Transannular Cyclization in Cyclohexanes by Michael Addition of an Amine onto an α,β-Unsaturated Ester: Synthesis of 8-Benzyl-8-azatricyclo[4.2.1.0^{3,7}]nonane-7-acetic Acid Ethyl Ester and 7-Benzyl-7-azabicyclo[2.2.1]heptane-1-acetic Acid Ethyl Ester

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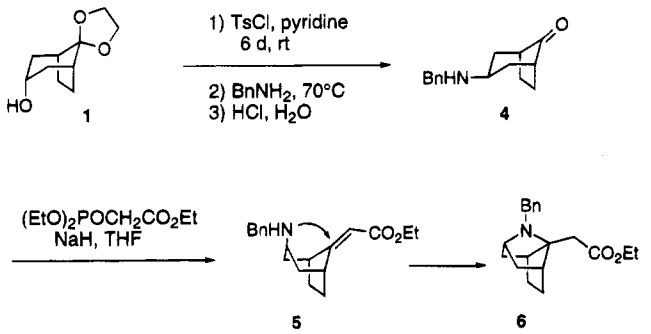
Intramolecular cyclization by amine displacement of a leaving group is a key reaction in many syntheses of the 7-azabicyclo[2.2.1]heptane ring system,[1] particularly those directed toward preparing epibatidine.[2,3] While the transannular Michael addition of amines has been utilized in the preparation of tropinones from cyclohepta-2,6-dienone[4,5] and azabicyclo[3.3.1]nonan-3-ones from cycloocta-3,7-dienone,[6] no similar reaction has been reported in the cyclohexane ring system.

When the α,β-unsaturated ester **5** was prepared by Wadsworth–Emmons reaction,[7] it was found that the amine underwent Michael addition onto the double bond of the unsaturated ester. The unsaturated ester **5** was evident in the NMR of the crude product mixture, and it could be precipitated as a salt. However, the free base of **5** cyclized to 8-azatricyclo[4.2.1.0^{3,7}]nonane **6** slowly on standing at room temperature, typically reacting at a rate of 10–15% conversion per day when concentrated and more rapidly when diluted. Unsaturated ester **5** could not be purified by chromatography on silica gel, and it gave 95% conversion to azatricyclononane **6** when Kugelrohr distilled (130 °C, 1 Torr).



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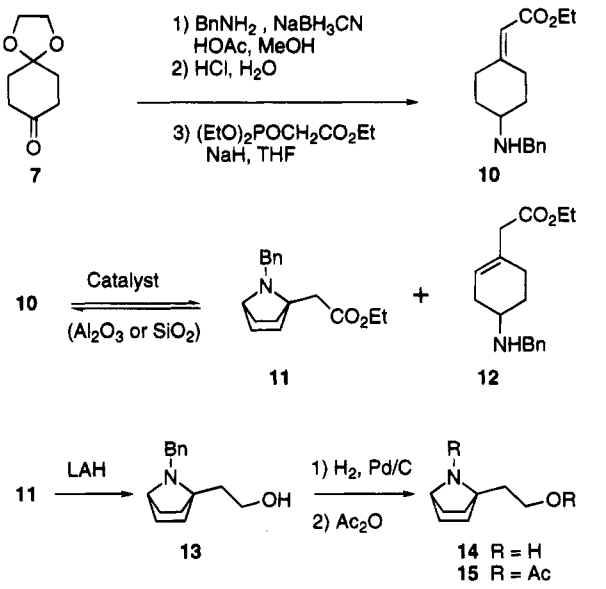
It seemed that the cyclization to azatricyclononane **6** might be something of a special case because the two-carbon bridge stabilizes the boat conformation of the cyclohexane ring and brings the 1- and 4-"flag-pole" substituents closer together in **5** than in unconstrained cyclohexanes. Since this type of transannular Michael addition was unprecedented in cyclohexanes, the reaction was attempted with the simple cyclohexane analog. In this case, the cyclization did not occur spontaneously and the unsaturated ester **10** could be easily isolated. The first hint that cyclization could be induced was the formation of the 7-azabicyclo[2.2.1]heptane **11**, to the extent of about 10% conversion, when the unsaturated amino ester **10** was Kugelrohr distilled. Repeated distillation or flash vacuum pyrolysis ultimately produced mixtures with up to 45% azabicycloheptane **11**, but substantial amounts of material were lost as nonvolatile byproducts. There was also a buildup of unconjugated ester **12**, and results were highly variable. Heating the unsaturated ester **10** alone tended to cause deconjugation rather than cyclization. Heating **10** in toluene under reflux for 3 h caused no detectable reaction.



