Ar and NH), 6.6 (d, J = 9 Hz, 2 H, Ar), 4.3 (m, 2 H, CH_2). Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.71; H, 5.19; N, 10.37. Found: C, 67.09; H, 5.37; N, 10.51.

Acknowledgment. We are grateful to our service support staff for expertly performing spectroscopic and combustion analyses and their helpful discussions.

Registry No. **5**, 99-92-3; **6**, 2719-21-3; **7**, 73549-48-1; **7** (*E*-oxime derivative), 75626-40-3; **8**, 15535-99-6; **9**, 75626-41-4; **11a**, 75626-42-5; **11a** (*E*-oxime derivative), 75626-43-6; **11a** (*Z*-oxime derivative), 75626-44-7; **12**, 75626-45-8; **13**, 75626-46-9; **14**, 75626-47-0; **16**, 75626-48-1; **17**, 75626-49-2; **18**, 75626-50-5; **19**, 75626-51-6; **19** (*E*-oxime derivative), 75626-52-7; **19** methyl ester (*E*-oxime derivative), 75626-53-8; **19** methyl ester (*Z*-oxime derivative), 75626-54-9; **20**, 75626-55-0; **21**, 75626-56-1; **22**, 75626-57-2; **23**, 75626-58-3; **24**, 75626-59-4; **25**, 75626-60-7; **26a**, 75626-61-8; **26b**, 75626-62-9; **26c**, 75640-91-4; **26d**, 75626-63-0; **26e**, 75626-64-1; **27a**, 75626-65-2; **27b**, 75626-66-3; **27c**, 75626-67-4; **27d**, 75626-68-5; **30a**, 75626-69-6; **30b**, 75626-70-9; **31**, 75626-71-0; **32**, 75626-72-1; 1,1'-carbonyldiimidazole, 530-62-1; aniline, 62-53-3; 4-[[(benzyloxy)carbonyl]amino]acetophenone, 72531-10-3; dihydropyran, 110-87-2; (tetrahydropyran-2-yl)hydroxylamine, 6723-30-4; furoyl chloride, 527-69-5; benzoyl chloride, 98-88-4; *O*-acetylmandeloyl chloride, 1638-63-7; trifluoroacetic anhydride, 407-25-0; benzyl (-)-(*R*)-4-chloro-4-oxo-2-[[(benzyloxy)carbonyl]amino]butyrate, 75626-73-2; benzaldehyde, 100-52-7; benzyl 4-oxo-2-[[(benzyloxy)carbonyl]amino]butanoate, 75626-74-3; 2-aminobutyrolactone hydrobromide, 6305-38-0; sodium 2-(benzyloxy)carbonyl]amino]-4-hydroxybutanoate, 75626-75-4.

Transannular Reactions of Dibenzo[*a*,*d*]cycloalkenes. 3.[1] Nature of the Amine to Olefin Ring Closure

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An efficient, regiospecific, intramolecular amine to olefin addition is described. Evidence is presented which suggests that the reaction pathway has radical character and involves nitrogen participation. Factors considered are the structure of the substrate, the initiating base, the effect of reagent addition order, sensitivity to oxygen and other radical inhibitors, the ESR signature, and the fate of hydrogen at key reaction centers as determined by deuterium labeling.

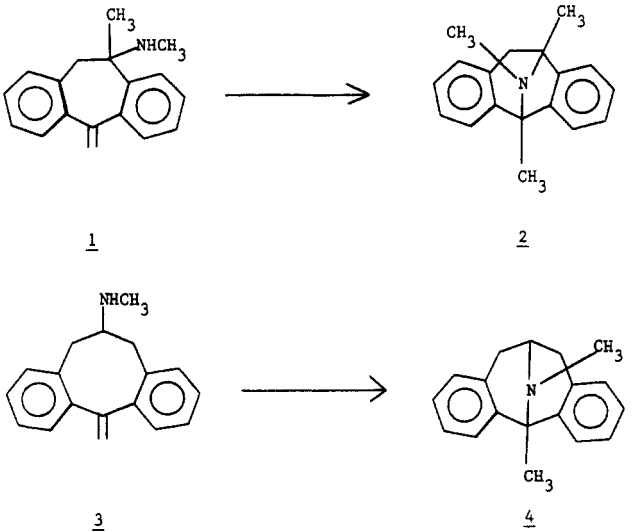
The direct addition of amines to simple olefins is an infrequently utilized synthetic reaction. In those cases where addition is observed, conditions sufficently basic for formation of the amide anion,[2] elevated temperatures, and protracted reaction times are required.[4] These conditions usually produce low yields of product mixtures.

