Regiospecific Synthesis of 6-Alkyltropan-2-ones

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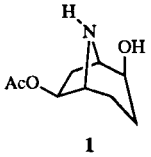
Received February 20, 1997

A new synthetic approach for the regiospecific alkylation of the 6-position of the tropane ring system has been developed. Alkylation, desulfonylation and deprotection of tropanes **5** and **12** furnished a series of 6-*endo*-alkyltropan-2-one derivatives **8a-e**, **15a-e** and **16a-e** (R = Me, Et, *n*-Pr, *n*-Bu, Bn) stereoselectively in good yields. The 6-*endo* isomers **15a-e** and 6-*exo* isomers **16a-e** were easily obtained as pure diastereoisomers.

J. Heterocyclic Chem., **34**, 1139 (1997).

Introduction.

Recently, the syntheses of a number of interesting 6-substituted tropane derivatives have been reported in the literature [1-5,6]. These include the natural product, bao gong teng A (**1**) [1,2], the pharmacological agent 6-methoxypseudococaine (**2**) [5, 7] and 6β-(4-methoxyphenyl)-tropan-3α-al (**3**) [6]. The syntheses of the 6-substituted tropanes have been developed around several synthetic strategies; these include the [3 + 2] cycloaddition reaction [1,2,8,9], the double Mannich reaction [5,7], intramolecular cyclization of substituted aminocycloheptane derivatives [4,10], solid phase Heck reactions with 3α-hydroxytrop-6-ene derivatives [6], and ring contraction of homotropane derivatives [3]. Although these approaches gave good yields of the corresponding 6-substituted tropanes, in some cases with high diastereoselectivity and enantioselectivity, the nature of the substituent has been limited to a hydroxyl, an aryl or an electron-withdrawing substituent. In light of this limitation, it was of interest to develop a synthetic method in which simple alkyl substituents could be introduced easily at the 6-position of the tropane skeleton. Herein we wish to report a new synthetic approach for the regiospecific alkylation of the tropane ring system to furnish 6-alkyltropan-2-one derivatives in a stereoselective fashion.



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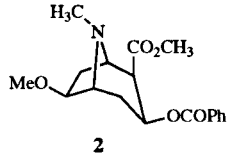

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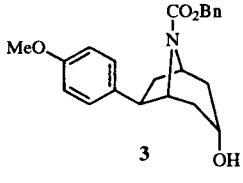

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Results and Discussion.

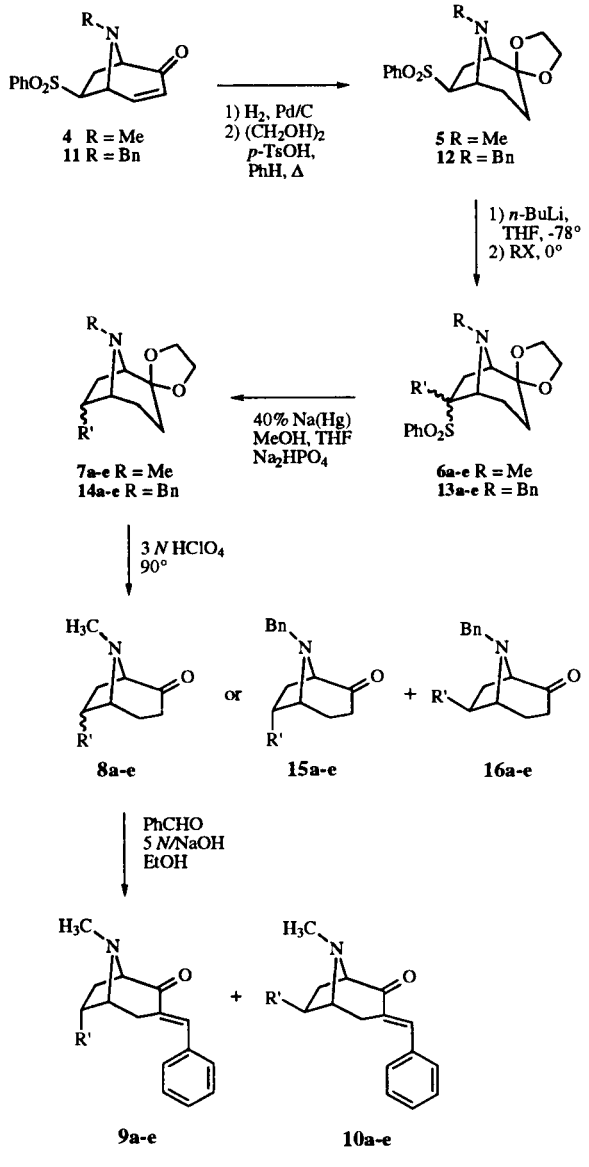
The synthesis of *N*-methyl 6-alkyltropan-2-one derivatives was envisaged to proceed *via* alkylation, desulfonylation and deprotection of the 6-*exo*-benzenesulfonyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one ethylene ketal (**5**) [9,11]. The ketal **5** was prepared from readily available **4** in a straightforward fashion (Scheme 1) [9,11,12]. Treatment of **5** with *n*-butyllithium at -78° in dry tetrahydrofuran and concomitant addition of an alkyl halide furnished the alkylated sulfone derivatives **6a-e** as a mixture of isomers in high yields (Table 1). As expected for the bicyclic system, the *endo*-benzenesulfonyl isomers **6a-e** were determined to be the major products [13,14]. The stereochemistry at the C(6)-carbon atom for the major isomer of **6a** and **6c** was unequivocally established by X-ray crystallography [15].

The observed stereofacial selectivity of the alkylation was consistent with that observed for the alkylation of other benzenesulfonyl bicyclic hydrocarbon systems and suggests that the geometry (pyramidal or planar) of the sulfonyl carbanion of **5** has little influence on the stereochemical control of the reaction [13,14]. For the tropane system, the steric effects experienced by the approaching electrophile appears to govern the selectivity of the alkylation. Therefore, since the β-face is more accessible, the product resulting from *exo*-alkylation dominates. Moreover, as the steric bulk of the approaching electrophile increased, *exo*-selectivity was also increased (Table 1).

The desulfonylation of the alkylated products **6a-e** was achieved with 40% sodium amalgam in sodium monohydrogen phosphate buffered methanol/tetrahydrofuran solution (Scheme 1). This procedure was found to minimize the amount of mercury waste [11] and afforded the 6-alkyl tropane derivatives **7a-e** in high yields (80-91%) as a mixture of isomers (Table 1). The 6-*endo* isomers of **7a-e** were found to be the major products resulting from the *exo*-hydrogen abstraction of the intermediate species generated by reductive C-S cleavage *in situ*. The products **7a-e** were characterized as a mixture of isomers since the isomers were not easily separated by column chromatography. The isomer ratios **7a-e** were determined by ^{1}H nmr (Table 1). Hydrolysis of the ketals **7a-e** afforded the tropan-2-ones **8a-e** as a mixture of isomers (72-87% yield).

The stereochemistry of the *N*-methyltropane derivatives at C(6) was established for each isomer by conversion of

Scheme 1



the mixture **8a-e** into the corresponding benzylidene derivatives **9a-e** and **10a-e** (Scheme 1). It had been demonstrated previously by Katritsky *et al* that the *endo*/*exo* isomers of a 6-cyanotropan-2-one derivative could be separated by chromatography as the benzylidene derivative [16]. Condensation of the mixture **8a-e** with benzaldehyde gave the benzylidene derivatives **9a-e** and **10a-e** (70-82% yield) [16]. The conversion of **8a-e** into **9a-e** and **10a-e** not only facilitated the separation of 6-*exo* and 6-*endo* isomers by column chromatography, it also served to alter the chemical environment of the 6-alkyl substituent to the extent that unequivocal assignment of the stereochemistry at C(6) for each isomer was possible by ^{1}H nmr and ^{1}H-^{1}H decoupling experiments. The 6-*endo* stereochemistry was confirmed for the major isomers **9a-e** by the observation

Table 1

Stereoselective Alkylation and Desulfonylation of *N*-Methyltropane Derivatives.