7 10 11 12 13 14 R = H 15 R = Ac

It was then discovered that the cyclization could be catalyzed by neutral alumina.[8] With this catalyst, a maximum conversion of around 45% to cyclized product **11** could be achieved in ethyl ether, dioxane, or toluene heated under reflux. After prolonged reaction, the deconjugated ester **12** began to build at the expense of the azabicycloheptane **11** and starting ester **10**. In refluxing toluene, ester **10** and an equal weight of neutral alumina gave a 29:42:28 mixture of **10**:**11**:**12** after 4 h of reflux. Using 10-fold more catalyst for only 1 h gave a 17:33:46 mixture, but only 36% of the material could be recovered.

To avoid the base-catalyzed double bond isomerization of **10** to **12**, more acidic catalysts were investigated. Both acidic alumina and silica gel proved to be effective catalysts that minimized the amount of double bond deconjugation during the equilibration of **10** and **11**. Chromatography grade silica gel was the more active catalyst by weight. The amino ester **10** and an equal weight of silica gel heated in toluene under reflux afforded a 44:56 equilibrium mixture of **10** and the azabicycloheptane **11** in less than 38 min. The same equilibrium ratio was obtained starting from azabicycloheptane **11**. There was less than 1% conversion to deconjugated ester **12**.

The cyclized tertiary amine **11** is less polar than the secondary amine starting material **10**. Consequently,

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there should be a shift in equilibrium toward **11** as the reaction solvent becomes less polar. Indeed, equilibration in refluxing heptane afforded a 34:66 mixture of **10** and **11**.

The amount of catalyst employed had a direct effect on the reaction rate. The reaction of amino ester **10** in the presence of 10% by weight of silica gel in heptane heated under reflux took about 14 h to equilibrate. Despite the slower reaction rate, using a minimum amount of catalyst had the advantage of higher material recovery after filtration.

Convenient isolation of azabicycloheptane **11** was achieved after first reacting the crude product mixture with acetic anhydride. When the acetylation of secondary amines **10** and **12** was complete, the azabicycloheptane **11** was selectively extracted into aqueous acid and recovered after treatment with base. This typically gave product **11** of >95% purity without any chromatography during the four-step synthesis, in an overall yield of 35–45% from cyclohexane-1,4-dione monoketal (**7**). Some samples of azabicycloheptane **11** showed partial conversion back to **10** upon storage as the free base, possibly due to catalysis by glass. Storage in the cold or as a salt is advisable.

The cyclization of **5** to **6** was reexamined under conditions that equilibrated **10** and **11**. A freshly prepared sample of **5** underwent complete conversion to azatricyclononane **6** when heated in heptane under reflux with 10% by weight of silica gel. No uncyclized starting material **5** could be detected by ^{1}H NMR after 45 min. Even without added catalyst, about 20% cyclization occurred after 45 min under these conditions. This facile silica gel catalyzed cyclization explains the earlier failure to isolate **5** by chromatography.

The NMR spectra of the cyclized amines **6** and **11** showed evidence of slow inversion at the pyramidal nitrogen, as is typical with this ring system.[9] The signal due to the *N*-benzyl CH_2 was broadened in the ^{1}H NMR at room temperature, as were several signals in the ^{13}C NMR spectrum. The NMR spectra of salts of **6** and **11** in some cases showed evidence of asymmetry due to slow proton exchange at the nitrogen chiral center while in others proton exchange was fast enough that the symmetry appeared to be preserved. The ^{1}H-COSY of **6** showed coupling entirely consistent with the conformation of the azatricyclo[4.2.1.0^{3,7}]nonane ring system.

The fact that the azabicycloheptane **11** is thermodynamically favored over the unsaturated ester **10** is not easily predictable from simple calculations of steric strain and bond energies. Modified MM2 calculations[10] suggest that the azabicycloheptane **11** is more sterically strained than **10** by around 16 kcal/mol, while bond energy estimates[11] indicate addition of the amine to the double bond could provide between 7 and 20 kcal/mol. Evidently, the change in bond energy is sufficient to compensate for the increased steric strain.

