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Transannular Reactions of Substituted Bicyclo[3.3.1]nonane-3-*endo*-carbonitriles: Synthesis of Bifunctional 4-Azahomoadamantanes[1a]

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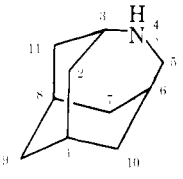
The synthesis of 2-*exo*-hydroxy-4-azahomoadamantanes has been accomplished employing three routes. Reactions have been studied that can lead to transannular cyclizations of the cyano group in substituted bicyclo[3.3.1]nonane-3-*endo*-carbonitriles. The nitrile function has been shown to participate in cyclizations under oxidizing and reducing conditions. 3-Azatricyclo[5.3.1.$0^{4,9}$]undec-5-ene (**16**), a representative of a new heterocyclic "cage" series, has been synthesized.

There has been considerable interest during the past decade in the synthesis and chemistry of adamantane-related "cage" compounds which are pharmacologically active.[2,3] Research in this area has naturally been extended to heterocyclic analogues of "cage" compounds.[3] Several derivatives of 4-azahomoadamantane (**1**) have been reported to show



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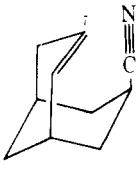
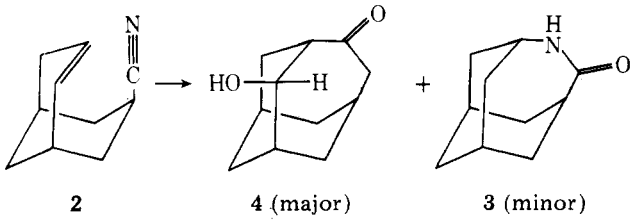


2

antiarrhythmic, hypoglycemic, and antiviral activity.[4-7] Most of the reported 4-azahomoadamantanes have been substituted at nitrogen (4 position) or across the 4–5 bridge.[4-7] There have also been a few examples of 4-azahomoadamantanes with substitution at the 3[8-10] and the 9 positions.[11]

The availability of bicyclo[3.3.1]-6-nonene-3-*endo*-nitrile (**2**) from adamantanone[12] led us to explore its usefulness as a precursor to 2-substituted 4-azahomoadamantanes as well as its behavior in transannular reactions. In principle, a nitrile may act as both an electrophile and a nucleophile in a given reaction.[13] Generation of an electrophilic center at C-7 of the bicyclo[3.3.1]nonane skeleton can lead to interception by the nitrile nitrogen and generate the 4-azahomoadamantane skeleton. Nucleophilic attack at the nitrile carbon can either *precede* or follow reaction of the nitrile nitrogen with the electrophilic center at C-7. In fact, Korsloot and Keizer have identified a small amount (2%) of 4-azahomoadamantan-5-one (**3**) from the reaction of **2** with 95% H_2SO_4.[14] This product could arise from initial protonation of the double bond followed by an intramolecular Ritter reaction. The major product, 3-*exo*-hydroxyadamantanone (**4**), is obviously formed by initial protonation of the nitrile followed by transannular double-bond participation. We wish to describe some transannular chemistry of nitrile **2** and several facile routes to 2-substituted 4-azahomoadamantanes as well as to a functionalized azatricycloundecane cage compound.

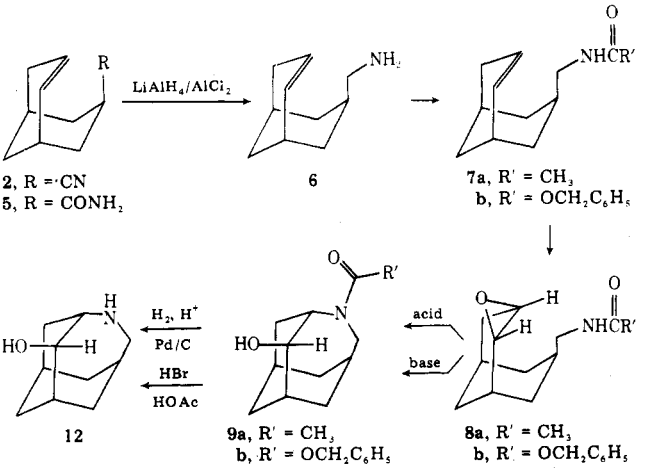


2 **4** (major) **3** (minor)

Results and Discussion

Three routes were devised for the transformation of the bicyclic unsaturated nitrile **2** into azahomoadamantane **12**. The first approach (Scheme I) was patterned after a sequence employed by Spurlock in the synthesis of 4-*exo*-hydroxy-2-azaadamantane[15] and served as an unambiguous route to **12**. Reduction of **2** with lithium aluminum hydride/aluminum chloride ($LiAlH_4/AlCl_3$, 1:1) to the *endo*-amine **6** proceeded in 76% yield and provided a good nucleophile before the epoxide leaving group was introduced on carbon.[16] Alternatively, **6** was obtained (70%) from $LiAlH_4$ reduction of the amide **5**. After the amine **6** was protected as the acetamide **7a** or the benzylcarbamate **7b**, *m*-chloroperbenzoic acid (MCPBA)

Scheme I



2, R = CN
5, R = $CONH_2$

6

7a, R' = CH_3
b, R' = $OCH_2C_6H_5$

12

9a, R' = CH_3
b, R' = $OCH_2C_6H_5$

8a, R' = CH_3
b, R' = $OCH_2C_6H_5$

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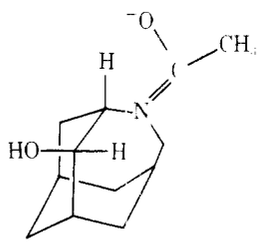
oxidation led to *N*-acetyl-3-*endo*-(aminomethyl)-6,7-*exo*-epoxybicyclo[3.3.1]nonane (**8a**) or the benzyloxycarbonyl-protected epoxide **8b**. Treatment of **8a** under acidic (*p*-toluenesulfonic acid in benzene) or basic (sodium hydride in refluxing dimethoxyethane) conditions resulted in cyclization to *N*-acetyl-2-*exo*-hydroxy-4-azahomoadamantane (**9a**) in 80% yield (Scheme I). The hydroxyacetamide **9a** exhibits an amide carbonyl at 1615 cm^{-1}; *N*-acetylhexamethylenimine has an amide carbonyl absorption at 1639 cm^{-1}.[17] The lower energy carbonyl absorption indicates an increased amount of s character in the C–O bond of the amide. The ^1H NMR spectrum of **9a** in deuteriochloroform shows broad doublets at δ 4.77 and 4.01 in a 1:1 ratio, which together integrate for one proton, and acetyl methyls at δ 2.21 and 2.10.