	Alkylation			Desulfonylation		
R'	Compound	*endo*/ *exo* [a]	yield (%)	Compound	*endo*/ *exo*	yield (%)
Me	**6a**	3:2	98	**7a**	3:1	85
Et	**6b**	3:2	96	**7b**	3:1	91
Pr	**6c**	5:2	80	**7c**	5:1	87
Bu	**6d**	5:2	76	**7d**	6:1	83
Bn	**6e**	10:1	92	**7e**	2:1	80

[a] Orientation refers to benzenesulfonyl group.

that the two vicinal protons H(5) and H(6) (bridgehead and 6-*exo* proton) were coupled (J = 6 Hz). For the minor isomers **10a-e**, the 6-alkyl substituent was in an *exo* orientation. As a result, no coupling was observed in the ^{1}H nmr for H(5) and H(6) (bridgehead and 6-*endo* proton) due to a dihedral angle of approximately 90°.

The fact that the benzylidene group facilitated the separation of the 6-*endo* and 6-*exo* isomers suggested that the 6-*endo* and 6-*exo* *N*-benzyl 6-alkyl tropan-2-ones may be more easily separated than the corresponding *N*-methyl analogs to afford the individual diastereoisomers in pure form. The synthesis of *N*-benzyl-6-alkyltropan-2-one derivatives was accomplished using a similar synthetic approach proceeding through the alkylation, desulfonylation and deprotection of 6-*exo*-benzenesulfonyl-8-benzyl-8-azabicyclo[3.2.1]octan-2-one ethylene ketal **12** (Scheme 1). Ketal **12** was prepared from **11** [9] using the same methodology previously developed in our laboratories [11]. Treatment of **11** with *n*-butyllithium at -78° in dry tetrahydrofuran followed by addition of an alkyl halide furnished the alkylated *N*-benzylsulfone derivatives **13a-e** again as a mixture of isomers in high yields (95-97%, Table 2).

In the *N*-benzyltropane ring system, the stereoselectivity of the alkylation was reversed relative to the *N*-methyl derivatives. Despite the propensity of bicyclic benzenesulfonyl compounds to give *exo*-alkylated products regardless

Table 2

Stereoselective Alkylation, Desulfonylation and Hydrolysis of *N*-Benzyltropane Derivatives

	Alkylation			Desulfonylation/Hydrolysis		
R'	Compound	*endo*/ *exo* [a]	yield (%)	Compound	*endo*/*exo*	yield (%)
Me	**13a**	1:2	95	**15a/16a**	2:1	55
Et	**13b**	1:3	95	**15b/16b**	5:2	55
Pr	**13c**	1:3	95	**15c/16c**	5:2	64
Bu	**13d**	1:3	97	**15d/16d**	3:1	55
Bn	**13e**	1:4	97	**15e/16e**	2:1	55

[a] Orientation refers to benzenesulfonyl group.

of the initial stereochemistry of the benzenesulfonyl group [13,14], the major product of the alkylation of **12** was the result of an *endo*-approach of the electrophilic alkylating agent to give **13a-e** (Table 2). The stereochemistry at the C(6)-carbon atom for the major isomer of **13a** was unequivocally established by X-ray crystallography [15]. It is believed that the *N*-benzyl group of the sulfonyl carbanion of **11** occupied the region above the C(6)-C(7) carbon bridge to minimize steric interactions with the ethylene ketal moiety. As a result, the approach of the electrophile (RX) was hindered at the β-face of the intermediate anion and alkylation from the α-face was preferred. This afforded the 6-*endo*-alkyl derivatives **13a-e** stereoselectively (Table 2).

Desulfonylation of the *N*-benzyl alkylated products **13a-e** afforded the *N*-benzyl-6-alkyltropane derivatives **14a-e**. The *endo*/*exo* isomer ratios were determined by ^{1}H nmr. The *N*-benzyl-6-alkyl ethylene ketals were not characterized at this step, but instead were carried onto the subsequent deprotection without further purification. Conversion of the ketal derivatives **14a-e** into the corresponding *N*-benzyl-6-alkyltropan-2-ones **15a-e** and **16a-e** was achieved in boiling perchloric acid. The nmr spectra of the crude product mixture confirmed that the hydrolysis reaction did not effect the *endo*/*exo* isomer ratios for **15a-e**/**16a-e** (Table 2). The 6-*endo* isomers **15a-e** and 6-*exo* isomers **16a-e** were then separated by column chromatography and characterized in a similar fashion to the *N*-methyl derivatives by ^{1}H nmr and ^{1}H-^{1}H decoupling experiments. Again, the 6-*endo* isomers **15a-e** from desulfonylation were found to be the major products while the 6-*exo* isomers **16a-e** were present as the minor products. The isomer ratios (*endo*/*exo*) of the 6-alkyl derivatives **15a-e**/**16a-e** were surprisingly similar to those obtained for the *N*-methyl analogs **7a-e**. From these results it is apparent that although the *N*-benzyl group of **12** provided increased stereoselectivity in the kinetically controlled alkylation reaction, it does not affect the stereochemical course of the desulfonylation reaction to furnish **14a-e**.

In summary, we have demonstrated that alkylation, desulfonylation and deprotection of either *N*-methylsulfone **5** or *N*-benzylsulfone **12** is an extremely facile and direct method for the regiospecific and stereoselective alkylation of the 6-position on the tropane ring system. In particular the *N*-benzyl analogs **15a-e** and **16a-e** should prove to be versatile intermediates for the preparation of complex 6-alkyltropane derivatives.

EXPERIMENTAL

All chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI, unless otherwise noted. Ether (E. M. Science) and tetrahydrofuran were dried by distillation from sodium/benzophenone. Methanol was dried by distillation over Drierite®. Chromatography refers to flash chromatography on silica gel (Silica Gel 60, 230-400 mesh, E. M. Science) and petrol refers to petroleum ether (pentanes) with a boiling point range of 30-60°. Reported melting points are uncorrected. The ^{1}H and ^{13}C nmr spectra were recorded on a Varian 300 MHz Multiprobe nmr spectrometer in deuteriochloroform. Elemental analyses were obtained from Atlantic Microlab, Inc., Norcross, GA.

General Procedure for the Preparation of Hydrochloride Salts.

Some of the compounds were converted into the corresponding hydrochloride salts for ease of handling and storage. The base (1 g) was dissolved in a minimum amount of tetrahydrofuran (1-2 ml) and added to a cooled (0°) etheral solution (10 ml) of hydrogen chloride (saturated). The hydrochloride salts then crystallized upon standing at room temperature and were collected by vacuum filtration. Fractional moles of water in some of the analytical samples could not be prevented despite vigorous drying (65°, 18 hours) under vacuum (0.01 mm Hg).

6-Benzenesulfonyl-6,8-dimethyl-8-azabicyclo[3.2.1]octan-2-one Ethylene Ketal (**6a**).

To a cooled solution of the ketal **5** [11] (1.00 g, 3.09 mmoles) in dry tetrahydrofuran (20 ml) at -78° under a nitrogen atmosphere, *n*-butyllithium (2.32 ml, 1.60 *M*, in hexanes) was added dropwise by syringe. Upon addition of the *n*-butyllithium, a yellow precipitate was seen. The slurry was stirred at -78° for an additional 15 minutes. Iodomethane (289 ml, 4.64 mmoles) was then added dropwise by syringe. The solution was stirred for 30 minutes at-78° and then allowed to warm up to room temperature over 1 hour. The solution was poured into water (20 ml) and the organic layer was removed. The aqueous layer was extracted with dichloromethane (3 x 50 ml). The combined organic portions were washed with brine (50 ml), dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was chromatographed (silica gel, ethyl acetate:petroleum ether, 1:1) to give a white solid, 1.02 g (98%), mp 126-127°; ^{1}H nmr: δ 7.87 (d, J = 7.3 Hz, 2H), 7.60 (m, 1H), 7.51 (t, J = 7.7 Hz, 2H), 4.00-3.73 (m, 4H), 2.98 (m, 2H), 2.76 (m, 1H), 2.61 (s, 3H), 2.16 (m, 2H), 1.67 (m, 3H), 1.35 (s, 3H); ^{13}C nmr: δ 133.2, 129.2, 128.9, 128.0, 107.3, 70.3, 65.3, 64.9, 63.4, 63.2, 36.4, 35.5, 28.3, 28.2, 19.2.