The azabicycloheptane **11** has a new, easily accessible, achiral structural motif that may be viewed as a homoproline derivative or a nortropane. The ester is easily reduced with LAH to the alcohol **13** which may be elaborated without ring-opening of the azabicycloheptane. The amine may be deprotected (e.g., **13** to **14**) and then further derivatized (e.g., **14** to **15**). The synthetic route also allows the incorporation of different *N*-alkyl side chains by starting with primary amines other than benzylamine. The azabicycloheptane **11** should find a wide range of uses as a unique entity for exploitation in medicinal chemistry.

Experimental Section

General. MS (CI) were obtained with ionization by 1% NH_3 in CH_4. Elemental analyses were performed by the Analytical Section at Parke-Davis or by Robertson Labs. GC's were obtained on a 2 m 10% SE-30 column at 140 °C for 1 min and then heated to 240 °C over 10 min with He carrier gas (flow rate: 4 m/min) and flame ionization detection. Salts were prepared from the base and a slight excess of the acid in Et_2O or EtOH and were then triturated with anhydrous Et_2O. Salts were converted to amine free bases by dissolution in water, addition of 1 equiv of K_2CO_3, and extraction into Et_2O. Starting materials were purchased from Aldrich Chemical Co. or prepared by cited methods.

4-Methylphenylsulfonic Acid (1α,3α,5α)-Spiro[bicyclo-[3.2.1]octane-8,2′-[1,3]dioxolan]-3-yl Ester (2). (1α,3α,5α)-Spiro[bicyclo[3.2.1]octane-8,2′-[1,3]dioxolan]-3-ol (**1**)[12] (11.5 g, 72.7 mmol) in pyridine (80 mL) was stirred with *p*-toluenesulfonyl chloride (20.5 g, 106 mmol) at rt for 6 d. Water (10 mL) was added over 30 min with cooling on ice. After 1 h, water (60 mL) was added, and the separated oil was stirred (or seeded) to induce crystallization. The solid was filtered off, washed with water, and air dried to afford pure tosylate **2** (17.96 g, 85% yield), mp 93–94.5 °C: ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J = 8 Hz, 2 H), 7.29 (d, J = 8 Hz, 2 H), 4.72 (t, J = 5.1 Hz, 1 H), 3.84 (m, 4 H), 2.40 (s, 3 H), 2.15 (dd, J = 15.6, 4.9 Hz, 2 H), 1.8 (m, 8 H); MS (CI) m/z (relative intensity) 339 (2.5, MH^+), 167 (100, M − OTs + H_2^+). Anal. Calcd for $C_{17}H_{22}O_5S_1$: C, 60.34; H, 6.55. Found: C, 60.12; H, 6.54.

(1α,3β,5α)-*N*-(Phenylmethyl)spiro[bicyclo[3.2.1]octane-8,2′-[1,3]dioxolan]-3-amine (3). The tosylate **2** (5.11 g, 15.1 mmol) and benzylamine (20 mL) were stirred and heated at 60 °C for 24 h. Most of the remaining benzylamine was distilled off at up to 70 °C under vacuum (1 Torr). The residue was treated with aqueous Na_2CO_3, extracted with Et_2O, and column chromatographed on silica gel with *i*-PrOH/$CHCl_3$ (1:40 to 1:6 gradient) to afford the amine **3** (1.64 g, 39% yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 4 H), 7.22 (m, 1 H), 3.89 (s, 4 H), 3.75 (s, 2 H), 2.82 (m, 1 H), 1.83 (m, 6 H), 1.62 (t, J = 11.5 Hz, 2 H), 1.40 (d, J = 8.0 Hz, 2 H), 1.3 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 140.3, 128.4 (2 C), 128.2 (2 C), 126.6, 116.6, 64.7, 63.8, 51.3, 48.6, 38.8 (2 C), 36.4 (2 C), 25.4 (2 C); MS (CI) m/z (relative intensity) 274 (100, MH^+). Note: Benzylamine must be removed before the ketal hydrolysis to avoid problems with imine formation during the isolation of ketone **4**.

