidence supporting this hypothesis for bicyclo[3.2.1] and bicyclo[3.2.2] systems is presented.

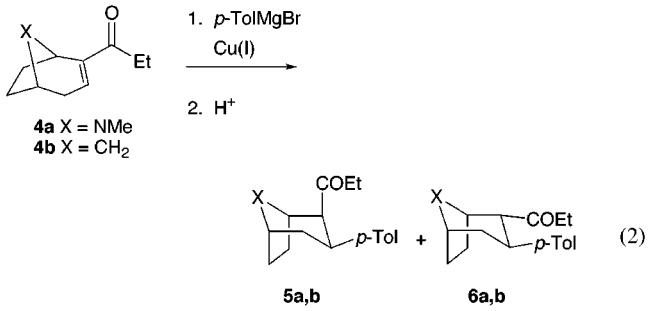
Table 1. Product Ratios for Conjugate Addition to 4a and 4b According to Eq 2

entry	X	proton source	temp °C	overall % yield	ratio **5**: **6**
1[a]	NMe	HCl/Et_2O	−70	73	88:12
2[a]	NMe	HCl (aq)	0	92	35:65
3[b]	NMe	HCl (aq)	23	80	0:100
4	CH_2	HCl/Et_2O	−70	41	28:72

[a] Reference 4. [b] Reference 8.

Results and Discussion

Bicyclooctanes. The conjugate addition of aryl cuprates to various 2-propionylbicyclo[3.2.1]oct-2-enes was carried out to test the necessity of a β-heteroatom for achieving stereocontrol during enolate quench (eq 2, Table 1). Conjugate addition to the tropane analogue **4a** followed by low-temperature ethereal HCl quench resulted in an 88:12 ratio of the cis and trans adducts (**5a**, **6a**, respectively). The same reaction quenched with aqueous HCl at 0 °C disfavored the cis isomer (35:65 cis/trans ratio). At room temperature, only the trans isomer was observed. When the reaction was performed on the carbon analogue, **5b**, and the quench performed with ethereal HCl at low temperature, an inseparable mixture of **5b** and **6b** was obtained in a 28:72 ratio.



(2)

6-Azabicyclo[3.2.2]nonanes. This chemistry was next extended to the 6-azabicyclo[3.2.2]non-3-ene and 6-azabicylo[3.2.2]non-2-ene ring systems.[9] Conjugate addition

(1) Singh, S. *Chem. Rev.* **2000**, *100*, 925−1024.
(2) Carroll, F. I.; Howell, L. L.; Kuhar, M. J. *J. Med. Chem.* **1999**, *42*, 2721−2736.
(3) Meltzer, P. C.; Liang, A. Y.; Madras, B. K. *J. Med. Chem.* **1996**, *39*, 371−379.
(4) Davies, H. M. L.; Saikali, E.; Huby, N. J. S.; Gilliatt, V. J.; Matasi, J. J.; Sexton, T.; Childers, S. R. *J. Med. Chem.* **1994**, *37*, 1262−1268.
(5) Davies, H. M. L.; Kuhn, L. A.; Thornley, C.; Matasi, J. J.; Sexton, T.; Childers, S. R. *J. Med. Chem.* **1996**, *39*, 2554−2558.
(6) 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*, 2719−2725.
(7) Meltzer, P. C.; Liang, A. Y.; Brownell, A. L.; Elmaleh, D. R.; Madras, B. K. *J. Med. Chem.* **1993**, *36*, 855−862.
(8) The reaction was treated with aqueous HCl in a water bath at ambient temperature to prevent significant heating of the mixture during the exothermic quench. The 2α-isomer was isolated in 80% yield.

