Synthesis of Bridgehead Nitrogen Heterocycles via Cyclization of α-Ammonio 5-Hexenyl Radicals

Ernest W. Della* and Paul A. Smith

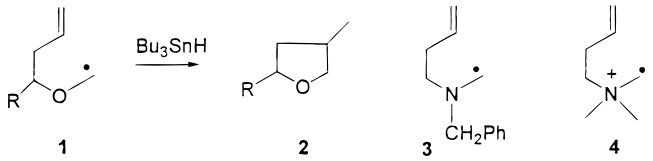
Department of Chemistry, Flinders University, Bedford Park, South Australia 5042, Australia

Received July 13, 1998

Ring-closure of the 2,2-dimethyl-2-azonia-5-hexenyl radical (**4**) proceeds smoothly and efficiently to give the 5-exo isomer essentially quantitatively, in accordance with predictions based on MP4SDTQ/6-31G* ab initio calculations on the thermodynamic stability of α-ammonio radicals. The corresponding 5-hexynyl radical species **15** and its 6-phenyl derivative **19** display similar behavior affording the analogous 5-*exo*-3-methylenepyrrolidinium salts in high yield. In none of these cases were the products of reduction were detected. All of the radical intermediates were generated conveniently by treatment of the iodomethyl and/or phenylselenomethyl salts with tributyltin hydride. Application of this procedure to monocyclic precursors such as 1-methyl-1-iodomethyl-4-methylene-1-azoniacyclohexyl iodide (**31**) provided an attractive entry into quaternary derivatives of the 1-azabicyclo[2.2.1]heptyl system in good yield via a three-step sequence from 1-methylpiperidone. Dequaternization of the bicyclic salts so obtained unexpectedly leads to rupture of one of the rings rather than loss of the *N*-methyl group. The 1-azabicyclo[2.2.1]heptane could be accessed readily via tin hydride-induced cyclization of the corresponding *N*-phenylethylammonium salt **54**, followed by Hofmann elimination with potassium *tert*-butoxide.

Introduction

Substitution of the α-methylene group in the 5-hexenyl radical by a group incorporating a first row heteroatom, in particular O or NR, has been found[1−4] to exert a profound influence on the facility for ring closure of the modified radical relative to the parent species. On one hand, Rawal and associates[1] observed that the oxo radical **1** undergoes smooth *exo-trig* cyclization to give the mixture of diastereomeric tetrahydrofurans **2** in high yield. By contrast, Padwa and associates[4] found that the corresponding 2-aza-2-benzylhexenyl radical **3** failed to cyclize, and only the product of reduction, 2-aza-2-benzyl-5-hexene, was isolated. These observations are consistent with ab initio calculated data[5] on radicals with α-heteroatom substitution, which demonstrate that radical stabilization afforded by the presence of α-nitrogen is significantly greater than that by α-oxygen. The reluctance of the nitrogeneous species **3** compared with the ability of **1** to undergo cyclization, therefore, can be ascribed to a significantly higher activation barrier in the case of the former as a result of its greater thermodynamic stability. Accordingly, despite the fact that 5-hexenyl radical cyclizations have been employed extensively[6] in synthesis, the failure of **3** to ring close seemingly precludes access to nitrogen-based heterocycles via 2-aza 5-hexenyl radicals.



Intuitively, one would anticipate that the stabilizing influence of the lone pair on the nitrogen atom in **3** would be eliminated if the electrons were otherwise involved in bond formation, a premise for which we have provided[7] theoretical support by an ab initio study at the MP4SDTQ/6-31G* level as described by Coolidge and Borden.[5e] Thus, our calculations of the energies associated with the isodesmic reaction depicted in eq 1 predict that, whereas the reaction involving the species with $X = NH_2$ is highly endothermic, in agreement with data obtained by Coolidge and Borden, it becomes significantly exothermic when $X = NH_3^+$. The attachment the of quaternary nitrogen to the electron-deficient center in the ammoniomethyl radical is found to exert such a powerful destabilizing effect

(1) Rawal, V. H.; Singh, S. P.; Dufour, C.; Michoud, C. *J. Org. Chem.* **1993**, *58*, 7718 and references therein.

(2) Journet, M., Malacria, M. *J. Org. Chem.* **1992**, *57*, 3085. Agnel, G.; Malacria, M. *Synthesis* **1989**, 687.

(3) Baban, J. A.; Marti, V. P. J.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1723.

(4) Nimmesgern, H.; Padwa, A.; Wong, G. K. S. *Tetrahedron Lett.* **1985**, *26*, 957. Nimmesgern, H.; Padwa, A.; Wong, G. K. S. *J. Org. Chem.* **1985**, *50*, 5620.