Anal. Calcd. for $C_{17}H_{23}NO_4S$: C, 60.51; H, 6.87; N, 4.18. Found: C, 60.28; H, 6.82; N, 4.14.

General Procedure for the Alkylation of Ketal **5**.

To a cooled solution of ketal **5** [11] (1.00 g, 3.09 mmoles) in dry tetrahydrofuran (20 ml) at -78° under a nitrogen atmosphere, *n*-butyllithium (2.32 ml, 1.60 *M*, in hexanes) was added dropwise by syringe. Upon addition of the *n*-butyllithium, a yellow precipitate was seen. The slurry was then allowed to warm up to 0° over 30 minutes while stirring. To the solution at 0° the alkyl halide (4.64 mmoles) was added dropwise by syringe. The solution was stirred for 3 hours at 0° and then allowed to warm up to room temperature over 1 hour. The solution was poured into water (20 ml) and the organic layer was removed. The aqueous layer was extracted with dichloromethane (3 x 50 ml). The combined organic portions were washed with brine (50 ml), dried over sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by chromatography (silica gel, ethyl acetate:petroleum ether, 3:1) to afford **6b-e**.

6-Benzenesulfonyl-6-ethyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one Ethylene Ketal (**6b**).

This compound was obtained as a white solid, 1.09 g (96%), mp 101-102°; ^{1}H nmr: δ 7.88 (d, J = 8.3 Hz, 2H), 7.60 (m, 1H),

7.50 (t, J = 7.7 Hz, 2H), 4.00-3.70 (m, 4H), 3.40 (br s, 1H), 2.98 (d, J = 6.0 Hz, 1H), 2.87-2.68 (m, 1H), 2.58 (s, 3H), 2.25-2.03 (m, 2H), 1.82-1.55 (m, 3H), 1.24 (q, J = 7.1 Hz, 2H), 0.80 (t, J = 7.4 Hz, 3H); ^{13}C nmr: δ 133.2, 128.9, 128.6, 127.6, 107.4, 73.8, 64.9, 63.4, 62.5, 61.2, 35.9, 35.4, 32.0, 28.4, 19.2, 9.80.

Anal. Calcd. for $C_{18}H_{25}NO_4S$: C, 61.51; H, 7.17; N, 3.99. Found: C, 61.41; H, 7.25; N, 3.97.

6-Benzenesulfonyl-8-methyl-6-propyl-8-azabicyclo[3.2.1]octan-2-one Ethylene Ketal (**6c**).

This compound was obtained as a white solid, 900 mg (80%), mp 159-160°; ^{1}H nmr: δ 7.87 (d, J = 8.2 Hz, 2H), 7.60 (m, 1H), 7.51 (t, J = 7.7 Hz, 2H), 4.02-3.70 (m, 4H), 3.22 (br s, 1H), 2.98 (d, J = 6.0 Hz, 1H), 2.88-2.68 (m, 1H), 2.59 (s, 3H), 2.25-2.10 (m, 2H), 1.90-1.60 (m, 3H), 1.57-1.40 (m, 2H), 1.25-1.00 (m, 2H), 0.62 (t, J = 7.1 Hz, 3H); ^{13}C nmr: δ 133.3, 128.9, 128.5, 127.7, 107.5, 74.0, 64.9, 63.4, 62.5, 61.9, 41.5, 36.1, 35.4, 28.4, 19.3, 18.3, 14.4.

Anal. Calcd. for $C_{19}H_{27}NO_4S$: C, 62.44; H, 7.45; N, 3.83. Found: C, 62.35; H, 7.49; N, 3.78.

6-Benzenesulfonyl-6-butyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one Ethylene Ketal (**6d**).

This compound was obtained as a colorless oil, 888 mg (76%) and converted into a hydrochloride salt, which was obtained as a white solid, mp 214-216°; ^{1}H nmr (free base): δ 7.87 (d, J = 7.6 Hz, 2H), 7.60 (m, 1H), 7.51 (t, J = 7.7 Hz, 2H), 4.02-3.70 (m, 4H), 3.23 (br s, 1H), 2.98 (d, J = 6.0 Hz, 1H), 2.78 (m, 1H), 2.59 (s, 3H), 2.30-2.05 (m, 2H), 1.90-1.60 (m, 3H), 1.55-1.30 (m, 2H), 1.28-1.12 (m, 2H), 1.08-0.90 (m, 2H), 0.71 (t, J = 7.0 Hz, 3H); ^{13}C nmr (free base): δ 133.2, 128.8, 128.5, 127.6, 107.4, 73.9, 64.9, 63.3, 62.4, 61.8, 39.0, 36.1, 35.4, 28.3, 27.1, 23.0, 19.2, 13.7.

Anal. Calcd. for $C_{20}H_{29}NO_4S$•HCl: C, 57.75; H, 7.27; N, 3.37. Found: C, 57.68; H, 7.32; N, 3.29.

6-Benzenesulfonyl-6-benzyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one Ethylene Ketal (**6e**).

This compound was obtained as a white solid, 1.18 g (92%), mp 112-114°; ^{1}H nmr: δ 7.96 (d, J = 7.3 Hz, 2H), 7.65 (m, 1H), 7.57 (t, J = 7.3 Hz, 2H), 7.11 (m, 3H), 6.77 (m, 2H), 3.97-3.70 (m, 4H), 3.15 (m, 1H), 3.03 (d, J = 14.2 Hz, 1H), 2.90 (d, J = 14.3 Hz, 1H), 2.85 (m, 1H), 2.72 (m, 1H), 2.62 (d, J = 13.7 Hz, 1H), 2.35 (s, 3H), 2.14 (m, 2H), 2.00 (m, 1H), 1.67 (m, 1H); ^{13}C nmr: δ 139.5, 137.3, 133.3, 129.8, 129.1, 129.0, 127.5, 126.1, 107.2, 73.7, 64.8, 63.7, 63.2, 62.0, 44.9, 34.8, 34.0, 28.5, 19.1.

Anal. Calcd. for $C_{23}H_{27}NO_4S$: C, 66.80; H, 6.58; N, 3.39. Found: C, 66.64; H, 6.63; N, 3.36.

General Procedure for the Desulfonylation of Sulfones **6a-e**.

To a three-neck flask equipped with a mechanical stirrer, anhydrous sodium monohydrophosphate (14.2 g, 100 mmoles) and dry methanol (30 ml) was added a solution of sulfone **6a-e** (10.0 mmoles) in dry tetrahydrofuran (30 ml). Sodium amalgam (40%) was pipetted portionwise into the slurry over 1 hour. The rate of addition of amalgam was controlled such that the reaction did not become too vigorous. Amalgam was added until the reaction was complete by tlc. The reaction was quenched with methanol (10 ml) and allowed to cool to room temperature. The organic solution was carefully decanted away from the inorganic residue. The inorganic material was rinsed with tetrahydrofuran (3 x 40 ml). The combined organic portions were then concentrated under reduced pressure. The resulting slurry was dissolved in water (100 ml) and extracted with dichloromethane (4 x 60 ml). The combined organic layers were washed with brine, dried over sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified either by chromatography (silica gel, chloroform:methanol, 19:1) or by bulb-to-bulb distillation (0.1 mm Hg) to afford **7a-e**.

6,8-Dimethyl-8-azabicyclo[3.2.1]octan-2-one Ethylene Ketal (**7a**).

This compound was obtained as a colorless oil, 1.68 g (85%), bp 72-76° (0.1 mm Hg). The oil was converted to the fumarate salt (2-propanol) to afford a white solid, mp 172-173°; ^{1}H nmr (free base): δ 3.92-3.70 (m, 4H), 2.70 (m, 2H), 2.43 (m, 2H), 2.25 (s, 3H), 2.15 (m, 1H), 1.60-1.40 (m, 3H), 1.17 (m, 1H), 0.96 (d, J = 7.0 Hz, 3H); ^{13}C nmr (free base): δ 109.0, 67.6, 64.6, 63.9, 63.7, 40.9, 31.8, 31.1, 27.8, 24.7, 14.6.