These data indicate that two conformational isomers (**10**



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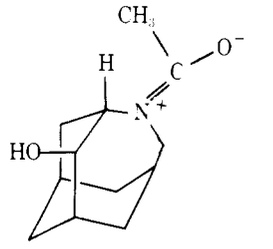

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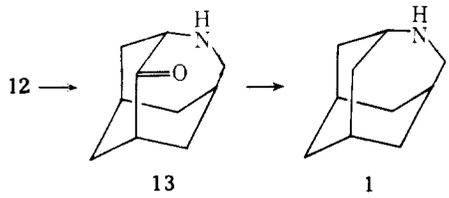
and **11**) are present at ambient temperature in solution. The downfield doublet at δ 4.77 is assigned to the bridgehead proton at C-3 in isomer **10**, which is deshielded by the amide carbonyl. The upfield doublet at δ 4.01 is assigned to the bridgehead proton at C-3 in conformer **11**. Examination of the ^1H NMR spectra of **9a**, run in bromobenzene-d_5 and methanol-d_4, which changes the relative ratio of the conformers, leads to the assignment of the acetyl methyl at δ 2.10 to conformer **10** and the acetyl methyl at δ 2.21 to conformer **11**. Acetamide **9a** proved to be resistant to cleavage by aqueous acid, aqueous base, and hydrazine, even under reflux.

The existence of acetamide **9** as two conformers, **10** and **11**, is in accord with recent studies on the conformation of amides of relatively rigid seven-membered ring amines.[18] This explains not only the deshielding of the proton syn to the amide oxygen (cf. **10**) but also the great reluctance of amide **9** to undergo base- or acid-catalyzed hydrolysis.

In order to obtain the free amino alcohol **12**, the synthetic route outlined in Scheme I was repeated utilizing the more labile benzyloxycarbonyl protecting group. Preparation of *N*-(benzyloxycarbonyl)-2-*exo*-hydroxy-4-azahomoadamantane (**9b**) in three steps from **6** proceeded in 91% yield. Cleavage of the benzyloxycarbonyl protecting group in **9b** was accomplished by hydrogenolysis over palladium on charcoal in acidic ethanol or by hydrogen bromide in acetic acid to afford 2-*exo*-hydroxy-4-azahomoadamantane (**12**).

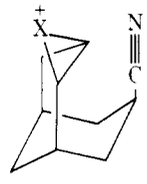
The cage skeleton of **12** is confirmed in the following manner. Oxidation of **12** with Jones reagent under conditions described by Mueller and DiPardo[19] produced 4-azahomoadamantan-2-one (**13**). Wolff–Kishner reduction of amino ketone **13** gave the known compound 4-azahomoadamantane (**1**),



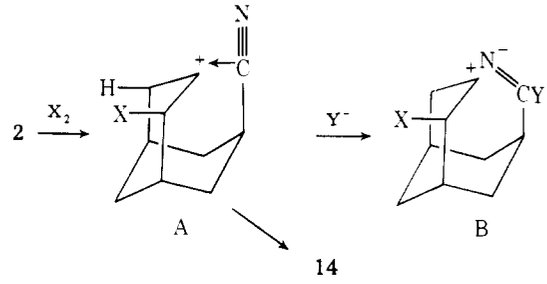
13 **1**

identical with a sample prepared by the method of Sasaki and co-workers,[12,20] thus providing confirmation of the 4-azahomoadamantane ring skeleton for **9–13**. The position and exo stereochemistry of the hydroxyl group in **12** are based on the assumption of backside attack of the amide nitrogen in **8** on the epoxide. Support for the exo assignment to the hydroxyl group is obtained from the ^1H NMR spectrum of **12**, which shows a broadened singlet for the proton at C-2. Examination of molecular models of **12** indicates that the HC–CH dihedral angles for the protons at C-2/C-1 and C-2/C-3 are 90°; hence, the coupling constants should approach zero.

A second approach to **12** involved halogen addition to the unsaturated nitrile **2**. Addition of bromine to **2** afforded 6-*exo*-bromobicyclo[3.3.1]-7-nonene-3-carbonitrile (**14**) as the major product in 66% yield. A number of minor products were produced but not identified. Chlorination of **2** proceeded to the allylic chloride **15**. Formation of allylic halides rather than ring closure via nitrogen seems surprising in view of the acid-catalyzed conversion of **2** to **3**, in which the nitrile nitrogen presumably attacks the electrophilic center created at C-7.[14] However, examination of models shows that although the π electrons of C≡N are capable of stabilizing a positive charge at C-7 (cf. A) by transannular interaction, the geometry



A′

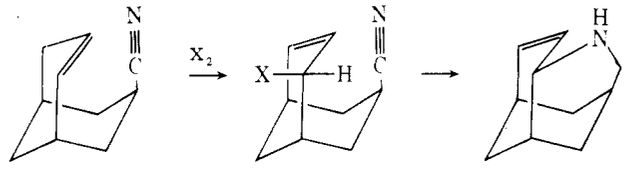


A B

14

is unfavorable for participation by nitrogen unless attack by a nucleophile Y^- on C≡N changes its hybridization and geometry (cf. B).[22] The generation of a stabilized intermediate A′ or A in which the endo side is blocked also explains the formation of allylic bromination or chlorination products **14–15** via loss of a proton. All attempts to effect addition of bromine or BrOAc[21] to the double bond of **2** even in solvents favoring ionic reactions (acetic acid, methanol) led to allylic bromination.[23]

Reaction of **14** with $LiAlH_4/AlCl_3$ (1:1) gives the new "cage" amine 3-azatricyclo[5.3.1.$0^{4,9}$]undec-5-ene (**16**) in 56% yield.

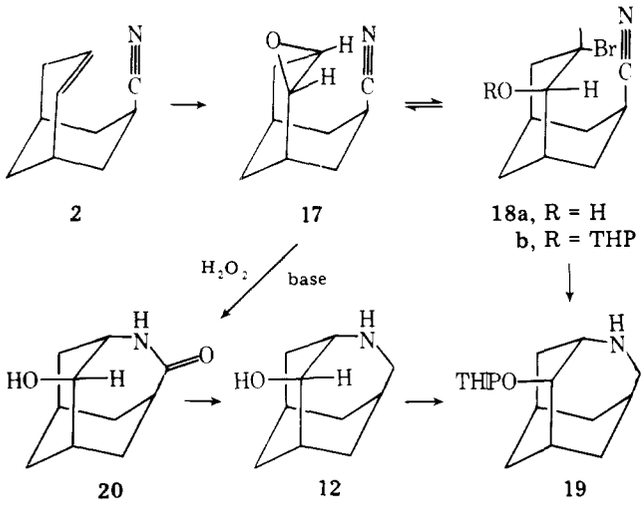


2 **14**, X = Br; **15**, X = Cl **16**

Presumably, the amine formed on reduction of the cyanide led to **16** via transannular allylic halide displacement. Further studies with these ring systems are underway.