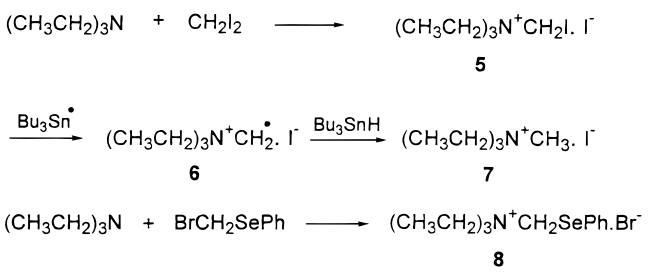
(5) For leading references, see: (a) Brocks, J. J.; Beckhaus, H.-D.; Beckwith, A. L. J.; Rüchardt, C. *J. Org. Chem.* **1998**, *63*, 1935. (b) Jurisic, B. S.; Timberlake, J. W.; Engel, P. S. *Tetrahedron Lett.* **1996**, *37*, 6473. (c) Gauld, J. W.; Radom, L. *J. Phys. Chem.* **1994**, *98*, 777. (d) Bordwell, F. G.; Zhang, X.-M.; Alnajjar, M. S. *J. Am. Chem. Soc.* **1992**, *114*, 7623. (e) Coolidge, M. B.; Borden, W. T. *J. Am. Chem. Soc.* **1988**, *110*, 2298. (f) Pasto, D. J.; Krasnansky, R.; Zercher, C. *J. Org. Chem.* **1987**, *52*, 3062.

(6) (a) Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1996; Vol. 48, p 301, Chapter 2, 1996. (b) For an extensive review on radicals in natural product synthesis, see: Curran, D. P.; Fevig, T. L.; Jasperse, C. P. *Chem. Rev.* **1991**, *91*, 1237. (c) Curran, D. P. *Synlett* **1991**, 63. (d) Radikale, C. In *Methoden der Organischen Chimie*; Regitz, M., Giese, B., Eds.; Houben-Weyl: Stuttgart, 1989; Band E 19a. (e) Curran, D. P. *Synthesis* **1988**, 417 (Part 1), 489 (Part 2). (f) Newman, W. P. *Synthesis* **1987**, 665. (g) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (h) Giese, B. In *Radicals in Organic Synthesis: Formation of Carbon Carbon Bonds*; Baldwin, J. E., Ed.; Pergamon: New York, 1986. (i) Hart, D. J. *Science* **1984**, *223*, 883. (j) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, p 162.

(7) Della, E. W.; Elsey, G. M. Unpublished observations.

10.1021/jo9813538 CCC: $18.00
Published on Web 02/26/1999

Scheme 1



on the species that it possesses considerably higher ground-state energy than either the ethyl or aminoethyl radical. When translated to the 2,2-dimethyl-2-azonia-5-hexenyl radical **4**, these data suggest that the barrier to cyclization of **4** should be lower than that of radical **3**.

$$CH_3CH_3 + XCH_2^{\bullet} \rightarrow CH_3CH_2^{\bullet} + XCH_3 \qquad (1)$$

	calcd[7] ΔH (kcal/mol)
$X = NH_2$	+8.2
$X = NH_3^+$	−6.5

In a recent communication paper,[8] we reported experimental verification of the validity of these predictions and showed that, unlike the neutral radicals **3**, α-ammonio radicals **4** undergo facile ring closure. We now wish to disclose the results of this work in full and to describe additional applications of this transformation as a valuable synthetic strategy. Since our original paper, two reports have appeared[9,10] describing the use of radical cyclization of nitrogenous distonic radicals in synthesis.

Results and Discussion

Generation of α-Ammonio Radicals. Generation of radicals adjacent to a positive nitrogen atom has been described in the literature, and the existence of these so-called distonic radicals has been accepted for more than two decades. Although a number of ESR and molecular orbital studies have been conducted on α-ammonio radicals,[11−14] to our knowledge there was no precedence at the commencement of this investigation for the use of these intermediates in synthetic organic chemistry. Generation of those species above for characterization purposes was generally achieved via hydrogen abstraction by reagents such as the *tert*-butoxy radical, but a more convenient precursor and practical technique for its conversion into the radical were required for the synthetic pathways we had envisaged.

We have shown that the process depicted in Scheme 1 represents a viable method of accessing the type of distonic radical exemplified by **4**. Thus, treatment of a typical tertiary amine, such as triethylamine (or *N*-ethylpiperidine), with diiodomethane leads to the quaternary salt **5**. Exposure of the latter to tributyltin hydride gave the salt **7** in quantitative yield in a process that is presumed to involve the intermediacy and subsequent trapping of the corresponding α-ammonio radical **6** by the reagent. For solubility reasons, reaction of these salts with Bu_3SnH requires a different solvent to the typical hydrocarbon medium generally employed for cyclization reactions of this kind. We discovered[15] that the protic solvent, 2-methyl-2-butanol, obviates the major problem of insolubility and it also possesses the added advantage that its boiling point (105 °C) provides favorable conditions for those cyclizations having a high activation barrier.