Anal. Calcd. for $C_{11}H_{19}NO_2$•$C_4H_4O_4$: C, 57.50; H, 7.40; N, 4.47. Found: C, 57.58; H, 7.42; N, 4.52.

6-Ethyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one Ethylene Ketal (**7b**).

This compound was obtained as a colorless oil, 1.92 g (91%), bp 80-84° (0.1 mm Hg). The oil was converted to the hydrochloride salt to afford a white solid, mp 191-193°; ^{1}H nmr (free base): δ 4.05-3.72 (m, 4H), 2.88 (br s, 1H), 2.80 (d, J = 6.0 Hz, 1H), 2.35 (s, 3H), 2.35-2.15 (m, 2H), 1.80-1.65 (m, 1H), 1.64-1.37 (m, 5H), 1.32-1.22 (m, 1H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C nmr (free base): δ 109.0, 67.2, 64.6, 63.8, 62.5, 40.9, 39.4, 30.1, 27.9, 24.7, 23.2, 13.9.

Anal. Calcd. for $C_{12}H_{21}NO_2$•HCl•$^1/_2H_2O$: C, 56.13; H, 9.03; N, 5.45. Found: C, 56.04; H, 8.87; N, 5.48.

8-Methyl-6-propyl-8-azabicyclo[3.2.1]octan-2-one Ethylene Ketal (**7c**).

This compound was obtained as a colorless oil, 1.96 g (87%), bp 88-94° (0.1 mm Hg); ^{1}H nmr: δ 4.02-3.75 (m, 4H), 2.86 (br s, 1H), 2.80 (d, J = 6.0 Hz, 1H), 2.35 (s, 3H), 2.30-2.12 (m, 1H), 1.65-1.47 (m, 4H), 1.45-1.20 (m, 6H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C nmr: δ 109.1, 67.3, 64.7, 64.0, 62.9, 41.0, 37.2, 32.7, 30.4, 28.0, 24.9, 22.8, 14.3.

Anal. Calcd. for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.21. Found: C, 69.20; H, 10.21; N, 5.99.

6-Butyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one Ethylene Ketal (**7d**).

This compound was obtained as a colorless oil, 1.99 g (83%), bp 110-115° (0.1 mm Hg). The oil was converted into the hydrochloride salt to afford a white solid, mp 171-172°; ^{1}H nmr (free base): δ 4.02-3.74 (m, 4H), 2.85 (br s, 1H), 2.78 (d, J = 6.0 Hz, 1H), 2.33 (s, 3H), 2.25-2.12 (m, 1H), 1.78-1.63 (m, 1H), 1.62-1.45 (m, 3H), 1.44-1.32 (m, 2H), 1.31-1.20 (m, 6H), 0.85 (m, 3H); ^{13}C nmr (free base): δ 109.0, 67.2, 64.5, 63.9, 62.8, 41.0, 37.3, 31.9, 30.3, 30.0, 27.9, 24.8, 22.8, 13.9.

Anal. Calcd. for $C_{14}H_{25}NO_2$•HCl•$^1/_4H_2O$: C, 59.98; H, 9.53; N, 5.00. Found: C, 59.98; H, 9.43; N, 5.02.

6-Benzyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one Ethylene Ketal (**7e**).

This compound was obtained as a colorless oil, 2.19 g (80%). The oil was converted into the hydrochloride salt to afford a white solid, mp 200-201°; ^{1}H nmr (free base): δ 7.23 (m, 5H), 3.94 (m, 4H), 4.05-3.80 (br s, 1H), 2.80 (m, 3H), 2.36 (s, 3H),

2.32-2.10 (m, 1H), 1.79 (m, 3H), 1.62 (m, 2H), 1.43 (m, 1H); ^{13}C nmr (free base): δ 141.7, 128.2, 128.1, 125.7, 108.9, 67.4, 64.7, 64.0, 62.9, 41.1, 39.1, 36.3, 30.2, 27.9, 25.2.

Anal. Calcd. for $C_{17}H_{23}NO_2$•HCl•$^2/_3H_2O$: C, 63.47; H, 7.93; N, 4.35. Found: C, 63.74; H, 7.66; N, 4.42.

General Procedure for the Hydrolysis of Ketal **7a-e**.

A solution of ketal **7a-e** (10.0 mmoles) in 3 *M* perchloric acid (240 mmoles) at 90° was stirred overnight. (Note: Reaction temperatures below 90° resulted in incomplete conversion while temperatures above 95° resulted in lower yields due to decomposition of material.) The reaction mixture was allowed to cool to room temperature and poured into a solution of 3 *M* sodium hydroxide (288 mmoles). The alkaline aqueous mixture was extracted with dichloromethane (3 x 100 ml). The combined organic fractions were washed with brine (50 ml), dried over sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified either by chromatography (silica gel, chloroform:methanol, 19:1) or by bulb-to-bulb distillation (0.1 mm Hg) to afford **8a-e**.

6,8-Dimethyl-8-azabicyclo[3.2.1]octan-2-one (**8a**).

This compound was obtained as a colorless oil, 1.18 g (77%), bp 58-62° (0.1 mm Hg). The oil was converted into the hydrochloride salt to afford a white solid, mp 204-206°; ^{1}H nmr (free base): δ 3.19 (d, J = 7.6 Hz, 1H), 3.06 (br s, 1H), 2.53 (m, 2H), 2.45 (s, 3H), 2.33 (m, 1H), 2.20 (m, 2H), 1.96 (m, 1H), 1.20 (m, 1H), 1.16 (d, J = 6.8 Hz, 3H); ^{13}C nmr (free base): δ 211.8, 70.8, 62.0, 36.6, 35.2, 34.0, 33.1, 22.9, 16.0.

Anal. Calcd. for $C_9H_{15}NO$•HCl•$^2/_3H_2O$: C, 53.54; H, 8.67; N, 6.93. Found: C, 53.56; H, 8.68; N, 6.89.

6-Ethyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one (**8b**).

This compound was obtained as a colorless oil, 1.20 g (72%), bp 66-70° (0.1 mm Hg). The oil was converted into the hydrochloride salt to afford a white solid, mp 178-180°; ^{1}H nmr (free base): δ 3.10 (d, J = 7.3 Hz, 1H), 3.02 (br s, 1H), 2.34 (s, 3H), 2.26 (m, 3H), 2.07 (m, 2H), 1.82 (m, 1H), 1.42 (m, 2H), 1.14 (m, 1H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C nmr (free base): δ 211.2, 70.3, 60.7, 41.8, 36.5, 33.3, 33.2, 24.4, 22.8, 13.4.

Anal. Calcd. for $C_{10}H_{17}NO$•HCl•$^1/_2H_2O$: C, 56.46; H, 9.00; N, 6.58. Found: C, 56.37; H, 9.01; N, 6.52.

8-Methyl-6-propyl-8-azabicyclo[3.2.1]octan-2-one (**8c**).

This compound was obtained as a colorless oil, 1.58 g (87%), bp 76-80° (0.1 mm Hg). The oil was converted into the hydrochloride salt to afford a white solid, mp 172-174°; ^{1}H nmr (free base): δ 3.12 (d, J = 6.7 Hz, 1H), 3.01 (br s, 1H), 2.36 (s, 3H), 2.25 (m, 3H), 2.07 (m, 2H), 1.84 (m, 1H), 1.45-1.20 (m, 4H), 1.15 (m, 1H), 0.85 (t, J = 7.0 Hz, 3H); ^{13}C nmr (free base): δ 211.4, 70.3, 60.9, 39.7, 36.5, 33.7, 33.5, 33.1, 23.0, 22.1, 14.1.

Anal. Calcd. for $C_{11}H_{19}NO$•HCl: C, 60.68; H, 9.26; N, 6.43. Found: C, 60.39; H, 9.21; N, 6.29.

6-Butyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one (**8d**).