(1α,3β,5α)-3-[(Phenylmethyl)amino]bicyclo[3.2.1]octan-8-one (4). The ketal **3** (1.63 g, 6 mmol) was heated in 1 M aqueous HCl (20 mL) at 70 °C for 8 h. The solution was treated with K_2CO_3 (3 g) and extracted with Et_2O (2 × 30 mL). The extract was dried and concentrated to give crude product (1.23 g, 95% pure by GC). Recrystallization from hexane–Et_2O gave pure ketone **4** (1.05 g, 77% yield) as colorless crystals, mp 86–87.5 °C: ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 4 H), 7.22 (m, 1 H), 3.76 (s, 2 H), 3.21 (m, 1 H), 2.20 (m, 4 H), 1.93 (m, 2 H), 1.73 (m, 4 H), 1.7 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 139.8 (br s), 128.5 (2 C), 128.1 (2 C), 127.1, 51.6, 49.2 (br s), 42.8 (2 C), 42.2 (br s), 23.3 (br s) (no peak due the ketone C was observed, possibly due to broadening caused by reversible hemiaminal formation); IR (KBr) no significant carbonyl absorption peak, possibly due to hemiaminal formation in the solid state; MS (CI) m/z (relative intensity) 230 (100, MH^+). Anal. Calcd for $C_{15}H_{19}N_1O_1$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.29; H, 8.39; N, 6.08.

[(1α,3β,5α)-3-[(Phenylmethyl)amino]bicyclo[3.2.1]oct-8-ylidene]acetic Acid Ethyl Ester (5). Sodium hydride (60% dispersion in oil, 0.156 g, 3.9 mmol) was washed with hexanes (2 × 3 mL) and stirred in THF (5 mL) with cooling on ice while triethyl phosphonoacetate (0.77 mL, 0.87 g, 3.9 mmol) was added

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dropwise. After 5 min, ketone **4** (0.638g, 2.79 mmol) was added as a solid under a stream of N_2. The solution was stirred at rt for 45 min, and then 5% aqueous $NaHCO_3$ (15 mL) and Et_2O (35 mL) were added. The Et_2O layer was washed with water (5 mL) and saturated NaCl (5 mL), dried ($MgSO_4$), and concentrated to an oil (0.97 g) containing mainly **5** and $(EtO)_2POCH_2CO_2Et$ (approximately 0.3 equiv) by ^1H NMR. The peaks ascribed to **5** are: ^1H NMR ($CDCl_3$) δ 7.29 (m, 4 H), 7.22 (m, 1 H), 5.59 (s, 1 H), 4.12 (q, J = 7.2 Hz, 2 H), 3.77 (br s, 1 H), 3.73 (s, 2 H), 3.02 (m, 1 H), 2.56 (br s, 1 H), 2.12 (m, 2 H), 1.75–1.35 (m's, 7 H), 1.23 (t, J = 7.2 Hz, 3 H). Hydrochloride salt of **5**: mp 193–196 °C; ^1H NMR (DMSO-d_6) δ 9.2 (br s, 2 H, NH_2), 7.52 (m, 2 H), 7.35 (m, 3 H), 4.05 (br s, 2 H), 4.04 (q, J = 7.2 Hz, 2 H), 3.89 (m, 1 H), 3.47 (m, 1 H), 2.69 (m, 1 H), 2.21 (m, 2 H), 1.75–1.5 (m's, 6 H), 1.15 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (DMSO - d_6) 171.2, 166.2, 132.8, 130.5 (2 C), 129.3, 129.0 (2 C), 107.8, 59.8, 50.8, 48.3, 41.8, 38.3, 37.0, 35.7, 26.4, 25.2, 14.6; IR (KBr) 1711, 1670 cm^{-1}; MS (CI) m/z (relative intensity) 300 (100, MH^+). Anal. Calcd for $C_{19}H_{25}N_1O_2$·HCl: C, 67.94; H, 7.80; N, 4.17; Cl, 10.56. Found: C, 67.57; H, 7.92; N, 4.09; Cl, 10.56.