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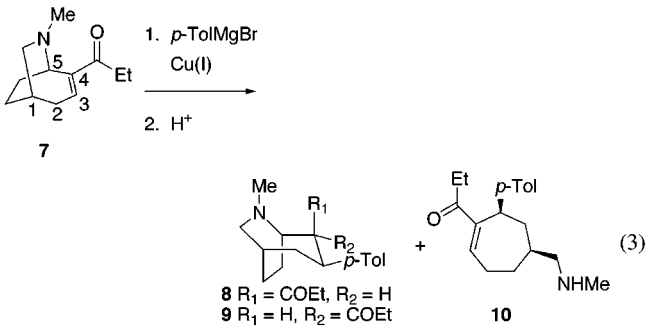
Table 2. Isolated Yields for Conjugate Addition to 7 According to Eq 3

entry	proton source	temp °C	overall % yield	ratio **8**:**9**:**10**
1	HCl/Et_2O	−70	67	99:1:0
2	HCl (aq)	23	66	13:9:78

between *p*-tolylmagnesium bromide−Cu(I) and **7**, which has the bridging nitrogen closer to the ketone group, followed by ethereal HCl quench at −70 °C resulted in the highly stereoselective formation of the cis isomer **8** (eq 3, Table 2). As observed with tropanes, initial attack of the aryl group occurred from the β face followed by highly selective quenching of the enolate from the α face. This reaction has been extended to several different aryl nucleophiles and azabicyclononane substitution patterns. The corresponding trans isomer **9**, when observed, was only isolated in trace amounts. In contrast to the corresponding tropane derivatives, when the quench was carried out at room temperature, the cis isomer **8** was still formed preferentially over the trans derivative **9** even when aqueous HCl is used. However, significant amounts of the ring-opened cycloheptenone (**10**) were also formed, presumably due to the increased ring strain of the azabicyclononane relative to the tropane skeleton.



The cis-substituted azabicyclononane **8** exists in a conformation similar to that of analogous tropanes, as shown by the characteristic ^1H NMR couplings of the ring protons.[7] For example, the H-3_{ax} proton resonance was a doublet of doublet of doublets with a large axial−axial coupling ($J \approx J \approx 5$ Hz). The H-4_{eq} proton resonance was a doublet of doublets with approximately equal couplings ($J \approx 5$ Hz) to both H-3 and H-5. In addition, NOE was observed between the H-2_{ax} proton and one of the H-7 protons.

When the analogous *N*-unsubstituted 6-azabicyclo-[3.2.2]nonane, **11**, was subjected to identical reaction conditions, the only product isolated was trans-substituted adduct **12a** (Scheme 1). Consistent with this assignment was the H-3 resonance (3.40 ppm), characterized by one small axial−equatorial coupling and two large axial−axial couplings. *N*-Methylation of this derivative gave the new compound **13a**, which is epimeric with **9** at *both* the 3- and 4-positions. Since the change of reactivity of **11** originated from the 1,4-addition step, the stereochemistry of the initial nucleophilic attack was further investigated.

To accomplish this goal, the 4-nitrophenylsulfonamide **13b**, derived from the isopropenylphenyl derivative **12b**, was synthesized. Extensive NOE studies of **13b** (Figure

(9) Details of the preparation of **7**, **11** and **14** are given in the Supporting Information.

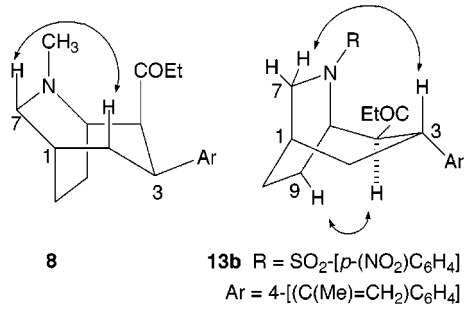
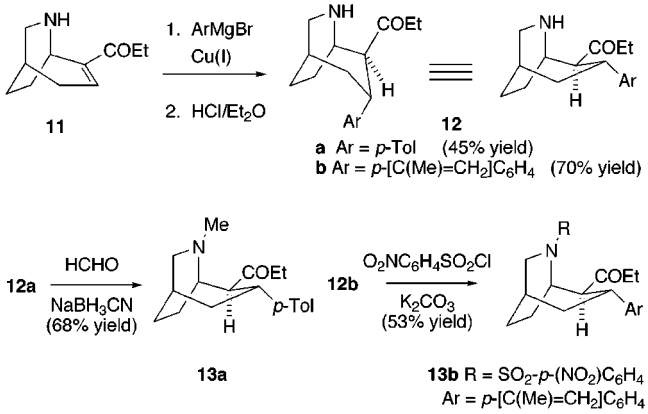


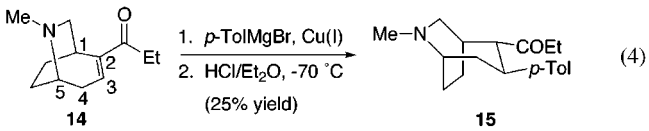
Figure 1. Diagnostic NOE data for **8** and **13b**. Arrows show observed enhancements.