Two other entries to amino alcohol **12** were provided via epoxidation of **2** to 6,7-*exo*-epoxybicyclo[3.3.1]nonane-3-*endo*-carbonitrile (**17**). Opening of this epoxide with hydrogen bromide in acetic acid afforded 7-*endo*-bromo-6-*exo*-hydroxybicyclo[3.3.1]nonane-3-*endo*-carbonitrile (**18a**), which was protected as the tetrahydropyranyl ether (**18b**) and reductively cyclized with lithium aluminum hydride/aluminum chloride (1:1). Deprotection of the crude product **19** afforded

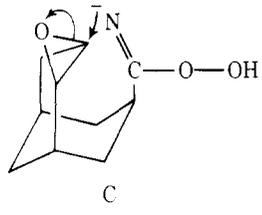
Scheme II



12 in 55% yield from **18b** (Scheme II). The fact that opening of the epoxide **17** with HBr in acetic acid, conditions comparable to the bromination of **2** in the same solvent, did not lead to formation of an allylic alcohol is presumably due to the greater stability of the oxonium ion A′ (X = OH) than the bromonium ion analogue (X = Br).

The trans stereochemistry of the bromohydrin **18a** is evident from its clean conversion into epoxide **17** on mild treatment with base and must result from backside opening by Br^- after the six-membered ring assumes a half-boat conformation.[24] $LiAlH_4/AlCl_3$ provides conditions under which the bromide is solvolyzed, allowing ring closure to **19.**

$LiAlH_4$ reduction of **17** to **12** was not successful. However, conditions were found under which nucleophilic attack at C≡N is followed by opening of the three-membered ring to produce in one step amide alcohol **20.** This was achieved by the use of alkaline hydrogen peroxide and probably proceeds as depicted in C. This reaction is complimentary to the Ritter



C

reaction and may be useful in the synthesis of secondary amides.

These studies suggest that, possibly due to geometrical reasons, the generation of an electrophilic center at C-6 or C-7 in the bicyclic nitriles **2, 14,** or **17** leads to transannular participation by the nitrogen only after conversion of the digonal nitrile into a trigonal or tetrahedral intermediate.

Experimental Section

General. Proton magnetic resonance spectra were obtained on Varian EM-360 60-MHz or Varian HA-100 100-MHz spectrometers and are reported as δ (parts per million downfield from a tetramethylsilane internal standard). Apparent splittings are given in all cases. Yields by ^1H NMR were determined by integration of an appropriate signal in the crude reaction mixture vs. a predetermined amount of an internal standard and are considered to be accurate to ca. ±10%. Infrared spectra were recorded on a Perkin-Elmer 457 spectrophotometer. Mass spectra were obtained on a Dupont 491 spectrometer at ~78 eV (except where indicated). Melting points were taken on a Thomas-Hoover or a Fischer-Johns apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Atlanta, Ga.

3-*endo*-(Aminomethyl)bicyclo[3.3.1]non-6-ene (6). Method A. To 3.79 g (0.023 mol) of **5**[12] in 100 mL of anhydrous ether, cooled in an ice–water bath, was added 1.85 g (0.048 mol) of $LiAlH_4$ in small portions. The ice–water bath was removed, and the reaction mixture was heated under reflux for 4 h and then cooled and quenched with solid $Na_2SO_4 \cdot 10H_2O$ until gas evolution ceased. The reaction mixture was filtered and the residue was washed extensively with ether followed by CH_2Cl_2. The filtrate was dried over anhydrous $MgSO_4$. Evaporation of solvent and distillation at reduced pressure [44–45 °C (0.2 torr)] afforded 2.93 g (70%) of **6**: NMR ($CDCl_3$) δ 5.83 (m, J_{vinyl} = 10 Hz, 1 H), 5.45 (m, J_{vinyl} = 10 Hz, 1 H), 2.60 (d, J = 6 Hz, 2 H), 2.55–0.96 (complex, 13 H including NH_2 at 1.00); IR (CCl_4) 3390, 3300, 3020, 2920, 2850, 2835, 1450, 1437, 1430, 1390, 1320, 1245, 1050, 1005, 927 cm^{-1} [lit.[25] bp 64–65 °C (0.24 mm); NMR δ 5.68 (m, 2 H), 2.62 (d, 2 H)].

Method B. To 3.9 g (0.1 mol) of $LiAlH_4$ in 100 mL of anhydrous ether, which was cooled in an ice–water bath, was added 13.3 g (0.1 mol) of $AlCl_3$ dissolved in 120 mL of anhydrous ether. This mixture was stirred for 5 min, and then 7.35 g (0.05 mol) of **2** in 100 mL of anhydrous ether was added rapidly through an addition funnel. The reaction mixture was stirred for 2 h and then quenched with solid $Na_2SO_4 \cdot 10H_2O$ followed by 25 mL of 50% NaOH solution. The mixture was filtered and the residue was washed with 750 mL of hot chloroform in several portions. The filtrate was washed with 50 mL of 5% NaOH solution, and the basic wash was back extracted with 50 mL of $CHCl_3$. The combined organic extracts were dried over anhydrous $MgSO_4$. Evaporation of solvent and distillation at reduced pressure provided 5.76 g (76%) of a clear oil, identical with that of method A. The amine was analyzed as its acetamide.

***N*-Acetyl-3-*endo*-(aminomethyl)bicyclo[3.3.1]non-6-ene (7a).** To 489 mg (3.24 mmol) of **6** was added 2 mL of Ac_2O. This solution was stirred for 30 min at room temperature and then quenched with 50 mL of ice water. The aqueous solution was stirred until the excess Ac_2O was hydrolyzed (~0.5 h) and then extracted with 4 × 50 mL of CH_2Cl_2. The aqueous phase was neutralized with solid $NaHCO_3$ and further extracted with 3 × 50 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$. Evaporation of solvent provided 621 mg of white solid, which was sublimed [75 °C (0.05 torr)] to give 546 mg (87%) of **7a:** mp 79–80 °C; NMR ($CDCl_3$) δ 6.43 (broad s, 1 H), 5.85 (m, J_{vinyl} = 10 Hz, 1 H), 5.53 (m, J_{vinyl} = 10 Hz, 1 H), 3.29 (m, 2 H), 2.73–1.00 (complex, 14 H including acetyl methyl at 2.00); IR (CCl_4) 3450, 3290, 3080, 3015, 2910, 2850, 1648, 1545, 1510, 1440, 1365, 1280, 1245, 860 cm^{-1}; MS *m/e* (% base) 194 (25), 193 (100), 178 (14), 150 (14), 134 (76), 119 (16), 92 (42). A second sublimation provided an analytical sample.