8-Benzyl-8-azatricyclo[4.2.1.0^{3,7}]nonane-7-acetic Acid Ethyl Ester (6). The crude mixture containing **5** (0.97 g) was stirred with silica gel (0.098 g, 230–400 mesh for chromatography) in heptane (20 mL) and heated under reflux overnight. The solution was filtered, the residue was rinsed with Et_2O, and the filtrate was concentrated to an oil (0.95 g) containing **6** and $(EtO)_2POCH_2CO_2Et$ (approximately 0.3 equiv) and no trace of **5** by ^1H NMR. The crude product in Et_2O (5 mL) was added to oxalic acid (0.26 g) in Et_2O. The gummy oxalate salt was triturated with Et_2O but showed no signs of crystallization after 3 d. The oxalate salt was dissolved in water (20 mL), excess $NaHCO_3$ was added, and the mixture was extracted with Et_2O (2 × 30 mL). The extract was dried ($MgSO_4$) and concentrated to afford **6** as an oil (0.687 g, 82% yield from **4**). Kugelrohr distillation (120–140 °C, 1 Torr) of 0.303 g afforded 0.298 g of **6** (pure by GC): ^1H NMR ($CDCl_3$) δ 7.30 (d, 2 H), 7.25 (t, 2), 7.18 (t, 1 H), 4.11 (q, 2 H), 3.57 (br s, 2 H, $PhCH_2N$), 2.91 (t, 1H, 1-H), 2.56 (s, 2H, 7-CH_2CO_2Et), 2.28 (m, 2 H, 3-H, 6-H), 2.13 (m, 2 H, 2b-H, 9b-H), 1.86 (m, 2 H, 4b-H, 5b-H), 1.60 (d, J = 8 Hz, 2 H, 4a-H, 5a-H), 1.20 (t, 3 H), 0.93 (d, J = 11.7 Hz, 2 H, 2a-H, 9a-H); ^1H COSY shows coupling of δ 2.91 with 2.13, 2.28 with 2.13, 2.28 with 1.86, 2.13 with 0.93, 1.86 with 1.60, 4.11 with 1.20; ^{13}C NMR ($CDCl_3$) δ 171.5, 140.4, 128.7 (2 C), 128.1 (2 C), 126.5, 78.1, 60.3, 56.7, 41.9, 39.1 (br s), 35.0, 28.7, 14.2; MS (CI) m/z (relative intensity) 300 (100, MH^+); IR (LF) 1732 cm^{-1}. Anal. Calcd for $C_{19}H_{25}N_1O_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.10; H, 8.53; N, 4.59.

***N*-(Phenylmethyl)-1,4-dioxaspiro[4.5]decan-8-amine (8).**[13] Cyclohexane-1,4-dione monoethylene glycol ketal (29.3 g, 0.188 mol) in MeOH (200 mL) was stirred with benzylamine (22.1 g, 24.8 mL, 0.206 mol) and acetic acid (12.4 g, 11.8 mL, 0.206 mol) with cooling on ice while sodium cyanoborohydride (11.4 g, 0.188 mol) was added in portions over 15 min. The solution was stirred at rt overnight, and then 1 M aqueous NaOH (30 mL) was added and most of the MeOH was removed under vacuum. Additional 1 M NaOH (200 mL) was added, and the mixture was extracted with Et_2O (150 mL then 3 × 50 mL). The combined extracts were washed with 1 M NaOH (50 mL), dried ($MgSO_4$), and concentrated under vacuum to afford the crude amino ketal **8** as an oil: ^1H NMR ($CDCl_3$) δ 7.29 (m, 4 H), 7.22 (m, 1 H), 3.90 (s, 4 H), 3.85 (s, 2H) 2.58 (m, 1 H), 1.88 (m, 2 H), 1.76 (m, 2 H), 1.48 (m, 4 H), 1.3 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 140.9, 128.4 (2 C), 128.0 (2 C), 126.8, 108.7, 64.3, 64.2, 54.4, 51.26, 32.8 (2 C), 30.1 (2 C).