Scheme 1



1) revealed enhancement between H-3_{ax} and one of the two H-7 resonances as well as enhancement between the H-4_{ax} and H-9_{ax} protons. This observation is consistent with the 3,4-diequatorial conformer of **13b**. Products **12a** and **12b** thus arose by initial endo attack of the aryl cuprate followed by protonation, again along an endo trajectory as the present study has predicted.

Conjugate addition to the 6-azabicyclo[3.2.2]nonane regioisomer with the nitrogen substituent away from the ketone functionality (**14**) produced the trans-substituted compound **15** in low yield as the major product (eq 4) as judged by the coupling pattern of the H-3 resonance.



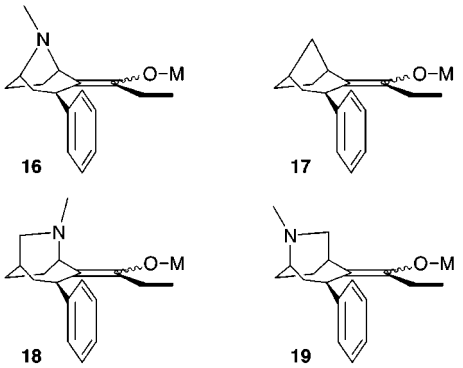
Discussion

Due to the high degree of potency of the 3β-aryl tropane-2β-carboxylates as compared to the relatively inactive 2α isomers, stereocontrol over protonation of the enolate following 1,4-additions to compounds such as **1** is of critical importance in the synthesis of these and other related dopamine transporter ligands. Of foremost importance is maintenance of kinetic conditions during the quenching of the reaction. Thus tropane **5a** was formed preferentially only when the quench was carried out at low temperature using anhydrous HCl in ethers and was not isolated at all if the quench was carried out at room temperature with aqueous acid, conditions where equilibrium to the thermodynamically more stable **6a** is rapid. Since the favored face of attack on the bicyclo[3.2.1] ring skeleton is typically the β face, however, these

results represent a reversal of the selectivity expected for a kinetic enolate quench. In the case of the bicyclo-[3.2.2] ring system, the endo/exo facial preference is not as clear, but in these cases, the observed stereoselectivity was even greater, which is not predicted by simple steric approach arguments.

Factors reported to affect the stereoselectivity of enolate protonation include substituent steric effects,[10] substituent electronic effects,[11−14] the nature of the quenching agent,[15,16] and effects of different metals, solvents, or additives that alter aggregation around the reactive centers.[17,18] In the present study, several scenarios can be suggested to account for kinetic protonation from the endo face. The most obvious cause would be metal salt chelation between the bridging heteroatom and the enolate. The distance between these two groups, however, is too great for a simple chelation interaction, either a solvent-separated interaction or severe distortion of the bicyclic enolate would be required.

Another possibility is that the stereocontrol is due to a stereoelectronic effect akin to that described in Mohrig's study of butanoate protonation,[12] in which significant stereoelectronic contributions to selectivity were described. In this report, inductively withdrawing substituents perpendicular to the plane of the enolate served to direct protonation to the opposite face even more effectively than did very bulky but inductively neutral groups. The transition state for protonation of highly electron-rich sp^2 carbons has also been investigated using ab initio molecular orbital calculations, and this study showed that the lowest-energy transition state had the electronegative β-substituent antiperiplanar to the incipient C−H bond.[19]



Just such an arrangement of a heteroatom substituent is expected in *N*-methyl-8-azabicyclo[3.2.1]octane enolate **16**, kinetic protonation of which favored approach from the α- face and gave rise to **5a** and **6a** in an 88:12 ratio. In the absence of the heteroatom, enolate **17** was preferentially protonated from the opposite face, giving **5b** and **6b** in a 28:72 ratio.