In the course of synthetic studies on bridged ring cyclic imines,[1,6] we observed a regiospecific amine to olefin addition which took place rapidly at room temperature in excellent yield. The characteristics of this reaction indicated it was not a nucleophilic addition, and we, therefore, undertook a closer study of its mechanism. Reported here are the results of that study.

Results

Our earlier work on bridged ring cyclic imines[1] revealed that the amino olefins 1 and 3 could be converted in high yield to the cyclic structures 2 and 4, respectively. Addition of 0.2 equiv of butyllithium to a stirred THF solution of 1 or 3 maintained under nitrogen at room temperature rapidly gave 2 or 4, respectively. The mechanism initially considered (Scheme I) involved formation of the amide anion 5 followed by intramolecular nucleophilic addition to the olefin. However, this formulation proved inadequate to explain all of the characteristics of the reaction. For example, successful reactions were always accompanied by a persistent deep bronze color. Exposure of the reaction mixture to air caused the bronze color to fade and the reaction to stop.

In THF dried over molecular sieves, the amount of butyllithium required varied considerably (0.5–1.2 equiv) from run to run. If this solvent was distilled from ben-



(1) B. E. Evans, P. S. Anderson, M. E. Christy, C. D. Colton, D. C. Remy, K. E. Rittle, and E. L. Engelhardt, *J. Org. Chem.*, **44**, 3127 (1979).

(2) March[3] describes the addition of amines to olefins as "...nearly always nucleophilic", noting that "...basic catalysts are sometimes used, so that RN^-H or R_2N^- is the actual nucleophile".

(3) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", 2nd ed., McGraw-Hill, New York, 1977, pp 704–705.

(4) A recent statement of the generally held view is provided by Barton and Ollis:[5] "Nucleophilic addition of ammonia and amines to simple alkenes is difficult but is possible with catalysts at high temperatures and pressures".

(5) D. H. R. Barton and W. D. Ollis, "Comprehensive Organic Chemistry: The Synthesis and Reactions of Organic Compounds", Vol. 2, Pergamon Press, New York, 1979, p 11.

(6) (a) D. C. Remy, P. S. Anderson, M. E. Christy, and B. E. Evans, *J. Org. Chem.*, **43**, 4311 (1978); (b) M. E. Christy, P. S. Anderson, S. F. Britcher, C. D. Colton, B. E. Evans, D. C. Remy, and E. L. Engelhardt, *ibid.*, **44**, 3117 (1979).