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.46; H, 9.91; N, 7.24.

***N*-Acetyl-3-*endo*-(aminomethyl)-6,7-*exo*-epoxybicyclo[3.3.1]nonane (8a).** To 1.93 g (0.01 mol) of **7a** in 100 mL of CH_2Cl_2 cooled in an ice–water bath was added dropwise 2.24 g (0.011 mol) of 85% *m*-chloroperbenzoic acid in 50 mL of CH_2Cl_2. The reaction mixture was stirred overnight and allowed to warm to room temperature, and 100 mL of 5% $NaHSO_3$ solution was added followed by basification with solid Na_2CO_3. The aqueous and organic layers were separated, and the aqueous layer was extracted with 4 × 100 mL of CH_2Cl_2. The combined organic extracts were washed with 4 × 25 mL of 5% NaOH solution and then dried over anhydrous $MgSO_4$. Evaporation of solvent and sublimation at reduced pressure [90 °C (0.05 torr)] gave 1.897 g (91%) of **8a:** mp 116–118 °C; NMR ($CDCl_3$) δ 5.93 (brs, 1 H), 3.40–2.90 (m, 4 H), 2.47–0.80 (complex, 14 H including acetyl methyl at 1.98); IR ($CHCl_3$) 3445, 3340, 2920, 2850, 1665, 1510, 1455, 1370, 1010, 965, 925, 885 cm^{-1}; MS *m/e* (% base) 210 (41), 209 (26), 150 (55), 109 (61), 106 (61), 73 (100), 60 (71), 30 (96). A second sublimation afforded an analytical sample.

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.76; H, 9.18; N, 6.68.

N-Acetyl-2-*exo*-hydroxy-4-azahomoadamantane (9a). Method A. *p*-Toluenesulfonic acid monohydrate (100 mg, 0.5 mmol) was treated with 20-mL portions of dry benzene and evaporated to remove the water. To the reaction flask was added 1.045 g (5 mmol) of **8a** and 100 mL of dry benzene. The reaction mixture was refluxed for 39 h and then cooled, and 400 mL of $CHCl_3$ was added. The organic solution was washed with 2 × 25 mL of saturated $NaHCO_3$ solution and dried over $MgSO_4$. Evaporation of solvent and sublimation [115 °C (0.05 torr)] provided 828 mg (79%) of **9a:** mp 135–137 °C; NMR ($CDCl_3$) δ 4.77 and 4.01 (each d, J = 6 Hz, 1 H), 4.97–3.83 (broad, exchangeable), 3.80–3.37 (m, 3 H), 2.80–1.07 (complex, 14 H including acetyl methyl at 2.21 and 2.10); IR ($CHCl_3$) 3600, 3390, 2915, 2850, 1615, 1420, 1385, 1365, 1345, 1320, 1075, 1035, 1010, 990, 970, 950, 915, 910, 875 cm^{-1}; MS *m/e* (% base) 210 (30), 209 (35), 191 (20), 166 (21), 150 (100), 149 (28). A second sublimation [115 °C (0.05 torr)] produced an analytical sample.

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.85; H, 9.17; N, 6.67.

Method B. In a 50-mL three-neck flask fitted with an addition funnel, argon inlets, and a bubbler was placed 125 mg (2.6 mmol) of 50% NaH. The NaH was rinsed with two portions of dry benzene, and 5 mL of dry DME was added. The mixture was cooled in an ice–water bath, and 209 mg (1 mmol) of **8a** in 5 mL of DME and 8 mL of THF was added dropwise. After 0.5 h, the ice–water bath was removed, 5 drops of DMF was introduced, and the reaction mixture was cooled and quenched with 2 mL of H_2O. The mixture was placed in a separatory funnel, 200 mL of $CHCl_3$ was added, and the organic solution was washed with 25 mL of $CHCl_3$. The combined organic solutions were washed with 25 mL of saturated NaCl solution and dried over anhydrous $MgSO_4$. Evaporation of solvent and sublimation [110 °C (0.05 torr)] provided 168 mg (80%) of **9a,** identical with that prepared by method A above.

Attempted Cleavage of Hydroxyacetamide 9a. Heating of hydroxyacetamide **9a** under reflux in 10% aqueous KOH for 11 h, with 10% H_2SO_4 for 18 h, or with 95% NH_2NH_2 at 100 °C in a sealed tube for 22 h led to recovery of at least 75% starting material.

***N*-(Benzyloxycarbonyl)-2-*exo*-hydroxy-4-azahomoadamantane (9b). Carbamate.** To 4.53 g (0.03 mol) of **6** in 50 mL of EtOH cooled in an ice–water bath was added dropwise 5.6 g (0.031 mol) of benzyl chloroformate. When approximately one-half of the acid chloride had been added, a second solution of 25 mL of 1.4 M Na_2CO_3 was added at such a rate that addition was finished slightly after the chloroformate. The reaction mixture was stirred for 5–10 min, and then 5 mL of H_2O was added. The reaction mixture was stirred for 45 min, and then most of the EtOH was removed by rotary evaporation. To the residue was added 100 mL of H_2O. The aqueous solution was extracted with 4 × 100 mL of $CHCl_3$. The combined organic extracts were dried over anhydrous $MgSO_4$. Evaporation of solvent gave 9.65 g of clear oil.

Epoxidation. The crude product was dissolved in 250 mL of CH_2Cl_2 and cooled in an ice–water bath. To the reaction mixture was added dropwise 6.75 g (0.033 mol) of *m*-CPBA in 125 mL of CH_2Cl_2. The reaction mixture was stirred overnight and allowed to warm to room temperature. After addition of 250 mL of CH_2Cl_2, 100 mL of saturated $NaHCO_3$ was added followed by 50 mL of 5% $NaHSO_3$. This mixture was stirred for 20 min and the layers were separated. The organic layer was washed with an additional 2 × 50 mL of saturated $NaHCO_3$ solution. The combined aqueous solutions were back washed with 50 mL of CH_2Cl_2. The combined organic extracts were washed with 50 mL of H_2O and 50 mL of saturated NaCl solution and then dried over Na_2SO_4. Evaporation of solvent provided 10.02 g of **8b** as an oil.