This compound was obtained as a colorless oil, 1.62 g (83%), bp 82-86° (0.1 mm Hg). This compound was converted into the hydrochloride salt to afford a white solid, mp 177-178°; ^{1}H nmr (free base): 3.21 (d, J = 6.7 Hz, 1H), 3.11 (br s, 1H), 2.44 (s, 3H), 2.35 (m, 3H), 2.16 (m, 2H), 1.92 (m, 1H), 1.46 (m, 2H), 1.32 (m, 4H), 1.22 (m, 1H), 0.89 (m, 3H); ^{13}C nmr (free base): 211.4, 70.4, 60.9, 40.0, 36.5, 33.6, 33.1, 31.2, 23.0, 22.7, 13.9.

Anal. Calcd. for $C_{12}H_{21}NO$•HCl: C, 62.18; H, 9.58; N, 6.04. Found: C, 61.94; H, 9.59; N, 5.95.

6-Benzyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one (**8e**).

This compound was obtained as a colorless oil, 1.90 g (83%). The oil was converted into the hydrochloride salt to afford a white solid, mp 120-121°; ^{1}H nmr (free base): δ 7.33-7.12 (m, 5H), 3.22 (d, J = 7.3 Hz, 1H), 3.12 (br s, 1H), 2.93-2.72 (m, 3H), 2.43 (s, 3H), 2.40 (m, 1H), 2.23 (m, 2H), 2.04 (m, 1H), 1.87 (m, 1H), 1.38 (m, 1H); ^{13}C nmr (free base): δ 210.9, 140.5, 128.4, 128.3, 126.0, 70.4, 60.9, 41.1, 37.3, 36.6, 33.2, 33.0, 23.3.

Anal. Calcd. for $C_{15}H_{19}NO$•HCl•$1^2/_3H_2O$: C, 60.93; H, 7.91; N, 4.74. Found: C, 60.61; H, 7.54; N, 4.70.

General Procedure for the Condensation of Ketones **8a-e**.

A 5 *M* sodium hydroxide solution (4.50 mmoles) was added dropwise to ketone **8a-e** (9.00 mmoles), followed by freshly distilled benzaldehyde (9.00 mmoles) in absolute ethanol (90 ml). The solution was stirred at room temperature for 1.5 hours. The ethanol was then removed under reduced pressure. The residue was taken up in chloroform (90 ml) and washed with water (90 ml), dried over sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified and the isomers separated by chromatography (silica gel) to afford **9a-e** and **10a-e** as pure isomers.

3-Benzylidene-6,8-dimethyl-8-azabicyclo[3.2.1]octan-2-one (**9a/10a**).

This compound was obtained as a colorless oil (ethyl acetate), 1.80 g (82%). The oil was converted into the hydrochloride salt to afford a white solid, mp 109-112°; **9a** (free base); ^{1}H nmr: δ 7.54 (s, 1H), 7.49-7.31 (m, 5H), 3.48 (d, J = 6.8 Hz, 1H), 3.29 (br s, 1H), 3.05 (dt, J = 17.0, 3.8 Hz, 1H), 2.89 (d, J = 17.0 Hz, 1H), 2.57 (s, 3H), 2.53 (m, 2H), 1.21 (m, 1H), 0.91 (d, J = 6.4 Hz, 3H); ^{13}C nmr: δ 201.6, 136.3, 135.2, 131.5, 130.4, 128.8, 128.4, 70.0, 62.2, 36.8, 35.7, 33.5, 27.4, 16.3; **10a** (free base); ^{1}H nmr: δ 7.59 (s, 1H), 7.49-7.34 (m, 5H), 3.56 (d, J = 7.4 Hz, 1H), 3.24 (dt, J = 16.8, 3.1 Hz, 1H), 3.08 (d, J = 5.1 Hz, 1H), 2.75 (d, J = 16.8 Hz, 1H), 2.63 (s, 3H), 2.04 (m, 2H), 1.83 (m, 1H), 1.17 (d, J = 6.5 Hz, 3H); ^{13}C nmr: δ 202.9, 137.0, 136.9, 135.3, 131.4, 130.6, 128.9, 128.4, 128.1, 71.2, 64.8, 37.8, 37.2, 35.8, 32.5, 22.6.

Anal. Calcd. for $C_{16}H_{19}NO$•HCl•$^2/_3H_2O$: C, 66.34; H, 7.42; N, 4.84. Found: C, 66.50; H, 7.43; N, 4.76.

3-Benzylidene-6-ethyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one (**9b/10b**).

This compound was obtained as a colorless oil (ethyl acetate:petroleum ether, 3:1), 1.84 g (80%). The oil was converted into the hydrochloride salt to afford a white solid, mp 231-234°; **9b** (free base); ^{1}H nmr: δ 7.55 (s, 1H), 7.44 (d, J = 7.3 Hz, 2H), 7.40 (m, 3H), 3.50 (d, J = 8.2 Hz, 1H), 3.35 (t, J = 5.9 Hz, 1H), 3.06 (dt, J = 17.0, 3.15 Hz, 1H), 2.85 (d, J = 17.0 Hz, 1H), 2.57 (s, 3H), 2.53 (m, 1H), 2.35 (m, 1H), 1.39-1.12 (m, 3H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C nmr: δ 201.6, 136.4, 135.3, 131.6, 130.5, 128.9, 128.5, 69.8, 61.4, 41.6, 37.0, 34.0, 27.6, 24.7, 13.4; **10b** (free base); ^{1}H nmr: δ 7.59 (s, 1H), 7.47 (d, J = 7.2 Hz, 2H), 7.37 (m, 3H), 3.54 (d, J = 6.7 Hz, 1H), 3.25 (dt, J = 16.2, 2.9 Hz, 1H), 3.17 (d, J = 5.1 Hz, 1H), 2.69 (d, J = 16.2 Hz, 1H), 2.60 (s, 3H), 2.00-1.75 (m, 3H), 1.56 (m, 1H), 1.45 (m, 1H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C nmr: δ 202.8, 136.9, 135.2, 131.5, 130.5, 128.8, 128.3, 70.8, 62.6, 45.4, 35.9, 35.3, 32.9, 29.8, 12.8.

Anal. Calcd. for $C_{17}H_{21}NO\cdot HCl$: C, 69.97; H, 7.60; N, 4.80. Found: C, 69.81; H, 7.56; N, 4.79.

3-Benzylidene-8-methyl-6-propyl-8-azabicyclo[3.2.1]octan-2-one (**9c/10c**).

This compound was obtained as a colorless oil (ethyl acetate:petroleum ether, 7:3), 1.92 g (79%). The oil was converted into the hydrochloride salt to afford a white solid, mp 224-227°; **9c** (free base); ^1H nmr: δ 7.56 (s, 1H), 7.49 (d, J = 7.3 Hz, 2H), 7.41 (m, 3H), 3.52 (d, J = 8.0 Hz, 1H), 3.35 (t, J = 5.7 Hz, 1H), 3.07 (dt, J = 17.0, 3.7 Hz, 1H), 2.86 (d, J = 17.0 Hz, 1H), 2.59 (s, 3H), 2.55 (m, 2H), 1.26 (m, 5H), 0.83 (t, J = 6.5 Hz, 3H); ^{13}C nmr: δ 201.6, 136.4, 135.4, 131.6, 130.5, 128.8, 128.4, 69.8, 61.5, 39.3, 37.0, 34.2, 33.8, 27.6, 22.0, 14.0; **10c** (free base); ^1H nmr: δ 7.59 (s, 1H), 7.49 (d, J = 7.3 Hz, 2H), 7.39 (m, 3H), 3.54 (d, J = 6.8 Hz, 1H), 3.25 (dt, J = 16.1, 3.1 Hz, 1H), 3.16 (d, J = 5.1 Hz, 1H), 2.69 (d, J = 16.1 Hz, 1H), 2.60 (s, 3H), 1.88 (m, 3H), 1.47 (m, 2H), 1.30 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C nmr: δ 202.9, 137.0, 135.3, 131.5, 130.7, 128.9, 128.5, 70.9, 63.0, 43.4, 39.4, 36.0, 35.6, 33.0, 21.5, 14.0.

Anal. Calcd. for $C_{18}H_{23}NO\cdot HCl$: C, 70.69; H, 7.91; N, 4.58. Found: C, 70.59; H, 7.87; N, 4.60.