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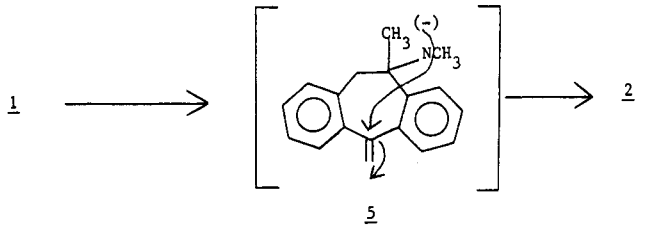
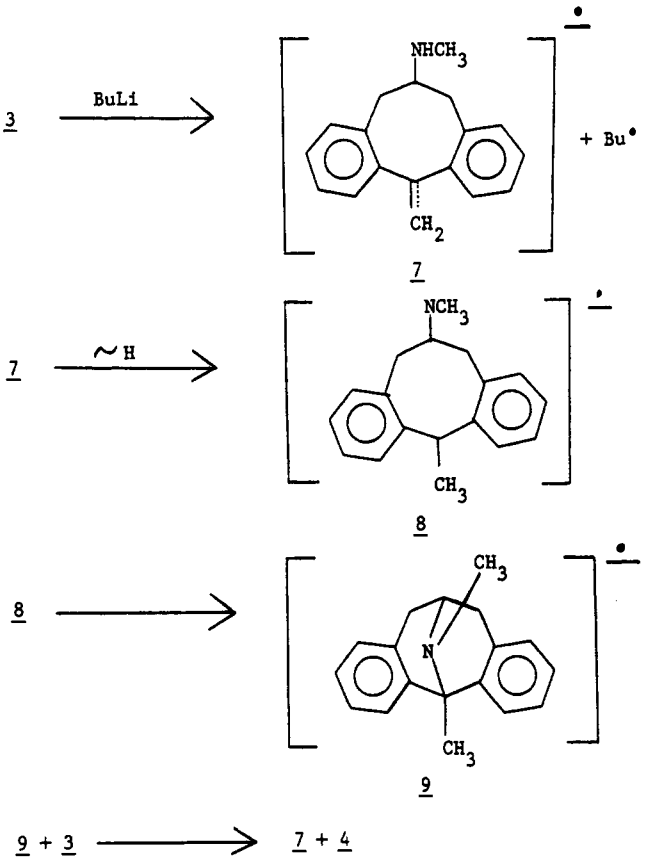
Scheme I



Scheme II



zophenone ketyl, however, the butyllithium requirement was reduced to approximately 0.2 equiv. Substitution of *N*-benzyl, *N*-phenyl, or *N*-hydrogen for *N*-methyl in **3** thwarted the reaction completely.

The deep bronze color of the reaction, the sensitivity to oxygen or other trace impurities, and the effect of changes in N substitutent all appeared inconsistent with the nitrogen anion addition mechanism and suggested instead that a radical process might be involved.[1,7] In agreement with this proposal, the reaction was found to be inhibited by as little as 0.07 equiv of the radical scavengers *p*-(or *m*-)dinitrobenzene.[9] Repeated additions of butyllithium eventually overcame this inhibition, but not until a substantial excess of the organometallic had been added.

Further support for a radical mechanism was provided by an ESR experiment. When the butyllithium-mediated cyclization of **3** to **4** in THF was carried out at −180 °C in the probe of an ESR spectrometer, a strong, broad (~100 G) signal was observed, the intensity of which initially increased and then decreased with time. The signal ($g \approx 2$) was indicative of a radical intermediate present in significant concentration during the reaction.

Additional evidence against the anion mechanism was provided by the failure of the strong base lithium diisopropylamide (LDA) to induce cyclization. While 0.2 equiv of butyllithium brought about complete cyclization of **3** in ca. 15 min, 0.2–1.0 equiv of LDA under identical conditions failed to produce any trace of product after 2 h. Subsequent addition of butyllithium to this reaction mixture caused rapid (<30 min) and complete cyclization. The specific characteristics of butyllithium and not simply those of a strong base appeared to be required for the reaction to occur.

Among the characteristics of butyllithium is the ability to participate in electron-transfer processes by one-electron donation.[10a] Another strong base known to have such one-electron-donating properties is sodium naphthalide.[11] This base was also found to be effective for cyclization of **3** to **4**.

That nitrogen anion formation is not involved in and, in fact, is detrimental to the reaction was suggested by an inverse addition experiment. Here, the amino olefin **3** was added to an excess of butyllithium in THF. In this experiment, in which relatively rapid and complete amide anion formation might be anticipated, cyclization to **4** was minimal. Instead, **3** underwent a relatively slow conversion in good yield to the butyl adduct **6**[12] (Scheme III). The starting amino olefin **3** was still evident (ca. 10%) in the reaction mixture even after 1.5 h. In a corollary experiment, the cyclization product **4** was found to be completely inert to butyllithium under identical conditions, demonstrating that the pentyl compound **6** is not formed by the action of butyllithium on initially generated **4**. Thus, conditions favoring amide anion formation prevent cyclization, leading instead to eventual side reaction.