4-[(Phenylmethyl)amino]cyclohexanone (9).[14] The crude amino ketal **8** was extracted into 1 M aqueous HCl (250 mL). After 15 min, GC of a basified aliquot showed 93% deprotection, and this was unchanged after 1 h. The solution was treated slowly with K_2CO_3 (100 g) and extracted with Et_2O (150 mL then 3 × 50 mL). The combined Et_2O extract was washed with water (2 × 50 mL) and then extracted with 1 M HCl (150 mL then 3 × 50 mL). After 25 min, the HCl extract was treated with K_2CO_3 and extracted as above, dried over $MgSO_4$, and concentrated under vacuum to afford the amino ketone (**9**) (26.5 g, 69% yield from **6**, 99% pure by GC): ^1H NMR ($CDCl_3$) δ 7.29 (m, 4 H), 7.22 (m, 1 H), 3.78 (s, 2 H), 2.95 (m, 1 H), 2.45 (m, 2 H), 2.24 (m, 2 H), 2.03 (m, 2 H), 1.69 (m, 2 H), 1.3 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 211.5, 140.4, 128.5 (2 C), 128.0 (2 C), 127.1, 52.9, 51.5, 38.37 (2 C), 31.9 (2 C); IR (LF) 1712 cm^{-1}. Hydrochloride salt, mp 230–235 °C dec: MS (CI) m/z (relative intensity) 204 (97, MH^+), 146 (100); IR (KBr) 1727 cm^{-1}. Anal. Calcd for $C_{13}H_{17}N_1O_1$·HCl: C, 65.13; H, 7.57; N, 5.84; Cl, 14.79. Found: C, 64.89; H, 7.47; N, 5.99; Cl, 15.01.

[4-[(Phenylmethyl)amino]cyclohexylidene]acetic Acid Ethyl Ester (10). Triethyl phosphonoacetate (25.8 mL, 29.1 mL, 0.13 mol) was added to NaH (5.20 g of 60% dispersion in oil, washed with hexanes, 0.13 mol) stirred in THF (200 mL) with cooling on ice. After 20 min, the aminoketone **9** (20.2 g, 0.1 mol) in THF (20 mL) was added, and the solution was stirred in the cold for 30 min and at rt for 1 h. Saturated $NaHCO_3$ (200 mL) was added, and the THF was removed under vacuum. The residue was extracted with Et_2O (200 mL then 2 × 100 mL). The combined extracts were dried ($MgSO_4$) and treated with HCl gas until precipitation of solid was complete. The solid was filtered off, washed thoroughly with Et_2O, and vacuum dried to afford the hydrochloride salt of **10** (28.45 g, 91% yield), mp 189–191 °C (softens above 183 °C): MS (CI) m/z (relative intensity) 174 (100, MH^+); IR (KBr) 1711, 1650 cm^{-1}. Anal. Calcd for $C_{17}H_{23}N_1O_2$·HCl: C, 65.90; H, 7.81; N, 4.52; Cl, 11.44. Found: C, 65.62; H, 7.77; N, 4.68; Cl, 11.85. Free base: ^1H NMR δ 7.29 (m, 4 H), 7.22 (m, 1 H), 5.59 (s, 1 H), 4.10 (q, J = 7 Hz, 2 H), 3.79 (s, 2 H), 3.57 (d t, J = 15, 3 Hz, 1 H), 2.74 (m, 1 H), 2.32 (d t, J = 14, 4 Hz, 1 H), 2.14 (m, 2 H), 1.99 (m, 2 H), 1.4 (br s, 1 H, NH), 1.33 (m, 2 H), 1.23 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.7, 161.9, 140.7, 128.4 (2 C), 128.0 (2 C), 126.9, 113.6, 59.5, 54.8, 51.2, 35.3, 34.1, 33.4, 26.9, 14.3.