3-Benzylidene-6-butyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one (**9d/10d**).

This compound was obtained as a colorless oil (ethyl acetate:petroleum ether, 2:3), 2.04 g (80%). The oil was converted into a hydrochloride salt to afford a white solid, mp 194-196°; **9d** (free base); ^1H nmr: δ 7.53 (s, 1H), 7.45 (d, J = 7.3 Hz, 2H), 7.37 (m, 3H), 3.49 (d, J = 7.8 Hz, 1H), 3.32 (t, J = 5.7 Hz, 1H), 3.02 (dt, J = 17.4, 5.1 Hz, 1H), 2.84 (d, J = 17.4 Hz, 1H), 2.55 (s, 3H), 2.52 (m, 1H), 2.39 (m, 1H), 1.20 (m, 7H), 0.76 (m, 3H); ^{13}C nmr: δ 201.6, 136.3, 135.3, 131.7, 130.4, 128.8, 128.4, 69.8, 61.5, 39.5, 36.9, 34.2, 31.2, 31.1, 27.6, 22.5, 13.8; **10d** (free base); ^1H nmr: δ 7.59 (s, 1H), 7.47 (d, J = 7.3 Hz, 2H), 7.39 (m, 3H), 3.54 (d, J = 6.4 Hz, 1H), 3.24 (dt, J = 16.9, 3.1 Hz, 1H), 3.17 (d, J = 5.0 Hz, 1H), 2.68 (d, J = 16.9 Hz, 1H), 2.61 (s, 3H), 1.92 (m, 3H), 1.48 (m, 2H), 1.26 (m, 4H), 0.87 (t, J = 6.4 Hz, 3H); ^{13}C nmr: δ 202.8, 136.9, 135.3, 131.4, 130.6, 128.9, 128.4, 70.8, 62.9, 43.6, 36.8, 35.9, 35.6, 32.9, 30.6, 22.6, 13.9.

Anal. Calcd. for $C_{19}H_{25}NO\cdot HCl$: C, 71.34; H, 8.19; N, 4.38. Found: C, 71.07; H, 8.11; N, 4.36.

6-Benzyl-3-benzylidene-8-methyl-9-azabicyclo[3.2.1]octan-2-one (**9e/10e**).

This compound was obtained as a white solid (ethyl acetate: petroleum ether, 1:1), 2.00 g (70%), mp 94-95°; **9e** ^1H nmr: δ 7.61 (s, 1H), 7.44 (m, 5H), 7.20 (m, 3H), 7.01 (d, J = 7.0 Hz, 2H), 3.54 (d, J = 7.9 Hz, 1H), 3.36 (m, 1H), 3.02 (m, 2H), 2.90 (m, 1H), 2.59 (s, 3H), 2.52 (m, 2H), 1.39 (q, J = 6.1 Hz, 2H); ^{13}C nmr: δ 201.8, 140.5, 136.5, 135.3, 131.9, 130.5, 129.0, 128.5, 128.4, 128.3, 126.0, 70.0, 61.4, 40.6, 37.6, 37.0, 34.1, 28.1; **10e** ^1H nmr: δ 7.61 (s, 1H), 7.48-7.17 (m, 10H), 3.61 (d, J = 4.4 Hz, 1H), 3.21 (m, 2H), 2.84 (m, 2H), 2.65 (s, 3H), 2.59 (m, 1H), 2.31 (m, 1H), 1.97 (m, 2H); ^{13}C nmr: δ 202.8, 140.7, 136.9, 135.2, 131.1, 130.7, 128.9, 128.7, 128.4, 128.3, 125.9, 70.7, 61.8, 44.8, 42.6, 35.6, 35.3, 32.5.

Anal. Calcd. for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41. Found: C, 83.06; H, 7.37; N, 4.42.

General Procedure for the Alkylation of Ketal **12**.

To a cooled solution of ketal **12** (1.00 g, 2.50 mmoles) in dry tetrahydrofuran (20 ml) at -78° under a nitrogen atmosphere, *n*-butyllithium (1.88 ml, 1.60 *M*, in hexanes) was added dropwise by syringe. Upon addition of the *n*-butyllithium, the solution turned dark orange. The reaction was stirred at -78° for an additional 15 minutes. The alkyl halide (3.75 mmoles) was then added dropwise by syringe. The solution was stirred for 30 minutes at -78° and then allowed to warm up to room temperature over 1 hour. Upon warming to room temperature, the solution turned pale yellow. The solution was poured into water (20 ml) and the organic layer was removed. The aqueous layer was extracted with dichloromethane (3 x 50 ml). The combined organic portions were washed with brine (50 ml), dried over sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by chromatography (silica gel, ethyl acetate:petroleum ether, 1:3) to afford **13a-e**.

6-Benzenesulfonyl-8-benzyl-6-methyl-8-azabicyclo[3.2.1]octan-2-one Ethylene Ketal (**13a**).

This compound was obtained as a white solid, 0.98 g (95%), mp 153-154°; 6-*exo*-Benzenesulfonyl-6-*endo*-methyl-**13a** had ^1H nmr: δ 7.86 (d, J = 7.4 Hz, 2H), 7.61 (t, J = 7.0 Hz, 1H), 7.52 (t, J = 7.8 Hz, 2H), 7.28 (m, 5H), 4.17 (d, J = 13.4 Hz, 1H), 4.02 (m, 2H), 3.88 (m, 2H), 3.75 (m, 1H), 3.11 (d, J = 7.3 Hz, 1H), 2.99 (br s, 1H), 2.84 (m, 1H), 2.67 (d, J = 13.4 Hz, 1H), 2.19 (m, 2H), 1.74 (m, 2H), 1.36 (s, 3H); ^{13}C nmr: δ 139.8, 139.3, 133.2, 129.2, 128.9, 128.8, 128.1, 126.8, 107.5, 70.0, 65.0, 63.5, 62.5, 61.2, 51.6, 36.2, 28.5, 28.0, 19.7. 6-*endo*-Benzenesulfonyl-6-*exo*-methyl-**13a**

A small amount of the minor *exo*-isomer **13a** was isolated in pure form by chromatography;. ^1H nmr: δ 7.82 (d, J = 7.8 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 7.13 (m, 3H), 6.63 (m, 2H), 4.10 (d, J = 12.4 Hz, 1H), 3.79-3.53 (m, 5H), 3.27 (m, 1H), 2.83 (m, 2H), 2.25 (m, 1H), 1.95-1.74 (m, 3H), 1.69 (s, 3H), 1.56 (m, 1H); ^{13}C nmr: δ 139.1, 138.7, 133.0, 129.9, 128.9, 128.7, 127.6, 126.4, 106.3, 72.5, 64.9, 63.4, 59.9, 57.3, 51.4, 35.6, 29.4, 18.7, 17.1.

Anal. Calcd. for $C_{23}H_{27}NO_4S$: C, 66.80; H, 6.58; N, 3.39. Found: C, 66.60; H, 6.59; N, 3.30.

6-Benzenesulfonyl-8-benzyl-6-ethyl-8-azabicyclo[3.2.1]octan-2-one Ethylene Ketal (**13b**).

This compound was obtained as a white solid, 1.02 g (95%), mp 158-160°; ^1H nmr: δ 7.84 (d, J = 7.4 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.9 Hz, 2H), 7.26 (m, 5H), 4.07 (m, 3H), 3.87 (m, 2H), 3.74 (m, 1H), 3.22 (br s, 1H), 3.09 (d, J = 7.3 Hz, 1H), 2.85 (m, 1H), 2.66 (d, J = 13.6 Hz, 1H), 2.27 (m, 1H), 2.12 (m, 2H), 1.76 (m, 2H), 1.09 (m, 1H), 0.63 (t, J = 7.4 Hz, 3H); ^{13}C nmr: δ 140.0, 133.2, 128.9, 128.8, 128.6, 128.5, 128.1, 126.8, 107.6, 73.7, 65.0, 63.5, 60.7, 57.8, 51.6, 36.4, 32.0, 28.6, 19.5, 9.5.