In the cyclizations of **1** and **3** to **2** and **4**, respectively, there occurs a formal transfer of hydrogen from nitrogen to the bridgehead methyl substituent. The actual fate of hydrogen at these sites has been investigated by using deuterium labeling.

When the butyllithium-mediated cyclization of **3** was quenched in D_2O, no incorporation of deuterium into the resulting **4** was observed. Similarly, when the reaction was carried out in perdeuteriotetrahydrofuran (THF-d_8), no deuterium incorporation into product was seen. Thus, the hydrogen atom added to the exocyclic methylene was not acquired nonspecifically from solvent or workup.

When **3** deuterated on nitrogen was subjected to butyllithium cyclization, however, approximately 90% of the deuterium was transferred specifically to the exocyclic methyl group in the resulting **4**. Thus, **3**, bearing 70% (average) deuterium on nitrogen, provided **4** containing approximately 21% (average) deuterium in the exocyclic methyl group.

Discussion

Taken together, these results indicate that the butyllithium-induced cyclizations of **1** and **3** are not simple

(7) For a brief summary of the properties of free radicals and free radical reactions, see ref 8.

(8) (a) A. R. Forrester, J. M. Hay, and R. H. Thomson, "Organic Chemistry of Stable Free Radicals", Academic Press, New York, 1968, p 7; (b) E. S. Gould, "Mechanism and Structure in Organic Chemistry", Holt, Rinehart, and Winston, New York, 1959, pp 672–695; (c) C. Walling and E. S. Huyser, *Org. React.*, **13**, 94–95 (1963).

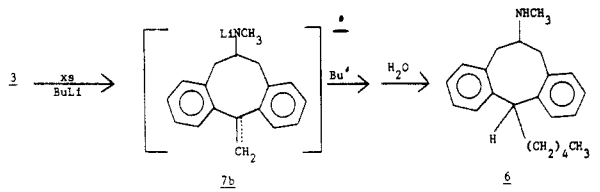
(9) The dinitrobenzenes are efficient electron acceptors and, as such, serve as potent inhibitors of radical reactions. For such uses of dinitrobenzenes, see ref 10.

(10) (a) G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Am. Chem. Soc.*, **86**, 1807 (1964); (b) G. A. Russell and R. K. Norris in "Organic Reactive Intermediates", S. P. McManus, Ed., Academic Press, New York, 1973, p 439.

(11) Reference 10b, pp 435–436.

(12) The adduct **6** is always observed (NMR, TLC) as a minor (~10%) but consistent contaminant in the normal cyclization of **3** to **4**.

Scheme III



additions of an amide anion to an exocyclic olefin. Rather, these reactions appear to be radical processes initiated by electron transfer from butyllithium, with the benzhydryl olefin as a likely initial acceptor. We suggest as a possible mechanism the process shown in Scheme II.[13]

The participation of the amine in a radical mechanism accounts for the sensitivity of the reaction to the nature of the N substituent, for the high retention of deuterium in the labeling studies, and for the formation of side product **6** in the inverse addition experiment.

In the latter experiment, conditions favored formation of an amide anion. In the parlance of Scheme II, intermediate **7** was circumvented, replaced perhaps by the dianion radical **7b**. The key hydrogen transfer step **7** → **8** was thereby precluded, and the stranded radical intermediate (**7b**) underwent instead a slow coupling reaction with butyl radical to give the observed **6** (Scheme III). This competing formation of **7** and **7b** would also explain the presence of a small amount of **6** in the "normal" cyclization of **3** to **4**.[12]