Rearrangement. To crude **8b** was added 300 mL of dry benzene and 300 mg (1.6 mmol) of $TsOH·H_2O$. This mixture was refluxed for 24 h and cooled, and 500 mL of $CHCl_3$ was added. The organic solution was washed with 2 × 50 mL of 5% NaOH, 50 mL of H_2O, and 50 mL of saturated NaCl and then dried over Na_2SO_4. Evaporation of solvent gave 8.79 g of crude solid, which was crystallized from $CHCl_3$/heptane to afford 8.79 g (91%) of **9b** from **6**: mp 115.5–117.5 °C (sealed tube); NMR ($CDCl_3$) δ 7.23 (s, 5 H), 5.07 (s, 2 H), 4.43 (m, 1 H), 3.93–3.13 (m, 4 H), 2.60–1.00 (complex, 11 H); IR ($CHCl_3$) 3610, 3430, 2910, 2850 (sh), 1675, 1415, 1335, 1305, 1125, 1105, 1020, 980, 925, 905, 875 cm^{-1}.

Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.23; H, 7.69; N, 4.65. Found: C, 71.64; H, 7.73; N, 4.65.

2-*exo*-Hydroxy-4-azahomoadamantane (12). Method A. To 20 mL of 30% HBr/HOAc was added 3.01 g (10 mmol) of **9b.** The reaction mixture was stirred overnight at room temperature and then quenched with 50 mL of H_2O. The aqueous solution was extracted with 3 × 25 mL of ether and then neutralized with solid Na_2CO_3 followed by 4 g of KOH. The aqueous solution was stirred for 1 h and then extracted with 5 × 10 mL of $CHCl_3$. The combined organic extracts were washed with 2 × 50 mL of saturated NaCl solution and dried over anhydrous Na_2SO_4. Evaporation of solvent and sublimation [115 °C (0.05 torr)] afforded 1.00 g (60%) of amino alcohol **12:** mp 297.5–298.5 °C (sealed tube); NMR ($CDCl_3$) δ 3.56 (brs, 1 H), 3.37 (brs, 2 H, exchanges in D_2O), 3.10 (m, 1 H), 3.01 (d, J = 2.6 Hz, 2 H), 2.73–1.00 (complex, 11 H); IR ($CHCl_3$) 3605, 3340, 2910, 2850, 1460, 1440, 1165, 1105, 1025, 930 cm^{-1}; MS *m/e* (% base) 168 (22), 167 (100), 150 (22), 149 (30), 139 (16), 138 (30), 124 (12), 108 (37), 96 (54), 94 (56).

Method B. A Parr bottle was charged with 3.01 g (10 mmol) of **9b,** 450 mg of 10% Pd/C catalyst, and 100 mL of 0.24 M HCl in EtOH. After flushing with H_2 three times, the hydrogenator was pressurized at 20 psi of H_2 and shaken overnight. After this time, the reaction mixture was filtered through Celite and the residue was washed with 200 mL of 0.24 M HCl in EtOH, 125 mL of EtOH, and 100 mL of H_2O. The acidic filtrate was neutralized with 10.6 g (0.1 mol) of solid Na_2CO_3 and then rotovaped to remove the solvent. To the residue was added 100 mL of 5% NaOH solution. The aqueous solution was extracted with 4 × 200 mL of $CHCl_3$. The combined organic extracts were washed with saturated NaCl solution and dried over anhydrous $MgSO_4$. Evaporation of solvent and sublimation [125 °C (0.05 torr)] provided 710 mg (43%) of **12,** identical with the material described in method A. The amino alcohol **12** was converted in 79% yield to the acetamide **9a** for confirmation of structure. This was accomplished by stirring with Ac_2O for 1.5 h followed by treatment with 15% NaOH in methanol for the same time period.

4-Azahomoadamantan-2-one (13). To 1.67 g (10 mmol) of **12** in 20 mL of acetone cooled in an ice–water bath was added dropwise 6 mL of 3 M H_2SO_4 solution (18 mmol) followed by 5 mL of Jones reagent (5.6 g of CrO_3 in 16 mL of H_2O mixed at ice bath temperature with 9 mL of concentrated H_2SO_4 in 8 mL of H_2O). The reaction mixture was stirred for 45 min at ice bath temperature and then for 4.25 h at room temperature. After this time, the excess reagent was destroyed with 4 mL of *i*-PrOH and 50 mL of H_2O was added followed by 20 g of sodium citrate dihydrate. The reaction flask was flushed with N_2, a small piece of amalgamated zinc was added, and the solvent was stirred for 14 min. The reaction mixture was cooled in an ice–water bath, and 50 mL of Et_2O was added followed by 20 mL of 20% NaOH solution. The layers were separated, and the aqueous portion was extracted with 4 × 100 mL of $CHCl_3$. The combined organic extracts were washed with 2 × 50 mL of saturated NaCl solution and dried over anhydrous Na_2SO_4. Evaporation of solvent and sublimation [110 °C (0.05 torr)] gave 1.051 g (64%) of amino ketone **13:** mp 264–265 °C (sealed tube); NMR ($CDCl_3$) δ 3.44 (m, J = 5.6 Hz, 1 H), 3.13 (d, J = 3 Hz, 2 H), 2.57 (m, 1 H), 2.43–1.27 (complex, 11 H); IR (CCl_4) 3360, 2910, 2850, 1720 (sh), 1700, 1455, 1440, 1350, 1300, 1270, 1255, 1210, 1155, 1105, 1065, 1040, 985, 970 cm^{-1}; MS *m/e* (% base) 166 (24), 165 (79), 137 (94), 136 (27), 122 (22), 108 (15), 94 (68), 82 (33), 80 (100). A second sublimation provided an analytical sample.

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.45; H, 9.21; N, 8.44.

4-Azahomoadamantane (1). To 330 mg (2 mmol) of **13** in 10 mL of ethylene glycol was added 3.5 mL (100 mmol) of 95% NH_2NH_2. This mixture was heated at 105 °C for 2 h, and then 7 g (104 mmol) of 85% KOH was added and the reaction temperature was raised to 185 °C. After 6 h, some H_2O/NH_2NH_2 had distilled and a white solid was present in the condenser. To the distillate was added 30 mL of H_2O; the solution was extracted with 4 × 50 mL of $CHCl_3$. The condenser was rinsed with 100 mL of $CHCl_3$. The combined extracts and rinse were washed with 3 × 30 mL of H_2O and 50 mL of saturated NaCl solution and dried over anhydrous Na_2SO_4. Evaporation of solvent and sublimation [100 °C (0.05 torr)] provided 144 mg (48%) of amine **1,** identical with an authentic sample prepared by the method of Sasaki.[20]