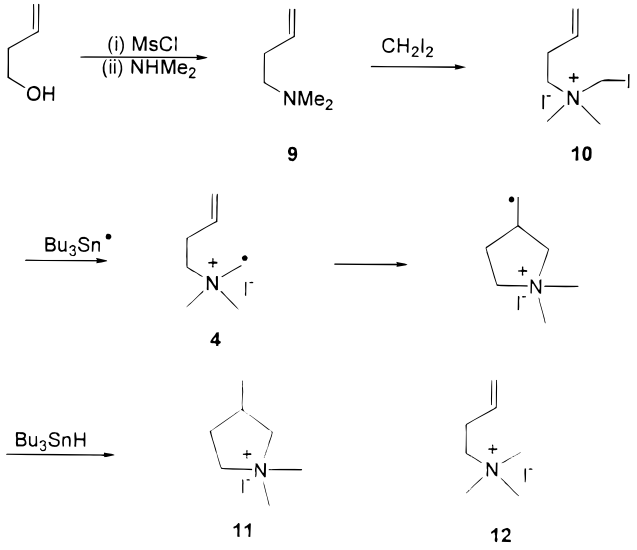
Nevertheless, as described below, some of the iodomethyl salts related to **5** were found to have limited solubility in 2-methyl-2-butanol, which led to poorer yields of product because a significant amount of starting material was always recovered. We have recently observed that the corresponding selenides **8**, obtained in excellent yields from reaction of tertiary amines (R_3N) with bromomethyl phenyl selenide, function as excellent alternatives to the iodides **5** as precursors to the α-ammonio radicals, a factor enhanced by their increased solubility over the iodomethyl salts. It is noteworthy that Beckwith and Pigou[16] report that the reaction of $PhSeCH_2Cl$ with alkoxide ions gives very poor yields of substitution and the predominant product is diphenyldiselenomethane. Formation of $PhSeCH_2SePh$ was attributed to the occurrence of a reaction pathway promoted by the strong basic character of RO^- ions. Clearly, the lower basicity of the amine is a distinct advantage in the synthesis of the selenide salts **8** because the unwanted side reactions that accompany the alkoxide substitutions are suppressed. Thus, the reaction of triethylamine with bromomethyl phenyl selenide gives an 82:18 mixture of **8** to triethylammonium bromide, from which the latter could be removed by chromatography on alumina. Fortunately, such purification was not required in the case of the amines used in this work because they gave the product of substitution only, presumably reflecting their less hindered nature compared with triethylamine.

Cyclization of Acyclic α-Ammonio Radicals

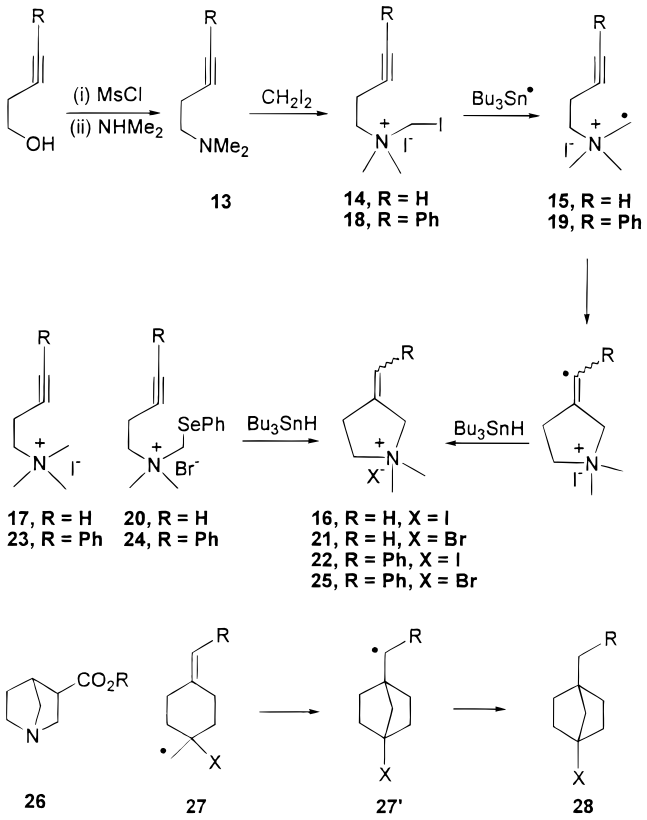
The 2,2-Dimethyl-2-azonia-5-hexenyl Radical. As illustrated in Scheme 2, the salt **10** leading to the ammonio-5-hexenyl radical **4** was synthesized by treatment at room temperature of *N*,*N*-dimethyl-3-butenylamine **9** with excess diiodomethane overnight. Addition of ether to the reaction mixture caused the precipitation of **10** in high yield. A solution of tributyltin hydride (1.1 equiv) and a catalytic quantity of AIBN in 2-methyl-2-butanol was added to a stirred solution (0.025 M) of **10** in 2-methyl-2-butanol held at 80 °C and irradiated with a 300 W incandescent lamp. After 30 min, the mixture was cooled, the solvent evaporated, and the residue washed with ether to remove neutral material. The crude product was assayed by ^1H and ^{13}C NMR analysis and found to consist of essentially pure 1,1,3-trimethylpyrrolidinium iodide **11** (96% yield; 51%, in the overall step sequence from 3-butenol). NMR signals associated with either the reduced product trimethyl-3-butenylammonium iodide **12** or the 6-*endo-trig* product were not

(8) Della, E. W.; Knill, A. M.; Smith, P. A. *J. Chem. Soc., Chem. Commun.*, **1996**, 1637.
(9) Bertrand, M. P.; Gastaldi, S.; Nouguier, R. *Synlett* **1997**, 1420.
(10) Rios, L. A.; Dolbier, W. R.; Paredes, R.; Lusztyk, J.; Ingold, K. U.; Jonsson, M. *J. Am. Chem. Soc.* **1996**, *118*, 11313.
(11) Anderson, N. H.; Norman, R. O. C. *J. Chem. Soc. B* **1971**, 993.
(12) Bonazzola, L.; Iacona, C.; Michaut, J. P.; Roncin, J. *J. Chem. Phys.* **1980**, *73*, 4175.
(13) Bonazzola, L.; LeRay, N.; Ellinger, Y. *Chem. Phys.* **1982**, *73*, 145.
(14) Bouma, W. J.; Dawes, J.; M. Radom, L. *Org. Mass. Spectrom.* **1983**, *18*, 12.
(15) Della, E. W.; Knill, A. M. *J. Org. Chem.* **1996**, *61*, 7529.
(16) Beckwith, A. L. J.; Pigou, P. E. *Aust. J. Chem.* **1986**, *39*, 77.