The protonation of *N*-methyl-6-azabicyclo[3.2.2]nonane enolate intermediates is also consistent with this model. Protonation of enolate **18**, where the nitrogen is adjacent to the ethyl ketone group and antiperiplanar to protonation from the α face, was selective in favor of the 2β product. In many cases, the 2α isomer was not observed in the crude reaction mixtures. In contrast to the tropane ring system, this 2β isomer was formed preferentially even when the quench was carried out with aqueous acid at room temperature. The opposite trend was observed when the nitrogen is removed from proximity to the ethyl ketone group. As illustrated by enolate model **19**, no assistance to protonation can be invoked due to a neighboring heteroatom, and only the 2α product was formed, and in lower yield.

A different trend of reactivity was observed with the *N*-unsubstituted 6-azabicyclo [3.2.2]nonanes **11**. The trans-substituted product **12** was the major product in this reaction.

However, NOE studies established that the enone had undergone 1,4-addition of the aryl group from the α face of the azabicyclononane ring. The expected α protonation of the resulting enolate provided the observed 3α,4β stereochemistry of these derivatives. While it is unclear why an unsubstituted nitrogen results in reversal of facial selectivity of nucleophilic attack (this is not observed with tropanes[5]), the product observed after quenching is still consistent with an electronic effect mediated by the neighboring heteroatom.

In conclusion, stereoselectivity in the metal-promoted conjugate addition of aryl nucleophiles to α,β-unsaturated tropane and 6-azabicyclo[3.2.2]nonane ketones appears to benefit from a switch of the expected exo approach of the protonating species to a preference for endo approach in the kinetic protonation of the enolate.

Experimental Section

^{1}H NMR spectra were run at either 300, 400, or 500 MHz, and ^{13}C NMR at either 75 or 125 MHz in $CDCl_3$ unless otherwise noted. Mass spectral determinations were carried out at 70 eV. Hexanes, THF, and Et_2O were dried over and distilled from sodium metal with benzophenone as the indicator. Acetonitrile, toluene, and methylene chloride were dried over and distilled from CaH_2. Column chromatography was carried out on Merck silica gel 60 (230−400 mesh). Commercially available reagents were used without additional purification unless noted. Melting points are uncorrected.

Reagents were purchased from Aldrich and used as received. Bicyclo[3.2.1]oct-2-ene **4b**[20] was prepared using literature procedures.

Copper-Catalyzed 1,4-Addition. Typical Procedure. A flame-dried flask was charged with $CuBr{\cdot}SMe_2$ (535 mg, 2.60 mmol), and a solution (Aldrich, 1.0 M) of *p*-TolMgBr in Et_2O (5.2 mL, 5.2 mmol) was added. The mixture was stirred at room temperature for 15 min and cooled to 0 °C under argon. A solution of **7** (100 mg, 0.517 mmol) in 10 mL of dry THF was added dropwise over 5 min. The reaction was stirred for 24 h while warming to room temperature. The mixture was cooled to −78 °C, and a 1 M solution of HCl in Et_2O (20 mL) was slowly added while keeping the internal temperature below −70 °C. The mixture was allowed to warm to 0 °C and poured into ice−

(10) Fleming, I. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3363−3369.
(11) Erdmann, P.; Schäfer, J.; Springer, R.; Zeitz, H. G.; Giese, B. *Helv. Chim. Acta* **1992**, *75*, 638−644.
(12) Mohrig, J. R.; Rosenberg, R. E.; Apostol, J. W.; Bastienaansen, M.; Evans, J. W.; Franklin, S. J.; Frisbie, C. D.; Fu, S. S.; Hamm, M. L.; Hirose, C. B.; Hunstad, D. A.; James, T. L.; King, R. W.; Larson, C. J.; Latham, H. A.; Owen, D. A.; Stein, K. A.; Warnet, R. *J. Am. Chem. Soc.* **1997**, *119*, 479−486.
(13) Banfi, L.; Guanti, G. *Tetrahedron: Asymmetry* **1999**, *10*, 439−447.
(14) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 440−442.
(15) Laval, G.; Audran, G.; Galano, J.-M.; Monti, H. *J. Org. Chem.* **2000**, *65*, 3551−3554.
(16) Gerlach, U.; Haubenreich, T.; Hünig, S.; Keita, Y. *Chem. Ber.* **1993**, *126*, 1205−1215.
(17) Mohrig, J. R.; Lee, P. K.; Stein, K. A.; Mitton, M. J.; Rosenberg, R. E. *J. Org. Chem.* **1995**, *60*, 3529−3532.
(18) Krause, N.; Ebert, S.; Haubrich, A. *Liebigs Ann. Recl.* **1997**, 2409−2418.
(19) Rosenberg, R. E.; Mohrig, J. R. *J. Am. Chem. Soc.* **1997**, *119*, 487−492.
(20) Davies, H. M. L.; Saikali, E.; Clark, T. J.; Chee, E. H. *Tetrahedron Lett.* **1990**, *31*, 6299−6302.