7-Benzyl-7-azabicyclo[2.2.1]heptane-1-acetic Acid Ethyl Ester (11). The amino ester **10** (24.5 g, 89.7 mmol) and silica gel (2.5 g, 230–400 mesh) were stirred in heptane (500 mL) heated under reflux for 16 h. The solution was filtered and concentrated under vacuum. Acetic anhydride (5 mL, 53 mmol) was added to the residue (24.5 g) in Et_2O (100 mL), and the solution was heated under reflux for 3 h. The cooled solution was diluted with Et_2O (150 mL) and then extracted with water (100 mL) and 0.3 M aqueous HCl (2 × 75 mL). The combined extracts were washed with Et_2O (25 mL) and then treated with K_2CO_3 (18 g) portionwise. The mixture was extracted with Et_2O (3 × 100 mL), and the extract was dried ($MgSO_4$) and concentrated under vacuum to give azabicycloheptane **11** (14.9 g, 61% yield) as an oil: ^1H NMR ($CDCl_3$) δ 7.31 (d, J = 7 Hz, 2 H), 7.26 (t , J = 7 Hz, 2 H), 7.19 (t, J = 7 Hz, 1 H), 4.10 (q, J = 7.1 Hz, 2 H), 3.44 (br s, 2 H), 3.11 (t, J = 4.5 Hz, 1 H), 2.61 (s, 2 H), 1.81–1.66 (m, 4 H), 1.59 (m, 2 H), 1.28 (m, 2 H), 1.21 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.6, 140.4, 128.6 (2 C), 128.1 (2 C), 126.6, 65.6, 60.3, 59.0 (CH by APT), 49.1, 39.3, 33.5 (br s), 28.4 (br s), 14.2; MS (CI) 274 (100, MH^+); IR (LF) 1735 cm^{-1} (C=O). Oxalate salt, mp 123–125 °C: MS (CI) m/z (relative intensity) 274 (100, MH^+), 273 (56, M^+); IR (KBr) 1733 cm^{-1}. Anal. Calcd for $C_{17}H_{23}N_1O_2$·$C_2H_2O_4$: C, 62.8; H, 6.93; N, 3.85. Found: C, 62.41; H, 6.77; N, 3.74. Fumarate salt, mp 110–112 °C: IR (KBr) 1731 cm^{-1}. Anal. Calcd for $C_{17}H_{23}N_1O_2$·$C_4H_4O_4$: C, 64.77; H, 6.99; N, 3.60. Found: C, 64.56; H 6.95; N, 3.47. Benzenesulfonate salt: mp 73–76 °C. Anal. Calcd for $C_{17}H_{23}N_1O_2$.$C_6H_6S_1O_3$: C, 64.01; H, 6.77; N, 3.25; S, 7.43. Found: C, 64.01; H, 6.77; N, 3.17; S, 7.27.

[4-[(Phenylmethyl)amino]-1-cyclohexene]-1-acetic Acid Ethyl Ester (12). Chromatography (silica gel, 20:1 $CHCl_3$/*i*-PrOH) of a mixture containing **10**, **11**, and **12** produced by reaction of **10** with neutral alumina catalyst in dioxane heated under reflux gave a pure sample of **12**: ^1H NMR ($CDCl_3$) δ 7.29 (m, 4 H), 7.22 (m, 1 H), 5.45 (m, 1H), 4.08 (q, J = 7.4 Hz, 2 H), 3.78 (s, 2 H) 2.91 (s, 2 H), 2.76 (m, 1 H), 2.30 (m, 1 H), 2.06 (m, 2 H), 1.89 (m, 2 H), 1.58 (br s, 1 H, NH), 1.47 (m, 1 H), 1.20 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.8, 140.6, 131.1, 128.4 (2 C), 128.0 (2 C), 126.9, 123.6, 60.5, 51.8, 51.1, 43.0, 32.6, 29.0, 27.5, 14.2. Hydrochloride salt: mp 167–168.5 °C; MS (CI) m/z (relative intensity) 274 (100, MH^+); IR (KBr) 1729 cm^{-1}. Anal. Calcd for $C_{17}H_{23}N_1O_2$.HCl: C, 65.90; H, 7.81; N, 4.52; Cl, 11.44. Found: C, 65.68; H, 7.87; N, 4.39; Cl, 11.49.

7-Benzyl-7-azabicyclo[2.2.1]heptane-1-ethanol (13). The ester **11** (1.95 g, 7.1 mmol) was stirred in Et_2O (20 mL) while 1