Scheme 2



Scheme 3



detected under the spectroscopic conditions employed. The structure of the cyclic salt **11** was established by consideration of its NMR spectral properties and by demethylation with DABCO in DMF[17] to give 1,3-dimethyl-1-azacyclopentane; the identity of the latter was established by comparison of its physical properties with those of an authentic specimen.[18] This result contrasts strongly with the observed[4] reluctance of radical **3** toward ring closure and is in accord with the predictions made above of the relative kinetic reactivity of the intermediate ammonio radical **4**.

The 2,2-dimethyl-2-azonia-5-hexynyl radical. One of our principal objectives was to extend this transformation to the synthesis of pyrrolidines containing an exocyclic methylene group in the expectation that these alkenes could be further elaborated into modified 5-hexenyl radical precursors. Accordingly, we investigated the facility for cyclization of the hexynyl radical species **15** and **19**. Access to the required precursors **14** and **18** was achieved from the (substituted) 3-butynol as depicted in Scheme 3.

The behavior of the parent alkyne **14** upon exposure to Bu_3SnH was disappointing, however, largely because it proved to be quite insoluble in hot (80 °C) solvent, and at the boiling point (105 °C) it began to decompose fairly rapidly. Although the target salt **16** was found to be the only detectable product, the optimum yield obtained for the conversion **14**→**16** was only 40% (23% overall from 3-butynol). Despite the fact that this transformation is not very efficient, it served to demonstrate that, aside from solubility problems, the actual cyclization proceeds very well. The intermediate 2-azonia-5-hexynyl radical **15** behaves in the same manner as its olefinic analogue **4** and yields only the 1,5 exo cyclization product; the product of reduction, **17**, was not detected.

More recently, we have observed that the solubility problem associated with these iodides could be circumvented by employing the corresponding α-phenylseleno substituted compound **20**, which proved to be a superior precursor to the radical cation **15**. This occurs principally because the salt **20** is much more soluble than **14** in 2-methyl-2-butanol, and when treated with Bu_3SnH under the standard conditions established it furnished excellent yields of cyclized material **21**, uncontaminated with the product of reduction. Both **20** and the phenyl-substituted derivative **24** were available in excellent yield by treatment of the corresponding amine **13** (R = H/Ph) with $PhSeCH_2Br$. Unlike triethylamine, the alkynylamines **13** gave only substitution product.

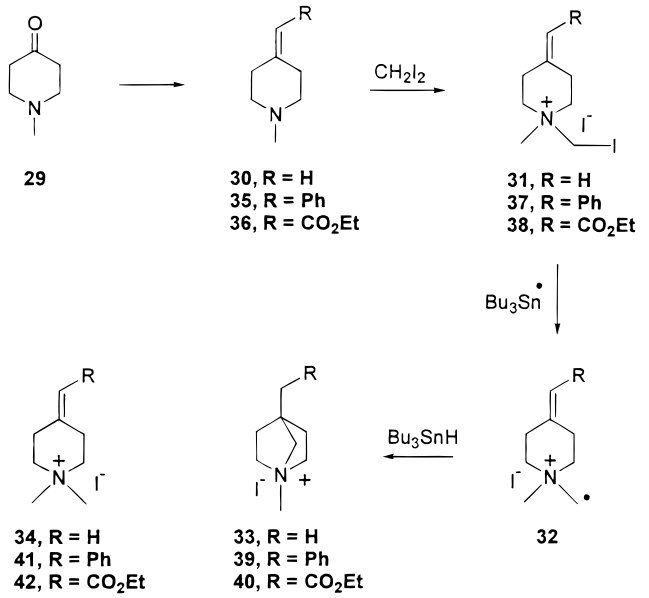
The alkynyl salt **18** was found to be readily soluble in 2-methyl-2-butanol, and when treated with Bu_3SnH at 80 °C, it afforded the target salt **22** smoothly and in high yield as a mixture of diastereomers (88%; 55% from 4-phenyl-3-butynol). Again, neither the product of reduction **23**, nor that arising from 6-*endo*-*trig* ring closure, was detected. The selenide **24** also proved to be an excellent source of cyclized material **25** via the radical **19**.

Synthesis of Bicyclic Heterocycles. Having demonstrated the viability of acyclic α-ammonio radical cyclization as a route to monocyclic heterocycles, we turned our attention to investigating whether this procedure could be extended to the synthesis of bridgehead nitrogen bicyclic heterocycles incorporating the 1-azabicyclo[2.2.1]heptyl system. Our interest in this study was aroused by the knowledge that compounds containing this structure, such as the ester **26**, have been shown[19] to possess powerful physiological properties and their potential in the treatment of conditions involving choline uptake including dementia caused by Alzheimer's

(17) Ho, T. L. *Synthesis*, **1972**, 702.
(18) Hawthorne, D. G.; Johns, S. R.; Willing, R. I. *Aust. J. Chem.* **1976**, *29*, 315.