water (50 mL). Diethyl ether (50 mL) was added, and the layers were separated. The organic layer was extracted with 10% HCl, and the aqueous extracts were combined, neutralized with $NaHCO_3$ (s), and basified to pH 11−12 with NH_4OH. The aqueous solution was then extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated to give crude **6-methyl-4β-propionyl-3β-*p*-tolyl-6-azabicyclo[3.2.2]nonane (8)** which was essentially pure by ^1H NMR. The crude mixture was chromatographed (10:9:1 pentane/Et_2O/Et_3N (R_f = 0.65)) to give the title product as a white crystalline solid. Yield: 99 mg (0.35 mmol, 67%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.9 Hz, 2 H), 7.03 (d, *J* = 7.9 Hz, 2 H), 3.31 (dd, *J* = 5.8, 5.5 Hz, 1 H), 3.19 (dd, *J* = 5.8, 5.5 Hz, 1 H), 3.14 (ddd, *J* = 10.7, 2, 2 Hz, 1 H), 3.09 (ddd, *J* = 13.4, 4.8, 4.6 Hz, 1 H), 2.82 (dd, *J* = 13.1, 13.1 Hz, 1 H), 2.46 (dd, *J* = 10.1, 2.7 Hz, 1 H), 2.35 (m, 1 H), 2.28 (s, 3 H), 2.36 (s, 3 H), 2.22 (m, 1 H), 2.11 (br s, 1 H), 2.05 (m, 2 H), 1.82−1.60 (m, 3 H), 0.82 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 141.3, 134.8, 128.5, 127.9, 62.3, 58.7, 57.8, 45.4, 38.9, 35.3, 35.2, 29.7, 22.1, 20.9, 20.7, 7.6; IR (KBr): 3019, 2943, 1712, 1513 cm^{-1}; MS *m/e* (rel int): 285 (M^+, 34), 228 (90), 82 (100). Anal. Calcd for $C_{19}H_{27}NO$: C, 79.95; H, 9.53; N, 4.91. Found: C, 79.66; H, 9.57; N, 4.86. Upon quenching at room temperature with either HCl (aq) or 1 M HCl solution in Et_2O, both **8** and the trans-substituted isomer **9** are formed as well as the ring-opened cycloheptene **10**.

6-Methyl-4α-propionyl-3β-*p*-tolyl-6-azabicyclo[3.2.2]nonane [9]: ^1H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.9 Hz, 2 H), 7.05 (d, *J* = 7.9 Hz, 2 H), 3.31 (m, 2 H), 3.04 (dd, *J* = 10.7, 5.8 Hz, 1 H), 2.69 (d, *J* = 10.7 Hz, 1 H), 2.66 (d, *J* = 10.7 Hz, 1 H), 2.51 (s, 3 H), 2.34 (m, 1 H), 2.29 (s, 3 H), 2.10 (m, 3 H), 1.98−1.70 (m, 5 H), 0.75 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.8, 141.9, 135.7, 129.1, 127.7, 58.6, 57.8, 57.6, 44.3, 43.8, 40.6, 36.6, 29.9, 21.9, 21.4, 20.9, 7.3; IR (neat): 3020, 2930, 1701, 1513, 1459 cm^{-1}; MS *m/e* (rel int): 285 (M^+, 24), 228 (100). Anal. Calcd for $C_{19}H_{27}NO$: C, 79.95; H, 9.53; N, 4.91. Found: C, 80.07; H, 9.42; N, 5.00.