6-*exo*-Bromobicyclo[3.3.1]non-7-ene-3-*endo*-carbonitrile (14). To 446 mg (3 mmol) of **2** in 2 mL of HOAc was added 15.5 mL (3.1 mmol) of a freshly prepared 0.2 M Br_2 in HOAc solution (1% Ac_2O). The reaction mixture was stirred for 20 min and then quenched with 125 mL of ice water. The white precipitate was filtered, washed with water, and dried under vacuum, providing 475 mg of crude **14.** Sublimation at 80 °C (0.05 torr) gave 457 mg (66%) of the bromonitrile **14:** mp 112.5–113 °C (sealed tube); NMR ($CDCl_3$) δ 6.17 (dd, J = 3 and 10 Hz, 1 H), 5.94 (dd, J = 5.2 and 10 Hz, 1 H), 4.88 (d, J = 3 Hz, 1 H), 2.96 (m, 1 h), 2.80–1.20 (br m, 8 H); IR ($CHCl_3$) 3035, 2925, 2855, 2235, 1640, 1455, 1440, 1395, 1370, 1360, 1345, 1335, 1330, 1325, 1285, 1160, 1070, 1030, 990, 930, 910, 905 cm^{-1}; MS *m/e* (% base) 228 (5), 226 (6), 147 (26), 146 (100), 131 (5), 129 (12), 119 (31), 104 (12), 93 (16).

Anal. Calcd for $C_{10}H_{12}NBr$: C, 53.12; H, 5.35; Br, 35.34. Found: C, 53.00; H, 5.37; Br, 35.31.

Reaction of 2 with Br_2/CCl_4. To 294 mg (2 mmol) of **2** in 50 mL of CCl_4 was added 10.8 mL (2.16 mmol) of 0.2 M Br_2/CCl_4 solution. After being stirred for 15 min (color disappeared), the reaction mixture was quenched with 10% $NaHSO_3$ solution. The acidic aqueous layer was neutralized with solid Na_2CO_3 and the layers were separated. The aqueous layer was extracted with 3 × 50 mL of CH_2Cl_2. The combined organic solutions were dried over anhydrous $MgSO_4$. Evaporation of solvent provided 478 mg of white solid. Yield of **14** was 77% by NMR integration against a bromodichloromethane internal standard.

Reaction of 2 with Acetyl Hypobromite. To 257 mg (1.54 mmol) of AgOAc suspended in 20 mL of CCl_4 cooled to −10 °C was added 8.25 mL (1.65 mmol) of 0.2 M Br_2/CCl_4 solution over a period of 45 min. After addition was completed, the reaction mixture was stirred for 1 h. To the solution of acetyl hypobromite was added 220 mg (1.5 mmol) of **2** in 25 mL of CCl_4 over a period of 10 min. The reaction

mixture was stirred for 75 min, allowed to warm to room temperature, and filtered to remove AgBr, and the residue was washed with 100 mL of CCl_4. The combined filtrate and washes were extracted with 20 mL of 5% $NaHSO_3$ solution. The aqueous wash was back extracted with 3×50 mL of $CHCl_3$, and the combined organic solutions were dried over $MgSO_4$. Evaporation of solvent produced 316 mg of **14** as a white solid (67% yield[15] by NMR integration against a bromodichloromethane internal standard).

6-*exo*-Chlorobicyclo[3.3.1]non-7-ene-3-*endo*-carbonitrile (15). To 1.47 g (10 mmol) of **2** in 5 mL of HOAc was added 10.5 g (11 mmol) of a 7.4% solution of Cl_2 in HOAc. The reaction mixture was stirred for 10 min and quenched with 100 mL of ice water. The resulting precipitate was filtered, washed with H_2O, and dried under vacuum to yield 1.223 g of crude material. Sublimation [110 °C (0.05 torr)] provided 1.116 g (61%) of allylic chloride **15:** mp 83–86 °C (sealed tube); NMR ($CDCl_3$) δ 6.02 (m, 2 H), 4.60 (dd, J = 2.2 and 1 Hz, 1 H), 2.94 (m, 1 H), 2.77–1.23 (complex, 8 H); IR (CCl_4) 3030, 2930, 2855, 2225, 1450, 1435, 1390, 1285, 1240, 1195, 1070, 1030, 985, 935, 915 cm^{-1}; MS m/e (% base) 183 (18), 181 (47), 146 (100), 91 (46). A second sublimation afforded an analytical sample.

Anal. Calcd for $C_{10}H_{12}NCl$: C, 66.12; H, 6.66; N, 7.71. Found: C, 65.87; H, 6.69; N, 7.67.

3-Azatricyclo[5.3.1.$0^{4,9}$]undec-5-ene (16). To 538 mg (14.2 mmol) of $LiAlH_4$ in 30 mL of anhydrous ether, which was cooled in an ice bath, was added 1.95 g (14.6 mmol) of $AlCl_3$ in 50 mL of anhydrous ether. The reaction mixture was stirred for 5 min, and then 1.547 g (6.86 mmol) of **15** in 30 mL of dry THF was added at a rapid dropping rate through an addition funnel. The reaction mixture was stirred for 2 h and quenched with solid $Na_2SO_4 \cdot 10H_2O$, followed by 3 mL of 50% NaOH solution. After filtration, the residue was washed with 750 mL of hot chloroform in several portions. The filtrate was washed with 50 mL of 5% NaOH solution, and the aqueous solution was back washed with 50 mL of $CHCl_3$. The combined organic solutions were dried over anhydrous $MgSO_4$. Evaporation of solvent provided 1.046 g of crude material (yield was 57% as determined by NMR with $CHBr_3$ as an internal standard). The crude material was taken up in 6 N HCl solution and washed with two 100-mL portions of ether. The aqueous solution was made basic with solid NaOH and extracted with 4×100 mL of ether. The organic extract was dried over $MgSO_4$. Evaporation of solvent produced a solid which was triturated with pentane. Filtration followed by sublimation [80 °C (0.07 torr)] provided pure **16:** mp 233.5–234.5 °C (sealed tube); NMR ($CDCl_3$) δ 6.30 (dd, J = 9 and 7.2 Hz), 5.37 (dd, J = 9 and 5 Hz), 3.80 (dd, J = 9.2 and 5.0 Hz), 2.91 (m, 2 H), 2.60–1.00 (complex, 10 H); IR (CCl_4) 3020, 2925, 2855, 1642, 1470, 1460, 1450, 1445, 1420, 1385, 1360, 1350, 1310, 1300, 1265, 1205, 1160, 1115, 1090, 1075, 1018, 955, 930, 915, 890, 880, 865, 855 cm^{-1}; MS m/e (% base) 150 (25), 149 (100), 148 (22), 134 (16), 120 (15), 108 (19), 106 (26), 80 (55).

Anal. Calcd for $C_{10}H_{15}N$: C, 80.48. H, 10.19. Found: C, 80.39; H, 10.19.