(19) For leading references, see: Boelsterli, J.; Eggnauer, U.; Pombo-Villar, E.; Weber, H.-P.; Walkinshaw, M.; Gould, R. O. *Helv. Chim. Acta* **1992**, *75*, 507−512 and ref 2a−k cited therein. Cottrell, I. F.; Hands, D.; Kennedy, D. J.; Paul, K. J.; Wright, S. H. B.; Hoogsteen, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1091−1097 and refs 1−3 cited therein.

Scheme 4

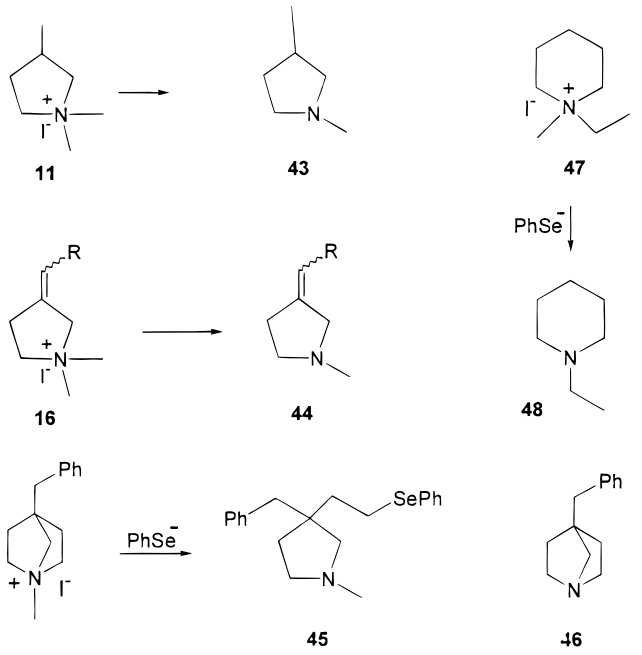


disease has been recognized. A viable entry to heterocyclic compounds such as **26** could reasonably be expected to arise from combining the cyclization of α-ammonio radicals above with the observation[20] that derivatives of the 4-methylenecyclohexylmethyl radical **27** undergo ring closure to bicyclo[2.2.1]heptanes **28**.

The proposed route (Scheme 4) commences with *N*-methylpiperidone (**29**), available commercially or by synthesis from 4-piperidinol,[21] which was smoothly transformed via alkene **30** into the salt **31** as described earlier. Treatment of a solution of the latter in refluxing 2-methyl-2-butanol with Bu_3SnH was performed under more forcing conditions (105 °C) than those employed for the acyclic salts **10**, **14**, and **18**, to assist the more difficult cyclization of the intermediate **32** (R = H). An excellent yield (88%) of the target bicyclic salt **33** was thereby obtained, matching the high-yielding analogous all-carbon isomerization (**27** → **27′**). The identity of the product was established unambiguously by analysis of its ^1H and ^{13}C NMR spectra, careful scrutiny of which confirmed that **33** was obtained uncontaminated by the product of reduction, *N*,*N*-dimethyl-4-methylenepiperidinium iodide **34**. An authentic sample of the latter was prepared in order to facilitate the NMR analyses.

Encouraged by the efficiency with which the ammonio radical **32** underwent cyclization, we sought to extend the technique to allow introduction of more useful functionality at the carbon bridgehead. This could be achieved by the simple expedient of selecting the appropriate Wittig reagent for reaction with *N*-methylpiperidone, and in this work, we chose to synthesize the alkenes **35** and **36** (Scheme 4). Treatment of the derived salts, **37** and **38**, with Bu_3SnH led to the formation of the 4-substituted 1-azonia-1,1-dimethylbicyclo[2.2.1]-heptane iodides **39** and **40** in excellent yields. The isomeric products of reduction, **41** and **42**, were not detected. In practice, the high solubility of the ester **38** in 2-methyl-2-butanol allowed the reaction to be performed at 80 °C, a desirable feature whenever possible because, as noted above, some of these salts show perceptible decomposition at higher temperatures. Although the phenyl-substituted compound **37** proved to be rather less soluble than the ester **38** and it was therefore necessary to maintain the temperature of the reaction at reflux, the conditions were found not to be deterimental in this case.

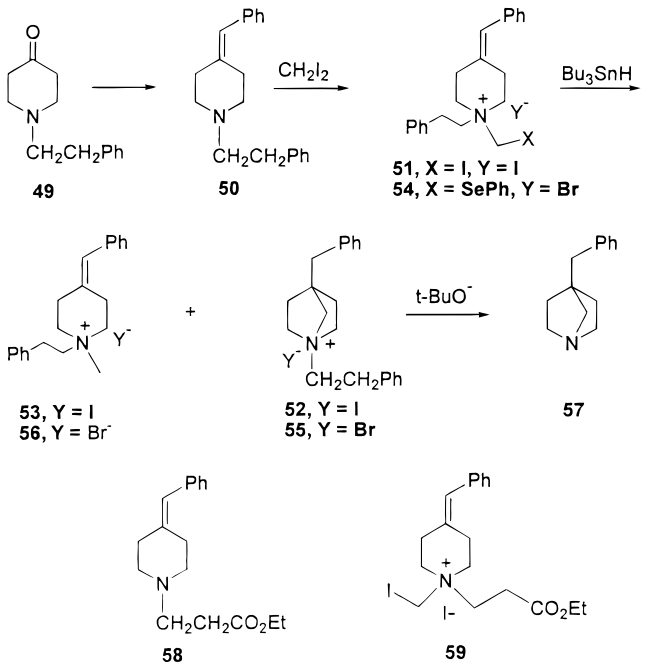
Dequaternization of the Derived Bicyclic Heterocyclic Salts. Ultimately, our objective was to synthesize the parent amines as well as their quaternary salts, and it was therefore essential to be able to demethylate the bicyclic salts so obtained. A number of procedures have been devised for the generation of free amines from quaternary ammonium salts, and reagents such as 1,4-diazobicyclo[2.2.2]octane (DABCO),[17] triphenylphosphine,[22] and the phenylselenide[23] and phenylthio[24] anions have been shown to be very effective, particularly in those cases where demethylation is involved. In view of its simplicity, dequaternization with DABCO/DMF was attempted on several of the heterocyclic salts, viz., **11**, **16**, **33**, and **39** prepared in this work. Under typical conditions,[17] both the monocyclic salts **11** and **16** were converted readily and in good yield into the corresponding amines **43** and **44**. However, DABCO proved to be ineffective for the demethylation of the bicyclic salts **33** and **39**, both of which were recovered unchanged under the most forcing conditions practicable.