5-(*N*-Methylaminomethyl)-1-propionyl-7-*p*-tolyl-cycloheptene [10]: ^1H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.2 Hz, 2 H), 7.05 (d, *J* = 8.2 Hz, 2 H), 7.02 (dd, *J* = 6.5, 6.5 Hz, 1 H), 4.20 (dd, *J* = 10.4, 6.7 Hz, 1 H), 2.78 (m, 1 H), 2.65 (m, 1 H), 2.49 (m, 1 H), 2.37 (s, 3 H), 2.28 (s, 3 H), 2.36 (m, 3 H), 2.27 (m, 1 H), 1.96 (m, 2 H), 1.84 (m, 1 H), 1.76 (m, 1 H), 1.45 (m, 1 H), 0.94 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 144.5, 142.1, 139.5, 135.4, 129.1, 127.0, 58.3, 44.6, 36.9, 36.5, 35.2, 31.2, 29.5, 23.8, 20.9, 8.51; IR (neat): 3325, 3046, 3017, 2971, 1670, 1636, 1511, 1449 cm^{-1}; HRMS calcd for $C_{19}H_{27}NO$ 285.2093; found 285.2095.

2β-Propionyl-3β-*p*-tolylbicyclo[3.2.1]octane [5b] and 2α-Propionyl-3β-*p*-tolylbicyclo [3.2.1]octane [6b]. A flame-dried flask was charged with CuBr·SMe_2 (650 mg, 3.20 mmol), and a solution (Aldrich, 1.0 M) of *p*-TolMgBr in Et_2O (6.7 mL, 6.7 mmol) was added. The mixture was stirred at room temperature for 15 min and cooled to 0 °C under argon. A solution of **4b** (110 mg, 0.67 mmol) in 10 mL of dry THF was added dropwise over 5 min. The reaction was stirred for 24 h while warming to room temperature. The mixture was cooled to −78 °C, and a 1 M solution of HCl in Et_2O (10 mL) was slowly added while keeping the internal temperature below −70 °C. The mixture was allowed to warm to 0 °C and poured into water (50 mL). Diethyl ether (50 mL) was added, and the layers separated. The aqueous layer was extracted with ethyl ether, and the combined extracts were dried ($MgSO_4$), filtered, and evaporated to give a greenish solid. This was chromatographed (50:1 pet. ether/Et_2O (R_f = 0.24)) to give a 28:72 mixture of **5b** and **6b** as a colorless oil. Yield: 70 mg (0.27 mmol, 41%). Repeated chromatography provided **6b**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.0 Hz, 2 H), 7.03 (d, *J* = 8.0 Hz, 2 H), 3.16 (td *J* = 11.5, 5.5 Hz, 1 H), 2.86 (dd, *J* = 11.5, 2.0 Hz, 1 H), 2.45−2.29 (m, 3 H), 2.27 (s, 3 H), 1.95 (ddd, *J* = 17.5, 15.0, 7.0 Hz, 1 H), 1.90−1.81 (m, 1 H), 1.76−1.42 (m, 1 H), 0.81 (t, *J* = 7.0 Hz, 3H); MS *m/e* (rel int) for the mixture of **5b** and **6b**: 256 (M^+, 51), 227 (64), 199 (49), 105 (100). Anal. Calcd for $C_{18}H_{24}O$ as the mixture of **5b** and **6b**: C, 84.32; H, 9.44. Found: C, 84.23; H, 9.55.

4β-Propionyl-3α-*p*-tolyl-6-azabicyclo[3.2.2]nonane [12a] (45% yield from **11**): ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.0 Hz, 2 H), 7.06 (d, *J* = 8.0 Hz, 2 H), 3.40 (ddd, *J* = 12.5, 12.5, 5.5 Hz, 1 H), 3.29 (d, *J* = 11.4 Hz, 1 H), 3.08 (dd, *J* = 11.4, 4.0 Hz, 1 H), 3.00 (m, 2 H), 2.30 (s, 3 H), 2.28−2.10 (m, 4 H), 2.06 (br s, 1 H), 1.96−1.66 (m, 5 H), 0.73 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.0, 141.3, 135.9, 129.2, 127.6, 65.2, 49.7, 44.7, 43.2, 41.7, 36.9, 29.2, 28.8, 26.0, 20.9, 7.12; IR (neat): 3368, 3018, 2932, 1701, 1514, 1459 cm^{-1}; MS *m/e* (rel int): 271 (M^+, 36), 214 (100). Anal. Calcd for $C_{18}H_{25}NO$: C, 79.66; H, 9.28; N, 5.16. Found: C, 79.60; H, 9.29; N, 5.06.