Anal. Calcd. for $C_{24}H_{29}NO_4S$: C, 67.42; H, 6.84; N, 3.28. Found: C, 67.48; H, 6.85; N, 3.26.

6-Benzenesulfonyl-8-benzyl-6-propyl-8-azabicyclo[3.2.1]octan-2-one Ethylene Ketal (**13c**).

This compound was obtained as a white solid, 1.05 g (95%), mp 170-172°; ^1H nmr: δ 7.84 (d, J = 7.5 Hz, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.52 (t, J = 7.7 Hz, 2H), 7.26 (m, 5H), 4.06 (m, 3H), 3.92 (m, 2H), 3.78 (m, 1H), 3.20 (br s, 1H), 3.12 (d, J = 8.0 Hz, 1H), 2.85 (m, 1H), 2.68 (d, J = 13.3 Hz, 1H), 2.25 (m, 1H), 2.07 (m, 2H), 1.77 (m, 2H), 1.40 (m, 1H), 0.93 (m, 1H), 0.73 (m, 1H), 0.55 (t, J = 7.2 Hz, 3H); ^{13}C nmr: δ 140.0, 133.2, 128.9, 128.8, 128.7, 128.4, 128.0, 126.9, 107.6, 73.7, 65.0, 63.5, 61.0, 57.8, 51.6, 41.5, 36.7, 28.5, 19.3, 18.0, 14.1.

Anal. Calcd. for $C_{25}H_{31}NO_4S$: C, 68.00; H, 7.08; N, 3.17. Found: C, 68.02; H, 7.12; N, 3.16.

6-Benzenesulfonyl-8-benzyl-6-butyl-8-azabicyclo[3.2.1]octan-2-one Ethylene Ketal (**13d**).

This compound was obtained as a colorless oil, 1.10 g (97%); ^{1}H nmr: δ 7.84 (d, J = 7.7 Hz, 2H), 7.60 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.26 (m, 5H), 4.07 (m, 3H), 3.91 (m, 2H), 3.77 (m, 1H), 3.21 (br s, 1H), 3.13 (d, J = 7.9 Hz, 1H), 2.86 (m, 1H), 2.68 (d, J = 13.2 Hz, 1H), 2.26 (m, 1H), 2.10 (m, 2H), 1.78 (m, 3H), 1.30 (m, 1H), 0.92 (m, 3H), 0.67 (t, J = 7.1 Hz, 3H); ^{13}C nmr: δ 140.0, 139.7, 133.2, 128.8, 128.7, 128.4, 128.0, 126.8, 107.5, 73.6, 65.0, 63.4, 61.0, 57.6, 51.6, 39.1, 36.7, 28.5, 26.7, 23.0, 19.3, 13.6.

Anal. Calcd. for $C_{26}H_{33}NO_4S$: C, 68.54; H, 7.31; N, 3.08. Found: C, 68.61; H, 7.26; N, 3.04.

6-Benzenesulfonyl-6,8-dibenzyl-8-azabicyclo[3.2.1]octan-2-one Ethylene Ketal (**13e**).

This compound was obtained as a white solid, 1.19 g (97%), mp 68-72°; ^{1}H nmr: δ 7.88 (d, J = 7.7 Hz, 2H), 7.64 (t, J = 7.1 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 7.24 (m, 5H), 7.10 (m, 3H), 6.61 (d, J = 6.6 Hz, 2H), 4.23 (d, J = 13.2 Hz, 1H), 4.21 (m, 1H), 4.00 (d, J = 13.2 Hz, 1H), 3.97 (m, 1H), 3.84-3.66 (m, 4H), 3.28 (br s, 1H), 3.18 (d, J = 14.8 Hz, 1H), 3.10 (d, J = 7.6 Hz, 1H), 2.91 (d, J = 14.8 Hz, 1H), 2.80 (m, 1H), 2.63 (d, J = 14.0 Hz, 1H), 2.29 (m, 1H), 1.80 (m, 1H); ^{13}C nmr: δ 139.8, 139.2, 137.0, 133.4, 130.3, 129.1, 128.7, 128.3, 128.2, 128.1, 126.8, 126.4, 107.5, 73.8, 65.0, 63.3, 63.1, 60.1, 51.4, 43.8, 33.5, 28.7, 19.6.

Anal. Calcd. for $C_{29}H_{31}NO_4S$: C, 70.99; H, 6.38; N, 2.86. Found: C, 71.00; H, 6.42; N, 2.78.

General Procedure for the Desulfonylation/Hydrolysis of Sulfones **13a-e**.

Desulfonylation.

To a three-neck flask equipped with a mechanical stirrer, anhydrous sodium monohydrogen phosphate (2.8 g, 20 mmoles) and dry methanol (10 ml) was added a solution of sulfone **13a-e** (2 mmoles) in dry tetrahydrofuran (10 ml). Sodium amalgam (40%) was pipetted portionwise into the slurry over 1 hour. The rate of addition of amalgam was controlled such that the reaction did not become too vigorous. Amalgam was added until the reaction was complete by tlc. The reaction was quenched with methanol (2 ml) and allowed to cool to room temperature. The organic solution was carefully decanted away from the inorganic residue. The inorganic material was rinsed with tetrahydrofuran (3 x 20 ml). The combined organic portions were then concentrated under reduced pressure. The resulting slurry was dissolved in water (50 ml) and extracted with dichloromethane (4 x 30 ml). The combined organic layers were washed with brine, dried over sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue (**14a-e**) was carried on to the subsequent reaction without further purification.

Hydrolysis.

A solution of crude ketal **14a-e** (2 mmoles) in 3 *M* perchloric acid (48 mmoles) was refluxed with vigorous stirring overnight. (Note: Reaction temperatures below 100° resulted in incomplete conversion.) The reaction mixture was allowed to cool to room temperature and poured into a solution of 3 *M* sodium hydroxide (58 mmoles). The alkaline aqueous mixture was extracted with dichloromethane (3 x 20 ml). The combined organic fractions were washed with brine (40 ml), dried over sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified and the isomers separated by chromatography (silica gel, ethyl acetate:petroleum ether, 1:9) to afford **15a-e** and **16a-e**.

8-Benzyl-6α-methyl-8-azabicyclo[3.2.1]octan-2-one (**15a**).

This compound was obtained as a colorless oil, 251 mg (55%). The oil was converted into the hydrochloride salt to afford a white solid, mp 226-228°; ^{1}H nmr (free base): δ 7.30 (m, 3H), 7.24 (m, 2H), 3.77 (s, 2H), 3.30 (d, J = 7.7 Hz, 1H), 3.09 (t, J = 4.4 Hz, 1H), 2.70-2.10 (m, 5H), 1.97 (m, 1H), 1.26 (dd, J = 13.1, 5.8 Hz, 1H), 1.15 (d, J = 6.9 Hz, 3H); ^{13}C nmr: δ 211.5, 138.5, 128.4, 128.3, 127.0, 69.2, 59.6, 53.6, 35.1, 33.8, 33.4, 23.5, 16.0.

Anal. Calcd. for $C_{15}H_{19}NO{\cdot}HCl$: C, 67.79; H, 7.58; N, 5.27. Found: C, 67.53; H, 7.57; N, 5.16.

8-Benzyl-6β-methyl-8-azabicyclo[3.2.1]octan-2-one (**16a**).

This compound was obtained as a yellow oil; ^{1}H nmr: δ 7.31 (m, 3H), 7.24 (m, 2H), 3.81 (ABq, J_{AB} = 13.5 Hz, $\Delta\nu_{AB}$ = 22.2 Hz, 2H), 3.31 (d, J = 7.3 Hz, 1H), 2.89 (br s, 1H), 2.47 (m, 1H), 2.27 (m, 3H), 2.01 (dd, J = 13.4, 8.9 Hz, 1H), 1.75 (m, 2H), 1.22 (d, J = 7.0 Hz, 3H); ^{13}C nmr: δ 213.0, 138.7, 128.2, 127.0, 69.7, 62.1, 52.0, 36.3, 33.7, 28.0, 23.0.

Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.54; H, 8.37; N, 6.06.

8-Benzyl-6α-ethyl-8-azabicyclo[3.2.1]octan-2-one (**15b**).