We decided, therefore, to use the more powerfully nucleophilic phenyselenide anion. A solution of this reagent in HMPA, generated conveniently by treatment of phenylselenol with 1 equiv of sodium hydride, was treated with a solution of the salt **39** in a small quantity of DMSO and the mixture then heated at 100 °C for 4 h. Under these conditions, dequaternization was found to be effective, but surprisingly, the product consisted entirely of ring opened material **45**; the 1-azabicyclo-

(20) Della, E. W.; Knill, A. M. *Aust. J. Chem.* **1994**, *47*, 1833.
(21) McElvain, S. M.; McMahon, R. E. *J. Org. Chem.* **1949**, *14*, 1.
(22) Pietraszkiewicz, M.; Salanski, P.; Jurczak, J. *J. Chem. Soc. Chem. Commun.* **1983**, 1184.
(23) (a) Reich, H. J.; Cohen, M. L. *J. Org. Chem.* **1979**, *44*, 3148. (b) Simanek, V.; Klasek, A. *Tetrahedron Lett.* **1969**, *35*, 3039.
(24) (a) Shamma, M.; Deno, N. C.; Remar, J. F. *Tetrahedron Lett.* **1966**, 1375. (b) Kametani, T., Kigasawa, K.; Hiiragi, M.; Wagatsuma, N.; Wakisaka, K. *Tetrahedron Lett.* **1969**, 635.

Scheme 5



[2.2.1]heptane **46** was not detected by NMR spectral analysis. This result was unexpected because we had observed that similar treatment of the piperidinium salt **47** affords *N*-ethylpiperidine **48** exclusively, demonstrating in this case that demethylation is the preferred course of reaction and that the ring remains intact.

We believe that N−C2 rather than N−CH_3 bond fission in **39** occurs as a consequence of two factors; one, that the increased s character of the nitrogen exocyclic orbital used to bond nitrogen to the methyl carbon is associated with an enhanced N−CH_3 bond strength, which in turn leads to an increase in the activation barrier for substitution at the methyl carbon. Second, nucleophilic substitution at the ring carbon is facilitated because this process is associated with relief of strain, a feature that presumably shows up in the transition state for reaction. Evidently, the combined effect of these factors is sufficient to ensure that nucleophilic attack at the methylene carbon (C2) is favored.

Failure to demethylate the bicyclic salt **39** has important ramifications because, if ultimately unsuccessful, it necessitates the use of a much less convenient N-alkyl substituent than methyl. The benzyl group is an attractive alternative because it can be removed readily by hydrogenolysis with Pd/C. However, we were discouraged from using it since attempts to iodomethylate *N*-benzylpiperidine gave a complex mixture of unidentified products. To circumvent this problem, we chose to carry out the sequence of reactions depicted in Scheme 5, commencing with commercially available *N*-phenylethylpiperidone **49**. This was converted via the alkene **50** into the salt **51**, treatment of which with Bu_3SnH afforded cyclized material **52**, which was contaminated with a significant amount (12%) of the reduced product **53**. A major difficulty associated with the iodide **51** is its poor solubility in 2-methyl-2-butanol, and the formation of **53** was ascribed to the effect of the reduced solubility of starting material and the consequence difficulty of maintaining the chain. Although the isomeric mixture of products **52** and **53** could be separated readily by chromatography on alumina, this represents an unacceptable complication in the synthetic procedure. Use of the corresponding selenide **54**, which was prepared by treatment of the amine **50** with $PhSeCH_2Br$ as discussed above, proved to be more successful. The salt **54** had a much improved solubility in the reaction medium, and subsequent treatment with tributyltin hydride afforded the bicyclic salt **55** in excellent yield and, importantly, without contamination by reduced product **56**.

When Hofmann elimination of the bicyclic heterocyclic salt **55** was attempted using potassium *tert*-butoxide, styrene was obtained accompanied by the amine **57**. It was found necessary to use *t*-BuOK as reagent over the commonly used base diisopropylethylamine (DIEA)[25] because, although DIEA promotes smooth Hofmann elimination in β-ammonio substituted esters, it was found to be ineffective in the case of the salt **55**. In view of the ease of preparation of the corresponding β-amino esters **58** via Michael addition, we had considered employing the corresponding salts **59**, incorporating the carbethoxyethyl instead of the phenylethyl substituent, as precursors to the radicals. Another advantage is that the derived bicyclic esters can be converted readily into the parent amines by DIEA. In practice, however, this did not represent a viable alternative, because it has been shown[25a] that β-*N*-carbethoxyethylammonium halide salts are very labile under the kind of conditions required in this work to promote the cyclization reactions.