6,7-*exo*-Epoxybicyclo[3.3.1]nonane-3-*endo*-carbonitrile (17). To 1.47 g (0.01 mol) of **2** in 150 mL of CH_2Cl_2, cooled in an ice–water bath, was added dropwise 2.24 g (0.011 mol) of *m*-CPBA in 50 mL of CH_2Cl_2. The reaction mixture was allowed to stir overnight and warm to room temperature. The mixture was quenched with 20 mL of 5% $NaHSO_3$ solution, and the aqueous layer was back washed with 50 mL of CH_2Cl_2. The combined organic layers were washed with 3×30 mL of saturated $NaHCO_3$ solution, and the basic extracts were washed with 50 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$. Evaporation of solvent and sublimation [80 °C (0.05 torr)] afforded 1.48 g (91%) of epoxynitrile **17:** mp 275.5–277.5 °C (sealed tube); NMR ($CDCl_3$) δ 3.23 (m, 2 H), 2.97 (m, 1 H), 2.70–1.50 (complex, 9 H), 1.14 (d, J = 13 Hz, 1 H); IR (CCl_4) 3005, 2980 (sh), 2930, 2860, 2235, 1460, 1445, 1365, 1355, 1005, 967, 940, 915, 890 cm^{-1}; MS m/e (% base) 164 (35), 163 (40), 162 (42), 148 (32), 134 (63), 120 (100), 107 (85), 97 (98).

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.54; H, 8.06; N, 8.59.

7-*endo*-Bromo-6-*exo*-hydroxybicyclo[3.3.1]nonane-3-*endo*-carbonitrile (18a). To 16.3 g (0.01 mol) of **17** in 10 mL of 75% aqueous HOAc was added 1.18 mL (1.05 equiv) of 48% HBr. The reaction mixture was stirred for 0.5 h and then quenched with 50 mL of H_2O. The aqueous solution was neutralized with solid $NaHCO_3$ and extracted with 4×50 mL of $CHCl_3$. The organic extracts were dried over anhydrous $MgSO_4$. Evaporation of solvent and crystallization of the residue with $CHCl_3$/heptane gave 1.76 g of the bromohydrin **18a.** Additional crystallizations of the mother liquor provided 0.34 g: total yield 2.10 g (86%); mp 137–138.5 °C (sealed tube); NMR ($CDCl_3$) δ 4.60–3.80 (m, 2 H), 3.20–2.77 (m, 2 H), 2.77–1.43 (complex, 9 H), 1.10 (br d, J = 13 Hz, 1 H); IR ($CHCl_3$) 3560, 3500, 2930, 2875, 2860, 2230, 1460, 1440, 1370, 1355, 1335, 1325, 1300, 1285, 1120, 1070, 1055, 1015, 985, 945, 925, 910 cm^{-1}; MS m/e (% base) 246 (12), 245 (16), 244 (12), 243 (15), 217 (12), 215 (13), 164 (100), 163 (50), 146 (62), 136 (55), 119 (25), 109 (57), 101 (94), 99 (73).

Anal. Calcd for $C_{10}H_{14}BrNO$: C, 49.20; H, 5.78; Br, 32.73; N, 5.74. Found: C, 49.05; H, 5.81; Br, 32.66; N, 5.69.

Reaction of 18a with Base. To 164 mg (2.44 mmol) of 85% KOH in 10 mL of EtOH was added 500 mg (2.05 mmol) of **18a.** The solution was stirred overnight at room temperature, and then most of the solvent was removed by rotary evaporation. Water (25 mL) was added to the residue, the aqueous solution was extracted with four 50-mL portions of $CHCl_3$, and the extract was dried over $MgSO_4$. Evaporation of solvent and sublimation at reduced pressure [130 °C (0.05 torr)] provided 305 mg (91%) of **17.**

THP-Protected 6-*exo*-Hydroxy-7-*endo*-bromobicyclo[3.3.1]nonane-3-*endo*-carbonitrile (18b). In a round-bottom flask 3.27 g (13.4 mmol) of **18a,** 2.75 mL (~30 mmol) of dihydropyran, 200 mg (1.05 mmol) of $TsOH \cdot H_2O$, and 60 mL of ether were combined. The reaction mixture was stirred at room temperature for 3.75 h, and then 200 mL of ether was added. The organic solution was washed with 3×20 mL of saturated $NaHCO_3$ solution and dried over $MgSO_4$. Evaporation of solvent gave 4.65 g of crude material. Crystallization from CH_2Cl_2/pentane afforded 3.00 g of **18b.** Evaporation of the mother liquor and a second crystallization provided an additional 0.45 g (total yield 79%) of THP ether **18b:** mp 108–112 °C (sealed tube); NMR ($CDCl_3$) δ 4.77 (m, 1 H), 4.60–3.23 (complex, 4 H), 2.98 (m, 1 H), 2.70–1.27 (complex, 15 H), 1.14 (br d, J = 14 Hz, 1 H); IR (CCl_4) 2905, 2860, 1200, 1185, 1175, 1150, 1120, 1075, 1020, 965, 900 cm^{-1}; MS m/e (% base) 330 (19), 328 (20), 228 (76), 226 (77), 146 (100).

Anal. Calcd for $C_{15}H_{22}BrNO_2$: C, 54.89; H, 6.76; Br, 24.34; N, 4.27. Found: C, 54.94; H, 6.80; Br, 24.25; N, 4.26.

Reductive Cyclization of 18b to 12. To 623 mg (16.4 mmol) of $LiAlH_4$ in 25 mL of anhydrous Et_2O cooled in an ice–water bath was added 1.95 g (14.6 mmol) of $AlCl_3$ in 30 mL of anhydrous Et_2O. This mixture was stirred for 5 min, and then 2.46 g (7.5 mmol) of **18b** in 40 mL of dry THF was added rapidly through an addition funnel. The mixture was stirred for 5 h and then quenched with $Na_2SO_4 \cdot 10H_2O$ followed by 5 mL of 50% NaOH solution. The reaction mixture was filtered and the residue was washed with 750 mL of hot $CHCl_3$. The filtrate was extracted with 50 mL of 5% NaOH solution, and the basic layer was extracted with 50 mL of $CHCl_3$. The combined filtrate and extract were dried over $MgSO_4$. Evaporation of solvent gave 2.1 g of **19** as an oil.