6-Methyl-4β-propionyl-3α-*p*-tolyl-6-azabicyclo[3.2.2]nonane [13a]. A solution of **12a** (46 mg, 0.17 mmol) in 5 mL acetonitrile was prepared and HCHO (37% solution, 75 uL, 0.87 mmol) added. The mixture was stirred for 5 min and $NaCNBH_3$ (16 mg, 0.25 mmol) added. The mixture was stirred for 1 h and HOAc (3 mL) slowly added over 30 min. The mixture was then added to 25 mL of $NaHCO_3$ (sat, aq) and the mixture neutralized with NH_4OH (50 mL). The aqueous layer was extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated to give crude **13a**, which was chromatographed (20:1 Et_2O/Et_3N) to give the title compound as a colorless oil. Yield: 33 mg (0.12 mmol, 68%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.1 Hz, 2 H), 7.05 (d, *J* = 8.1 Hz, 2 H), 3.63 (dd, *J* = 12.1, 11.7, 6.6 Hz, 1 H), 3.22 (d, *J* = 10.6 Hz, 1 H), 2.81 (d, *J* = 12.1 Hz, 1 H), 2.69 (br s, 1 H), 2.41 (s, 3 H), 2.41 (d, overlap, 1 H), 2.28 (s, 3 H), 2.20 (m, 3 H), 2.05 (m, 2 H), 1.93 (m, 1 H), 1.62 (m, 3 H), 0.80 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 141.6, 135.6, 129.1, 127.8, 63.7, 58.2, 54.6, 46.0, 45.0, 41.4, 33.5, 29.9, 26.6, 23.4, 20.9, 7.58; IR (neat) 2932, 2862, 1702, 1513, 1493 cm^{-1}; MS *m/e* (rel int): 285 (M^+, 20), 228 (100). Anal. Calcd for $C_{19}H_{27}NO$: C, 79.95; H, 9.53; N, 4.91. Found: C, 79.75; H, 9.58; N, 4.81.

3α-(4-Isopropenylphenyl)-4β-propionyl-6-azabicyclo[3.2.2]nonane [12b] (70% from **11**): ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.9 Hz, 2 H), 7.18 (d, *J* = 8.2 Hz, 2 H), 5.35 (s, 1 H), 5.05 (s, 1 H), 3.45 (ddd, *J* = 12.5, 12.2, 5.5 Hz, 1 H), 3.30 (d, *J* = 11.6 Hz, 1 H), 3.09 (dd, *J* = 11.3, 3.7 Hz, 1 H), 3.01 (m, 2 H), 2.31−2.15 (m, 3 H), 2.13 (s, 3 H), 2.07 (br s, 1 H), 1.96−1.67 (m, 6 H), 0.74 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.7, 143.6, 142.7, 139.1, 127.6, 125.5, 111.9, 65.1, 49.8, 44.7, 43.0, 41.6, 39.9, 29.2, 28.9, 26.0, 21.7, 7.1; IR (neat): 3367, 3084, 3025, 2971, 1702, 1627, 1458 cm^{-1}. Anal. Calcd for $C_{20}H_{27}NO$: C, 80.76; H, 9.15; N, 4.71. Found: C, 80.60; H, 9.29; N, 4.55.