Regardless of the detailed mechanism of this ring closure, it does appear to proceed by an efficient radical reaction in which the amine functionality is involved. Such N-centered reactions of neutral amines under radical conditions are not ordinarily observed. In the photochemistry of amines, for example, addition to olefins is reported to occur exclusively at the α-carbon atom of the amine (C–C bond formation). No N–C bond formation is seen.[14]

While reactions involving amino radicals are known, the requisite radicals are produced not from free amines but from compounds of type N–X (where X = Cl, N=N, etc.) by thermal or photochemical fission. Examples include haloamine cleavage to give synthetically useful protonated amino radicals (the Hofmann–Loeffler reaction)[15] and the thermolysis or photolysis of tetramethyltetrazene to give dimethylamino radical.[16]

The butyllithium-mediated cyclizations **1** → **2** and **3** → **4** described here represent an unusual, perhaps unique example of a synthetically useful radical reaction involving the nitrogen atom of a free amine. The scope and limitations of the reaction have not been investigated extensively. While it seems clear that the benzhydryl olefin and the medium-sized central rings play key roles in this process,[1] it is also possible that alternate conditions (photosensitization, radical initiator promotion, etc.) could extend the scope considerably.[17] It is also evident that at least some of the reported nucleophilic amine to olefin additions catalyzed by such agents as butyllithium, sodium naphthalide, or sodium metal and designated "nucleophilic" might be reconsidered as unrecognized examples of amine radical additions.

Experimental Section

Melting points (Thomas-Hoover melting point apparatus) and boiling points are corrected. Spectra were obtained as follows: IR spectra on a Perkin-Elmer 237 spectrophotometer; mass spectra on an AEI MS902 by direct insertion; ^{1}H NMR spectra on a Varian T-60 or EM 390 spectrometer using $(CH_3)_4Si$ as an internal standard; ESR spectra on a Varian E109-E EPR spectrometer (modulation amplitude 3.2 G). Analytical TLC was carried out on 250-μm, 5 × 20 cm, silica gel GF plates (Analtech, Inc.) by using ultraviolet light and Dragendorff spray for visualization. Unless otherwise specified, dry THF refers to tetrahydrofuran distilled under nitrogen from benzophenone ketyl.

Cyclization of 6-(Methylamino)-12-methylene-5,6,7,12-tetrahydrodibenzo[*a*,*d*]cyclooctene (3) to 12,13-Dimethyl-5,6,7,12-tetrahydrodibenzo[*a*,*d*]cycloocten-6,12-imine (4). (A) With Butyllithium; Effect of *p*-Dinitrobenzene. Two separate suspensions of the hydrochloride salt of **3**[1] (0.25 g, 0.87 mmol) in dry THF (4 mL) were stirred under N_2. To one reaction mixture (I) was added *p*-dinitrobenzene (10 mg, 0.06 mmol, 7 mol % based on **3**·HCl). The other (II) was used as control. Both solutions were treated, dropwise, with *n*-butyllithium in hexane (0.64 mL, 1.5 M, 110 mol % based on **3**·HCl) and stirred for 30 min. Thin-layer chromatography (chloroform shaken with and separated from 50% aqueous ammonia) using **3** and authentic **4**[1] for internal comparison showed **3** to have been converted partially to **4** in the control run II, while **3** remained unchanged in I. Another 0.1 mL (17 mol %, 127 mol % total) of *n*-butyllithium was added dropwise to each reaction mixture. Following an additional 30-min reaction period, TLC assay showed **3** to be still unchanged in reaction I but converted completely to product in reaction II. More *n*-butyllithium (1.0 mL, 171 mol %; 300 mol % total) was added to reaction mixture I. TLC assay after 20 min now showed product **4**[1] and butyl adduct **6** (see below) as the major components of reaction I along with some still unreacted **3**.

Similar results were obtained when *m*-dinitrobenzene was substituted for the para isomer.