Experimental Section

Preparation of the *N*-Iodomethyl Quaternary Ammonium Salts. Two general procedures were used for preparation of *N*-iodomethyl quaternary ammonium salts. Both methods gave high yields, although method B is usually quicker and better yielding. All salts were purified by recrystallization prior to cyclization.

Method A. The precursor amine was stirred with diiodomethane (3−5 equiv) for periods of up to 1 week, depending on the reactivity of the amine. The reaction progress was followed by NMR. The salt was isolated either by stirring the reaction mixture with dry diethyl ether or by dissolving it in methanol or acetone prior to adding ether.

Method B. The precursor amine was stirred with diiodomethane (3−5 equiv) in refluxing dry diethyl ether until no more solid appeared (ca. 3 days). Stirring the cooled mixture with excess dry ether afforded complete precipitation of the salt.

Preparation of Phenylselenomethyl Quaternary Precursors. The amine was dissolved in acetonitrile (1 g/5 mL) and stirred with bromomethyl phenylselenide (1.2 equiv) overnight, after which the solvent was removed and the product washed with ether and recrystallized.

Preparation of Authentic Samples of the Products of Bu_3SnH Reduction of the *N*-Iodomethyl Quaternary Ammonium Salts. These compounds were prepared by stirring the precursor amine with iodomethane (1.5 equiv) in ether (10 mL/g of amine) for 1 h. The reaction mixture was washed with excess diethyl ether and then filtered to give an essentially quantitative yield of the salts. Purification of the latter was effected by recrystallization.

Iodomethyltriethylammonium Iodide (5). Triethylamine (0.27 g, 2.7 mmol) was treated with diiodomethane (method A). The product was recrystallized from ethanol/ether to give iodomethyltriethylammonium iodide (**5**) as off-white crystals (0.92 g, 92%): mp 174−176 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 5.12 (s, 2H), 3.52 (q, J = 7.2 Hz, 6H), 1.39 (t, J =

(25) (a) Brown, A. R.; Rees, D. C.; Rankovic, Z.; Morphy, J. R. *J. Am. Chem. Soc.* **1997**, *119*, 3288. (b) Ouyang, X.; Armstrong, R. W.; Murphy, M. M. *J. Org. Chem.* **1998**, *63*, 1027.

7.2 Hz, 9H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 54.6, 27.5, 8.1. Anal. Calcd for $C_7H_{17}NI_2$: C, 22.78, H, 4.64, N, 3.8. Found: C, 23.26, H, 4.66, N, 3.76.

Methyltriethylammonium Iodide (7). A 0.025 M solution of iodomethyltriethylammonium iodide (**5**) (0.30 g, 0.81 mmol) in 2-methyl-2-butanol was deoxygenated and then brought to 100 °C using a tungsten lamp before a solution of tributyltin hydride (0.28 g, 0.98 mmol) in 2-methyl-2-butanol (1 mL) containing a catalytic amount of AIBN was added at once. The reaction mixture was refluxed under irradiation for 15 min, when the solution had clarified, after which an additional catalytic amount of AIBN in 2-methyl-2-butanol (1 mL) was added and the mixture heated for a further 10 min. The solvent was removed, and the resulting white solid was washed with dry diethyl ether (3 × 5 mL). The product (**7**) (0.19 g, 96%), mp 298−298 °C, had identical mp and ^{1}H and ^{13}C NMR spectra with those of an authentic sample prepared as described in the general procedure.

Phenylselenomethyltriethylammonium Bromide (8). Phenylselenomethyltriethylammonium bromide (**8**) was prepared from triethylamine (60 mg, 0.56 mmol) by the general procedure. The product was shown (^{1}H and ^{13}C NMR) to consist of an 82:18 mixture of **8** and triethylammonium bromide. Chromatography (alumina, 10% methanol/dichloromethane) gave title compound **8** (0.14 g, 70%) isolated as hygroscopic white crystals: ^{1}H NMR ($CDCl_3$) δ 7.77−7.8 (m, 2H), 7.37−7.4 (m, 3H), 5.12 (s, 2H), 3.58 (q, J = 7.2 Hz, 6H), 1.18 (t, J = 7.2 Hz, 9H); ^{13}C NMR ($CDCl_3$) δ 134.8, 129.9, 129.5, 126.4, 58.1, 53.2, 7.8.

Methyltriethylammonium Bromide. A 0.025 M solution of phenylselenomethyltriethylammonium bromide (**8**) (0.20 g, 0.56 mmol) in 2-methyl-2-butanol was deoxygenated and then treated as described above with a solution of tributyltin hydride (0.20 g, 0.67 mmol) and a catalytic amount of AIBN in 2-methyl-2-butanol (1 mL). Workup gave a crystalline product (0.1 g, 94%) that had mp and ^{1}H and ^{13}C NMR spectra identical to that reported for methyltriethylammonium bromide.