This compound was obtained as a colorless oil, 268 mg (55%). The oil was converted into the hydrochloride salt to afford a white solid, mp 188-190°; ^{1}H nmr (free base): δ 7.30 (m, 3H), 7.24 (m, 2H), 3.77 (s, 2H), 3.30 (d, J = 7.3 Hz, 1H), 3.15 (t, J = 4.1 Hz, 1H), 2.51-2.10 (m, 5H), 1.92 (dd, J = 13.4, 8.9 Hz, 1H), 1.52 (m, 2H), 1.26 (dd, J = 14.6, 5.0 Hz, 1H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C nmr (free base): δ 211.4, 138.5, 128.3, 128.2, 127.0, 68.9, 58.5, 53.5, 41.9, 33.5, 33.4, 24.6, 23.5, 13.5.

Anal. Calcd. for $C_{16}H_{21}NO{\cdot}HCl$: C, 68.68; H, 7.92; N, 5.01. Found: C, 68.76; H, 7.87; N, 5.05.

8-Benzyl-6β-ethyl-8-azabicylo[3.2.1]octan-2-one (**16b**).

This compound was obtained as a yellow oil; ^{1}H nmr: δ 7.30 (m, 3H), 7.24 (m, 2H), 3.80 (ABq, J_{AB} = 13.5 Hz, $\Delta\nu_{AB}$ = 17.5 Hz, 2H), 3.29 (d, J = 7.0 Hz, 1H), 3.01 (s, 1H), 2.47 (m, 1H), 2.31 (m, 2H), 1.94 (m, 2H), 1.79 (m, 2H), 1.55 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C nmr: δ 213.1, 138.6, 128.2, 126.9, 69.3, 60.0, 52.1, 43.9, 34.2, 33.8, 29.9, 28.4, 12.7.

Anal. Calcd. for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.80; H, 8.75; N, 5.79.

8-Benzyl-6α-propyl-8-azabicyclo[3.2.1]octan-2-one (**15c**).

This compound was obtained as a yellow oil, 329 mg (64%). The oil was converted into the hydrochloride salt to afford a white solid, mp 120-121°; ^{1}H nmr (free base): δ 7.30 (m, 3H), 7.26 (m, 2H), 3.76 (s, 2H), 3.31 (d, J = 7.0 Hz, 1H), 3.13 (br s, 1H), 2.49-2.10 (m, 5H), 1.92 (dd, J = 13.4, 8.9 Hz, 1H), 1.49-1.26 (m, 5H), 0.94 (t, J = 7.0 Hz, 3H); ^{13}C nmr (free base): δ 211.4, 138.5, 128.4, 128.2, 127.0, 68.8, 58.7, 53.5, 39.7, 33.9, 33.5, 23.6, 22.3, 14.2.

Anal. Calcd. for $C_{17}H_{23}NO{\cdot}HCl{\cdot}H_2O$: C, 65.47; H, 8.40; N, 4.49. Found: C, 65.73; H, 8.38; N, 4.38.

8-Benzyl-6β-propyl-8-azabicyclo[3.2.1]octan-2-one (**16c**).

This compound was obtained as a yellow oil; ^{1}H nmr: δ 7.31 (m, 3H), 7.24 (m, 2H), 3.80 (ABq, J_{AB} = 13.5 Hz, $\Delta\nu_{AB}$ = 17.3 Hz, 2H), 3.29 (d, J = 7.0 Hz, 1H), 3.00 (s, 1H), 2.45 (m, 1H), 2.31

(m, 2H), 2.10 (m, 1H), 1.95 (m, 1H), 1.79 (m, 2H), 1.68-1.40 (m, 2H), 1.34 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C nmr: δ 213.0, 138.6, 128.2, 127.0, 69.3, 60.4, 52.2, 41.7, 39.4, 34.5, 33.8, 28.4, 21.4, 14.1.

Anal. Calcd. for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 78.95; H, 9.04; N, 5.46.

8-Benzyl-6α-butyl-8-azabicyclo[3.2.1]octan-2-one (**15d**).

This compound was obtained as a yellow oil, 299 mg (55%). ^{1}H nmr: δ 7.31 (m, 3H), 7.24 (m, 2H), 3.77 (s, 2H), 3.31 (d, J = 6.7 Hz, 1H), 3.14 (br s, 1H), 2.49-2.10 (m, 5H), 1.92 (dd, J = 13.4, 9.1 Hz, 1H), 1.47 (m, 2H), 1.33 (m, 5H), 0.91 (t, J = 6.7 Hz, 3H); ^{13}C nmr: δ 211.5, 138.5, 128.4, 128.3, 68.9, 58.7, 53.6, 40.0, 33.6, 31.4, 23.6, 22.9, 14.0.

Anal. Calcd. for $C_{18}H_{25}NO$: C, 79.66; H, 9.28; N, 5.16. Found: C, 79.57; H, 9.22; N, 5.11.

8-Benzyl-6β-butyl-8-azabicyclo[3.2.1]octan-2-one (**16d**).

This compound was obtained as a yellow oil; ^{1}H nmr: δ 7.31 (m, 3H), 7.24 (m, 2H), 3.80 (ABq, J_{AB} = 13.7 Hz, $\Delta\nu_{AB}$ = 18.4 Hz, 2H), 3.29 (d, J = 7.3 Hz, 1H), 3.00 (br s, 1H), 2.46 (m, 1H), 2.29 (m, 2H), 2.07 (m, 1H), 1.95 (m, 1H), 1.79 (m, 2H), 1.68-1.42 (m, 2H), 1.33 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C nmr: δ 213.0, 138.6, 128.2, 126.9, 69.3, 60.3, 52.1, 42.0, 36.8, 34.5, 33.7, 30.5, 28.4, 22.6, 14.0.

Anal. Calcd. for $C_{18}H_{25}NO$: C, 79.66; H, 9.28; N, 5.16. Found: C, 79.64; H, 9.34; N, 5.05.

6α,8-Dibenzyl-8-azabicyclo[3.2.1]octan-2-one (**15e**).

This compound was obtained as a yellow oil, 336 mg (55%); ^{1}H nmr: δ 7.30 (m, 6H), 7.23 (m, 4H), 3.77 (s, 2H), 3.32 (d, J = 8.0 Hz, 1H), 3.20 (br s, 1H), 2.90-2.76 (m, 3H), 2.52 (m, 1H), 2.39 (m, 2H), 2.20 (m, 1H), 2.05 (m, 1H), 1.41 (dd, J = 13.7, 6.0 Hz, 1H); ^{13}C nmr: δ 211.0, 140.6, 138.33, 128.5, 128.4, 128.3, 127.1, 126.1, 68.8, 58.9, 53.6, 41.2, 37.6, 33.5, 33.3, 23.9.

Anal. Calcd. for $C_{21}H_{23}NO$: C, 82.59; H, 7.59; N, 4.59. Found: C, 82.91; H, 7.61; N, 4.45.

6β,8-Dibenzyl-8-azabicyclo[3.2.1]octan-2-one (**16e**).

This compound was obtained as a yellow solid, mp 78-79°; ^{1}H nmr: δ 7.36-7.14 (m, 10H), 3.81 (ABq, J_{AB} = 13.4 Hz, $\Delta\nu_{AB}$ = 30.0 Hz, 2H), 3.34 (d, J = 6.5 Hz, 1H), 3.03 (br s, 1H), 2.92-2.78 (m, 2H), 2.47 (m, 2H), 2.29 (m, 2H), 1.92 (m, 2H), 1.66 (m, 1H); ^{13}C nmr: δ 212.9, 140.9, 138.5, 128.8, 128.3, 128.2, 127.1, 126.0, 69.3, 58.9, 51.9, 43.4, 42.8, 34.2, 33.7, 28.0.

Anal. Calcd. for $C_{21}H_{23}NO$: C, 82.59; H, 7.59; N, 4.59. Found: C, 82.88; H, 7.67; N, 4.52.

Acknowledgements.

This work was supported by the National Institute on Drug Abuse (NIDA First Award DA08055; Predoctoral Award DA05742) and the National Institutes of Health NIDA-MIRDP program (DA07970).

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