(B) With Lithium Diisopropylamide. To a solution of amine **3**[1] (0.25 g, 1.0 mmol) in dry THF (3 mL) under N_2 was added dropwise a solution of lithium diisopropylamide (LDA) prepared from diisopropylamine (0.14 g, 1.4 mmol) and *n*-butyllithium/hexane (0.45 mL, 2.2 M, 0.99 mmol) in dry THF (2 mL). The LDA solution was added in 20% increments. Upon completion of the addition, the mixture was stirred at room temperature. TLC assay after 5 min and again after 2 h revealed only the starting amine **3**. *n*-Butyllithium/hexane (0.45 mL, 2.2 M, 1.0 mmol) was added and the mixture stirred 30 min. TLC assay indicated complete conversion to product **4**.[1]

(C) With Sodium Naphthalide. To a solution of amine **3**[1] (0.19 g, 0.76 mmol) in 2 mL of dry THF stirred at room tem-

(13) A referee has suggested an alternative mechanism in which the initiating step is removal of a hydrogen atom from nitrogen. Attack of the resulting nitrogen radical on the benzhydryl position gives the cyclic system of **4** with an exocyclic methylene radical at position 5. Hydrogen abstraction from another molecule of **3** by this radical provides the observed product **4** and continues the chain. This mechanism is also consistent with the data reported in this paper. Our preference for the mechanism of Scheme II, initiated by one electron transfer to the benzhydryl olefin, stems from two sources: (1) the lack of suitable precedents for amine radical reactions beginning directly from free amines, and (2) our frequent observation of (unwanted) reductions and couplings at the benzhydryl position, apparently radical mediated, on treatment of these and related tricyclic molecules with organometallic reagents (see, for example, formation of **6** above and the several examples noted in ref 6b).

(14) (a) Reference 8c, pp 109–110; (b) W. H. Urry and O. O. Juveland, *J. Am. Chem. Soc.*, **80**, 3322 (1958); (c) W. H. Urry, O. O. Juveland, and F. U. Stacey, *ibid.*, **74**, 6155 (1952).

(15) Reference 3, pp 1068–1069, and references cited therein.

(16) (a) A. Good and J. C. J. Thynne, *J. Chem. Soc. B*, 684 (1967); (b) R. E. Jacobson, K. M. Johnston, and G. H. Williams, *Chem. Ind. (London)*, 157 (1967); (c) D. Mackay and W. A. Waters, *J. Chem. Soc. C*, 813 (1966); (d) B. R. Cowley and W. A. Waters, *ibid.*, 1230 (1961).

(17) It should be noted, however, that several attempts to initiate the cyclization **3** → **4** by photochemical or electrochemical means proved futile. Thus, photolysis of **3** in THF (275-W GE sunlamp, 22 h) with 1-methoxynaphthalene[18] or *p*-dicyanobenzene[18] photosensitizer yielded only unchanged starting material. Attempted one-electron reduction of **3** in DMF at the Hg pool (−2.2 V) afforded two products, neither of which was the cyclic amine **4**.

(18) (a) A. J. Maroulis, Y. Shigematsu, and D. R. Arnold, *J. Am. Chem. Soc.*, **100**, 535 (1978); (b) D. R. Arnold and A. J. Maroulis, *ibid.*, **99**, 7355 (1977); (c) D. R. Arnold and A. J. Maroulis, *ibid.*, **98**, 5931 (1976); (d) R. A. Neunteufel and D. R. Arnold, *ibid.*, **95**, 4080 (1973); (e) Y. Shigematsu and D. R. Arnold, *J. Chem. Soc., Chem. Commun.*, 407 (1975).

perature under N_2 was added dropwise 0.3 mL (0.47 M, 0.14 mmol) of a solution of sodium naphthalide in THF [prepared from 0.115 g (5 mmol) of sodium metal and 0.69 g (5.4 mmol) of naphthalene in 10 mL of dry THF]. After 30 min, TLC assay indicated complete conversion to 4. The mixture was quenched in water, most of the THF removed in vacuo, and the residue extracted with ether (2 × 25 mL). The combined ether fractions were washed with water (1 × 20 mL), dried over K_2CO_3, and filtered, and the solvent was removed in vacuo to give crude 4, the identity of which was confirmed by NMR comparison with authentic 4:[1] ^{1}H NMR ($CDCl_3$) δ 1.9 (s, 3 H, CCH_3), 2.24 (s, 3 H, NCH_3), 2.5 (d, $J \approx 17$ Hz, 2 H, H_{5n} and H_{7n}), 3.17–3.7 (m, 3 H, H_{5x}, H_{7x}, and H_6), 6.80–7.50 (8 H, aromatic), 7.2–7.8 (1 H, ~12% naphthalene, aromatic).