Deprotection of 19. To the above oil in 75 mL of MeOH in an ice–water bath was added 2.85 g of $TsOH \cdot H_2O$ (15 mmol). The reaction mixture was stirred for 4 h and allowed to warm to room temperature. The MeOH was removed by rotary evaporation. To the residue was added 50 mL of 5% HCl solution, and the resulting solution was washed with 2×50 mL of Et_2O. The acidic solution was made basic with 10 mL of 50% NaOH solution, saturated with NaCl, and extracted with 4×100 mL of $CHCl_3$. The combined extracts were dried over anhydrous $MgSO_4$. Evaporation of solvent and sublimation [120 °C (0.07 torr)] provided 650 mg (52%) of **12.**

2-*exo*-Hydroxy-4-azahomoadamantan-5-one (20). To 1.63 g (10 mmol) of epoxynitrile **17** in 20 mL of EtOH cooled in an ice–water bath was added 4 g (35 mmol) of 30% aqueous H_2O_2 followed by 0.6 mL of 6 N NaOH. The reaction mixture was stirred for 0.5 h at ice bath temperature and for 25 h at room temperature. After the solvent was evaporated, 30 mL of H_2O was added and the aqueous solution was saturated with NaCl and extracted with 4×100 mL of $CHCl_3$. The combined organic extracts were dried over anhydrous Na_2SO_4. Evaporation of solvent and sublimation [190 °C (0.05 torr)] yielded 1.410 g (78%) of hydroxy lactam **20:** mp 302–307 °C dec (sealed tube); NMR ($CDCl_3$) δ 7.47 (d, J = 7.9 Hz, 1 H, exchanges in D_2O), 4.27 (brs, 1 H, exchanges in D_2O), 3.80 (brs, 1 H), 3.13 (m, 1 H), 2.87–1.17 (complex, 11 H); NMR (Me_2SO-d_6) δ 7.67 (d, J = 7.2 Hz, 1 H, exchanges in D_2O), 4.90 (d, J = 2.7 Hz, 1 H, exchanges in D_2O), 3.59 (brs, 1 H), 2.93 (m, 1 H), 2.67–1.10 (complex, 1 H); IR ($CHCl_3$) 3595, 3410, 3275, 2920, 2850, 1647, 1465, 1445, 1355, 1300, 1120, 1070, 1035, 990, 980, 955, 915, 900, 800 cm^{-1}; MS m/e (% base) 182 (3), 181 (5), 180 (5), 179 (6), 163 (22), 162 (41), 148 (31), 135 (35), 134 (61), 121 (67), 120 (86), 107 (84), 97 (81), 90 (82), 79 (100). A second sublimation provided an analytical sample.

Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.49; H, 8.34; N, 7.66.

Reduction of Amide 20 to 12. To 543 mg (3 mmol) of **20** in 100 mL of dry THF was added 1.0 g (26.3 mmol) of $LiAlH_4$. The reaction mixture was refluxed for 48 h and then quenched with $Na_2SO_4 \cdot 10H_2O$ followed by 2 mL of H_2O. The usual workup gave, after sublimation,

303 mg (60%) of amino alcohol **12**, identical with that described above.

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Registry No.—**1**, 22776-74-5; **2**, 26768-57-0; **5**, 26269-35-2; **6**, 53516-37-3; **7a**, 69631-64-7; **7b**, 69631-65-8; **8a**; 69631-66-9; **8b**, 69631-67-0; **9a**, 69668-45-7; **9b**, 69631-68-1; **12**, 69631-69-2; **13**, 69631-70-5; **14**, 69631-71-6; **15**, 69653-38-9; **16**, 69631-72-7; **17**, 69631-73-8; **18a**, 69631-74-9; **18b**, 69631-75-0; **19**, 69631-76-1; **20**, 69631-77-2; acetyl hypobromite, 4254-22-2; dihydropyran, 25512-65-6.

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Ortho Lithiation via a Carbonyl Synthon

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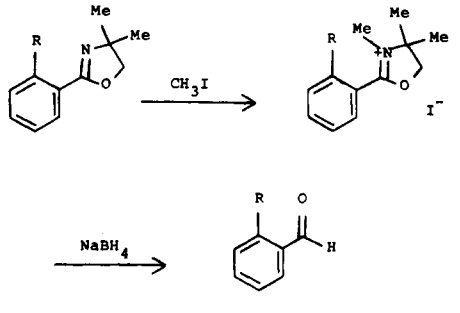
The use of the imidazolidine ring as an ortho-directing group in aryl and aralkyl metalation is described. This carbonyl synthon directs lithiation to the ortho position nearly quantitatively and affords the corresponding aromatic aldehyde on mild acid hydrolysis. Thus, lithiation of 1,3-dimethyl-2-phenylimidazolidine (**1**) with *n*-butyllithium–TMEDA, quenching with methyl iodide, and hydrolysis with 2 N HCl gave *o*-tolualdehyde (**3**) in 95% yield. The generality of this technique is discussed.

In recent years an increasing number of examples of heteroatom-facilitated ortho metalation have appeared. This process is a potentially valuable technique in synthetic organic chemistry because it allows one to prepare ortho-disubstituted aromatic compounds completely free of the isomeric meta or para isomers. The functional groups which are capable of directing metalation encompass a wide variety of structural types, including amides, amines, ethers, and halides.[1,2] One of the major limitations of the currently available directing groups is their poor versatility for further chemical transformations. One functional group which is especially difficult to obtain from these directing groups is an aromatic aldehyde. The only directing group which is easily transformed into an aromatic aldehyde is aryloxazoline.[3,4] This transformation is accomplished in two steps: formation of the quaternary salt, followed by $NaBH_4$ reduction (Scheme I).[5] We wish to report the use of the imidazolidine ring as a directing group for aromatic metalation. Not only does this group provide ortho lithiation regiospecifically and nearly quantitatively, it also gives rise to the corresponding aromatic aldehyde by mild acid hydrolysis.

The known 1,3-dimethyl-2-phenylimidazolidine (**1**) was prepared in 77% yield from benzaldehyde and *N,N'*-dimethylethylenediamine. Lithiation of an ethereal solution of **1** using 3 equiv of *n*-butyllithium *N,N,N',N'*-tetramethylethylenediamine (TMEDA) at 25 °C for 7 h gave the *o*-lithio derivative **2** in nearly quantitative yield, as shown by quenching experiments. Use of less than 3 equiv of organometallic reagent gave lower yields of **2**. When the anion solution was quenched with methyl iodide and hydrolyzed with 2 N HCl for 10 min at 25 °C *o*-tolualdehyde (**3**) was isolated in 95% yield. Similarly, quenching **2** with D_2O gave a 95% yield of *o*-deuteriobenzaldehyde (**4**). In order to examine the versatility and generality of this synthetic method we have quenched anion **2** with a variety of electrophiles. The results of these experiments are summarized in Table I.

The use of *n*-butyl bromide as the electrophile gave *o*-*n*-butylbenzaldehyde (**5**) in the moderate yield of 45%. If *sec*-butyl bromide was used, none of the expected *o*-*sec*-butyl-

Scheme I



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