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M $LiAlH_4$ in THF (7 mL, 7 mmol) was added over several minutes. A mild exotherm caused the Et_2O to boil. The mixture was stirred without heating for 2.5 h, and then 1 M aqueous NaOH (0.5 mL) and satd aqueous Na_2SO_4 (1 mL) were added dropwise. After vigorous stirring for 20 min, the mixture was filtered, the residue washed with THF, and the combined filtrate concentrated to give the alcohol **13** (1.64 g) as an oil: ^{13}C NMR ($CDCl_3$) δ 139.7, 128.7 (2C), 128.3 (2C), 67.4, 60.3, 58.9, 48.6, 32.7 (br s), 31.6, 27.5 (br s). Conversion to the hydrochloride salt gave a hygroscopic, glassy solid (1.73 g, 91% yield), mp 225–230 °C dec; ^1H NMR (DMSO-d_6) δ 10.77 (br s, 1 H, NH), 7.69 (m, 2 H), 7.37 (m, 3 H), 5.8 (br m, 1 H, OH), 4.28 (dd, J = 13.4, 3.4 Hz, reduced to d, J = 13 Hz by D_2O exchange, 1 H), 3.80 (dd, J = 13.4, 9.6 Hz, reduced to d, J = 13 Hz by D_2O exchange, 1 H), 3.52 (m, 2 H), 3.31 (t, J = 4.5 Hz, 1 H), 2.2–1.78 (m's, 8 H), 1.61 (m, 1 H), 1.52 (m, 1H); MS (CI) m/z (relative intensity) 232 (100, MH^+). Anal. Calcd for $C_{15}H_{21}N_1O_1 \cdot HCl - 0.38\ H_2O$: C, 65.60; H, 8.38; N, 5.10; Cl, 12.90; H_2O, 2.05. Found: C, 65.22; H, 8.58; N, 5.09; Cl, 12.80; H_2O, 2.49%.

7-Azabicyclo[2.2.1]heptane-1-ethanol (14). The hydrochloride salt of **13** (1.00 g) in ethanol (75 mL) was shaken with 20% Pd on carbon (0.2 g) under H_2 (4 atm) for 72 h. The mixture was filtered and concentrated under vacuum. The residue was triturated with Et_2O to afford the solid, hygroscopic hydrochloride salt of **14** (0.615 g, 92% yield), mp 120–126 °C: ^1H NMR (DMSO-d_6) δ 8.8 (br s, 2 H, NH_2^+), 4.78 (t, J = 5 Hz, 1 H, OH), 3.93 (t, J = 5.7 Hz, 1 H), 3.50 (m, reduced to t, J = 6.5 Hz by D_2O exchange, 2 H), 1.94 (t, J = 6.5 Hz, 2 H), 1.84 (m, 2 H), 1.65 (m, 4 H), 1.57 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 69.8, 57.0, 56.9, 35.0, 31.4 (2 C), 27.5 (2 C); MS (CI) m/z (relative intensity) 142 (100, MH^+). Anal. Calcd for $C_8H_{15}N_1O_1$ - 1.04 HCl - 0.19 H_2O: C, 52.64; H, 9.07; N, 7.67; Cl, 20.20; H_2O, 1.88. Found: C, 52.62; H, 9.11; N, 7.61; Cl, 20.22; H_2O, 1.99. Because of the somethat unsatisfactory elemental analysis of this hygroscopic compound, it was further characterized by derivatization to the acetate–acetamide **15**.

7-Acetyl-7-azabicyclo[2.2.1]heptane-1-ethanol Acetate Ester (15). The hydrochloride salt of **14** (0.10 g) was stirred with acetic anhydride (0.5 mL) and Et_3N (0.2 mL) at 65 °C for 35 min. Water (5 mL) was added, and after 10 min the mixture was extracted with Et_2O (30 mL). The extract was washed with saturated $NaHCO_3$ (5 mL) and concentrated to afford **15** as an oil (0.085 g, 66% yield) that was >99% pure by GC and analyzed correctly after Kugelrohr distillation (100 °C, 1 Torr): ^1H NMR ($CDCl_3$) δ 4.17 (t, J = 7 Hz, 2 H), 4.05 (br s, 1 H), 2.56 (t, J = 7 Hz, 2 H), 1.97 (s, 3 H), 1.95 (t, 3 H), 1.7 (m, 4 H), 1.5 (m, 2 H), 1.4 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 171.0, 169.0, 66.5, 62.5, 58.5 (br s), 34.8 (2 C), 33.1, 29.5 (2 C), 23.6, 21.0; IR (KBr) 1649, 1737 cm^{-1}; MS (CI) m/z (relative intensity) 226 (32, MH^+), 166 (100). Anal. Calcd for $C_{12}H_{19}N_1O_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.68; H, 8.62; N, 6.01.

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