(D) With Butyllithium, Inverse Addition: Formation of 12-*n*-Pentyl-6-(methylamino)-5,6,7,12-tetrahydrodibenzo[*a*,*d*]cyclooctene (6) Hydrochloride. *n*-Butyllithium/hexane (2 mL, 1.5 M) in dry THF (3 mL) was stirred at room temperature under N_2. To the solution was added in portions 0.25 g (0.88 mmol) of 3 hydrochloride.[1] TLC assay indicated conversion to a single, unidentified product was complete after 3 h. The reaction was quenched in water (20 mL) and the resulting mixture extracted with ether (3 × 20 mL). The combined ether extracts were washed with water (1 × 20 mL), dried over K_2CO_3, filtered, and evaporated to dryness in vacuo to give 0.32 g of crude 6. This material was dissolved in acetone, treated with excess ethanolic HCl, and evaporated to dryness in vacuo. The residue was recrystallized from acetone to give 0.05 g (16%) of 6·HCl: mp 219.5–221 °C; ^{1}H NMR ($CDCl_3$) δ 0.7–1.1 (br t, 3 H, $CH_3(CH_2)_4$), 1.15–1.55 (br, 6 H, $(CH_2)_3$), 1.8 (br, $^1/_3$ H, exch by D_2O, 16% H_2O), 2.25 (br m, 2 H, $(CH_2)_3CH_2$), 2.83 (s, 3 H, NCH_3), 2.97–3.95 (m, 5 H, benzylic and CHN), 4.33 (t, J = 7 Hz, 1 H, $HC(CH_2)_4$); mass spectrum, m/e (relative intensity) 307 (25, M^+), 277 (5, $M^+ - CH_3NH$), 276 (26, $M^+ - CH_3NH_2$), 250 (19, $M^+ - CH_3(CH_2)_3$), 236 (6, $M^+ - CH_3(CH_2)_4$), 220 (16), 219 (44), 206 (11), 205 (22), 179 (20), 132 (22), 112 (13), 105 (13), 57 (12), 44 (100), 42 (16), 36 (16).

Anal. Calcd for $C_{22}H_{30}NCl·0.15H_2O$: C, 76.22; H, 8.81; N, 4.04. Found: C, 76.14; H, 8.72; N, 3.86.

12,13-Dimethyl-5,6,7,12-tetrahydrodibenzo[*a*,*d*]cyclooctene-6,12-imine (4), Inert to Butyllithium. To a suspension of 4·HCl[1] (0.25 g, 0.87 mmol) in dry THF (3 mL) stirred at room temperature under N_2 was added dropwise 1.05 mmol of *n*-butyllithium (0.7 mL, 1.5 M). TLC assay after 5 min showed no change in the starting amine 4. Following addition of another 2 mL (3 mmol) of *n*-butyllithium, the mixture was stirred for 2 h. TLC assay showed no change. The mixture was treated carefully with water (2 mL) and the bulk of the THF removed in vacuo. The residue was extracted with ether (3 × 10 mL), and the combined ether fractions were washed with water (10 mL), dried over K_2CO_3, filtered, and evaporated to dryness in vacuo. The resulting oil (0.2 g) proved identical with 4[1] by TLC and by NMR.