3α-(4-Isopropenylphenyl)-6-(4-nitrophenylsulfonyl)-4β-propionyl-6-azabicyclo[3.2.2]nonane [13b]. A solution of **12b** (49 mg, 0.16 mmol), K_2CO_3 (46 mg, 0.33 mmol) in acetone (4 mL) was prepared, and 4-nitrobenzenesulfonyl chloride (45 mg, 0.18 mmol) was added. The reaction was stirred for 24 h and diluted with 10 mL of $NaHCO_3$ (satd/aq) and 5 mL of Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The organic layers were combined, dried ($MgSO_4$), and evaporated to give a yellow solid. The crude material was chromatographed (1:1 pentane/Et_2O) to give the title compound as a white solid. Yield: 42 mg, 0.087 mmol, 53%). Mp = 182−184 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.5 Hz, 2 H), 8.14 (d, *J* = 8.8 Hz, 2 H), 7.37 (d, *J* = 8.2 Hz, 2 H), 7.37 (d, *J* = 7.9 Hz, 2 H), 5.34 (s, 1 H), 5.05 (s, 1 H), 4.35 (d, *J* = 4.0 Hz, 1 H), 3.58 (d, *J* = 10.7 Hz, 1 H), 3.34 (ddd, *J* = 12.5, 12.5, 6.1 Hz, 1 H), 3.25 (dd, *J* = 10.4, 3.4 Hz, 1 H), 2.92 (d, *J* = 11.9 Hz, 1 H), 2.32 (m, 3 H), 2.20 (m, 1 H), 2.12 (s, 3 H), 1.95 (m, 1 H), 1.82 (m, 1 H), 1.65 (m, 3 H), 0.86 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.6, 150.1, 144.5, 142.6, 142.4, 139.5, 129.0, 127.6, 125.8, 124.3, 112.2, 63.0, 51.7, 46.7, 43.1, 40.2, 35.2, 28.9, 28.7, 24.7, 21.7, 7.36; IR (KBr): 3104, 3025, 2971, 2935, 1716, 1529 cm^{-1}; MS *m/e* (rel int): 482 (M^+, 1.6), 464 (1.2), 425 (2.4), 296 (100). Anal. Calcd for $C_{26}H_{30}N_2O_5S$: C, 64.71; H, 6.27; N, 5.81. Found: C, 64.49; H, 6.34; N, 5.79.

6-Methyl-2α-propionyl-3β-*p*-tolyl-6-azabicyclo[3.2.2]nonane [15]. A three-necked flask was charged with CuBr·SMe_2 (538 mg, 2.62 mmol) under argon, and a solution of *p*-tolylmagnesium bromide (Aldrich, 1.0 M in Et_2O, 13 mL, 13 mmol) was added, giving a green solution. The mixture was stirred for 10 min and then cooled to 0 °C. A solution of **14** (248 mg, 1.3 mmol) in 10 mL of dry THF was added dropwise over 5 min. The reaction was stirred overnight while slowly warming to room temperature. The reaction mixture was cooled to −78 °C, and a solution of anhydrous HCl (40 mL, 1.0 M in Et_2O) was added at a rate in order to keep the reaction temperature below −65 °C. The mixture was allowed to warm to −40 °C and poured over ice. The layers were separated, and the organic layer was extracted with 10% HCl. The aqueous solutions were combined,

basified to pH 11.5 with concentrated NH_4OH, and extracted with CH_2Cl_2. The organic extracts were combined, dried ($MgSO_4$), and evaporated to give the crude product, which was chromatographed (9:1 Et_2O/Et_3N) to give the title compound as the major product as a colorless oil. Yield: 92 mg (0.33 mmol, 25%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, J = 7.9 Hz, 2 H), 7.05 (d, J = 7.9 Hz, 2 H), 3.33 (ddd, J = 12.5, 11.9, 5.5 Hz, 1 H), 3.06 (d, J = 11.9 Hz, 1 H), 3.05 (d, J = 11.3 Hz, 1 H), 2.87 (dd, J = 6.1, 5.5 Hz, 1 H), 2.81 (d, J = 11.0 Hz, 1 H), 2.44 (s, 3 H), 2.32 (m, 1 H), 2.29 (s, 3 H), 2.10−1.96 (m, 3 H), 1.94 (dd, J = 5.5, 4.9 Hz, 1 H), 1.87−1.75 (m, 3 H), 1.59 (m, 1 H), 0.75 (t, J = 7.0 Hz, 3 H) (Assignments are based on $^1H-^1H$ COSY data); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.9, 140.5, 136.0, 129.2, 127.8, 61.5, 58.3, 56.6, 43.6, 40.3, 38.3, 36.9, 31.8, 21.9, 21.0, 18.7, 7.3; IR (neat): 3018, 2934, 1710, 1459 cm^{-1}; MS *m*/*e* (rel int): 285 (M^+, 41), 228 (44), 167 (41), 96 (100). Anal. Calcd. for $C_{19}H_{27}NO$: C, 79.95; H, 9.53; N, 4.91. Found: C, 79.77; H, 9.58; N, 4.80.

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Supporting Information Available: Full experimental procedures for the preparation and characteriazation of compounds **7**, **11**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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