Deuterium Labeling Studies. Butyllithium-Mediated Cyclizations of 3 to 4. (A) D_2O Quench. A suspension of 3·HCl[1] (0.25 g, 0.87 mmol) in dry THF (4 mL) was treated with *n*-butyllithium (0.82 mL, 1.5 M) as before and stirred for 2.5 h, at which time TLC assay indicated complete conversion to 4. The mixture was treated with D_2O (1.0 mL) and stirred 15 min, and the THF was removed in vacuo. Workup as described above provided 0.22 g of 4. The NMR was identical with that of authentic 4[1] and showed no reduction in any of the integrated intensities.

(B) In TFH-d_8. To a stirred slurry of 3·HCl[1] (0.25 g, 0.87 mmol), maintained at room temperature under N_2 in THF-d_8 (2 mL, Merck), was added *n*-butyllithium (0.7 mL, 1.5 M). The mixture was stirred 2.5 h, after which TLC assay indicated complete conversion to 4. Workup as above provided 0.22 g of 4. The NMR was identical with that of 4,[1] with undiminished integrated intensities throughout.

(C) With N-Deuterated 3 (3-*d*). A slurry of 3·HCl[1] (1.0 g, 3.5 mmol) in D_2O was treated with 40% NaOH in D_2O (2 mL) and 10 mL of ether and stirred 30 min. The ether layer was separated and stirred 30 min with fresh D_2O. This step was repeated twice. The ether layer was dried over K_2CO_3, filtered, and evaporated to dryness in vacuo. The NMR spectrum of the resulting 3-*d* (0.85 g) was identical with that of authentic 3[1] with the single exception that the broad NH singlet at δ 1.0 was reduced in intensity from 1 H in 3 to ca. 0.4 H in 3-*d* (ca. 0.6 D on amine nitrogen).

A solution of 3-*d* (0.21 g, 0.84 mmol) in dry THF (3 mL) at room temperature under N_2 was treated with 0.16 mL of *n*-butyllithium in hexane (1.5 M) and the mixture stirred for 1 h. TLC indicated complete conversion to 4. The mixture was quenched with water and worked up as above. The resulting 4-*d* was identical with authentic 4[1] by NMR with the single exception of the exocyclic *C*-methyl singlet at δ 1.85 which was reduced in intensity from 3 H in 4 to ca. 2.3 H in 4-*d*. These results indicated that the *C*-methyl group contained ca. 0.7 D (estimated retention of deuterium, ca. 100%). In the mass spectrum of 4-*d*, the monodeuterio molecule $C_{18}H_{18}ND$ was the only significant deuterium-containing species observed.

When 3 (free base; 0.6 g, 2.4 mmol) was deuterated by stirring overnight with DCl in D_2O (15 mL, 0.1 M), basification with anhydrous K_2CO_3 and workup as described above provided 3-*d* containing ca. 0.2 NH (ca. 0.8 ND) by NMR. Cyclization with *n*-butyllithium proceeded as described above to give 4-*d* containing ca. 0.7 D in the exocyclic methyl group (estimated retention, 88%). The mass spectrum again confirmed a monodeuterio compound (m/e 250) as the only significant deuterated molecule present.

On the basis of these data, deuterium retention during butyllithium-mediated cyclization of 3-*d* to 4-*d* was estimated at ≥90%.

Acknowledgment. The authors thank the following people for assistance in recording and interpreting spectral and analytical data: Dr. Byron Arison, Dr. David Cochran, and Mrs. Joan Murphy for NMR spectra; Dr. Robert Egan for ESR spectra; Mr. Robert Rhodes for mass spectra; Mr. K. B. Streeter and Mrs. Jan Stranick for microanalyses. We are also indebted to Professors Robert Stevens, Samuel Danishefsky, and Cal Meyers and to Drs. Raymond Firestone and Hari Ramjit for valuable discussions.

Registry No. 3, 70865-03-1; 3·HCl, 70313-47-2; 3-*d*, 75533-63-0; 4, 70313-49-4; 4·HCl, 70313-48-3; 4-*d*, 75548-47-9; 6, 75533-64-1; 6·HCl, 75533-65-2.