2-Methyl-2-aza-5-hexene (9). 3-Buten-1-ol[26] was converted into the corresponding mesylate by reaction with mesyl chloride as described.[27] Without further purification, the mesylate (2.0 g, 14 mmol) was stirred with 33% dimethylamine in ethanol (18.0 g, 135 mmol) overnight. The reaction mixture was dissolved in dichloromethane (250 mL) and the solution washed with saturated NaCl solution (2 × 100 mL), dried (Na_2SO_4), and evaporated to give the title compound **9** as an amber oil. Distillation afforded the pure amine (1.13 g, 86%), which had a bp (86 °C (760 mm)) identical with that reported.[28]

1-Iodo-2,2-dimethyl-2-azonia-5-hexenyl Iodide (10). Treatment of 2-methyl-2-aza-5-hexene (**9**) (0.5 g, 5 mmol) as described in method A and recrystallization of the crude product from methanol/2-methyl-2-butanol gave the salt **10** as fine yellow needles (1.25 g, 68%): mp 144−146 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 5.77 (m, 1H), 5.28 (s, 2H), 5.2 (m, 2H), 3.52 (m, 2H), 3.22 (s, 6H), 2.53 (m, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 130.3, 116.8, 61.3, 49.5, 31.4, 24.9. Anal. Calcd for $C_7H_{15}NI_2$: C, 22.91; H, 4.12; N, 3.82. Found: C, 23.01; H, 4.15; N, 3.71.

1,1,3-Trimethyl-1-azoniacyclopentyl Iodide (11). A 0.025 M solution of 1-iodo-2,2-dimethyl-2-azonia-5-hexenyl iodide (**10**) (0.20 g, 0.55 mmol) in 2-methyl-2-butanol was deoxygenated before being heated to 60 °C using a tungsten lamp and then treated with a solution of tributyltin hydride (0.30 g, 1.0 mmol) in 2-methyl-2-butanol (1 mL) containing a catalytic amount of AIBN. The reaction mixture was heated with irradiation for 15 min and a further catalytic amount of AIBN added with 2-methyl-2-butanol (1 mL) and heated with irradiation for a further 10 min. The solvent was evaporated, and the resulting white solid was washed with dry ether (3 × 5 mL) to yield the iodide **11** as white crystals (0.13 g, 96%): mp 180−182 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 3.65 (m, 1H), 3.52 (m, 2H), 3.16 (s, 3H), 3.06 (s, 3H), 3.06 (m, 1H), 2.6 (m, 1H) 2.3 (m, 1H), 1.7 (m, 1H), 1.08 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 70.87, 65.1, 52.7, 51.6, 30.4, 30.2, 17.7. These data were in agreement with literature values.[15]

2,2-Dimethyl-2-azonia-5-hexenyl Iodide (12). This salt was prepared from 2-methyl-2-aza-5-hexene (**9**) as described and crystallized from 2-methyl-2-butanol: mp 239−240 °C; ^{1}H NMR (DMSO-d_6) δ 5.75 (m, 1H), 5.2 (m, 2H), 3.4 (m, 2H), 3.1 (s, 9H), 2.5 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 132.9, 118.2, 63.8, 52.2, 26.6.

2-Methyl-2-aza-5-hexyne (13, R = H). 3-Butyn-1-ol (2.0 g, 28 mmol) was converted[27] into its mesylate, which, without purification, was stirred with 33% dimethylamine in ethanol (18.0 g, 135 mmol) overnight. Dichloromethane (250 mL) was added to the reaction mixture and the solution washed with saturated NaCl solution (2 × 100 mL) and then dried (Na_2SO_4). Evaporation of the solvent and distillation of the residue afforded the amine **13** (R = H) (1.1 g, 82%) with bp (107 °C (760 mm)) identical to that reported:[29] ^{1}H NMR ($CDCl_3$) δ 2.5 (t, J = 7.0 Hz, 2H), 2.36 (m, 2H), 2.27, (s, 6H), 1.99 (t, J = 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 82.7, 68.9, 58.1, 45.2, 17.4.

1-Iodo-2,2-dimethyl-2-azonia-5-hexynyl Iodide (14). This compound was prepared according to method A from 2-methyl-2-azahex-5-yne **13** (R = H) (1.0 g, 10 mmol) and crystallized from methanol/2-methyl-2-butanol as fine orange needles (2.89 g, 77%): mp 150−152 °C; ^{1}H NMR (DMSO-d_6) δ 5.2 (s, 2H), 3.2 (s, 6H), 3.65 (t, J = 6.3 Hz, 2H), 2.8 (m, 2H), 3.15 (t, J = 2.1 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 78.9, 74.2, 61.9, 51.3, 33.6, 13.3. Anal. Calcd for $C_7H_{13}NI_2$: C, 23.04**;** H, 3.59; N, 3.84. Found: C, 23.05; H, 3.5; N, 3.81.

1,1-Dimethyl-3-methylene-1-azoniacyclopentyl Iodide (16). A 0.01 M solution of 1-iodo-2,2-dimethyl-2-azonia-5-hexynyl iodide (**14**) (0.30 g, 0.82 mmol) in 2-methyl-2-butanol was deoxygenated and treated at reflux with a solution of tributyltin hydride (0.29 g, 0.98 mmol) and AIBN in 2-methyl-2-butanol (1 mL) as described above to yield fine, colorless crystals (80 mg, 40%) of the salt (**16**). Crystallized from ethanol/ether as fine, colorless crystals: mp 176−178 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 5.35 (d, J = 19.8 Hz, 2H), 4.35 (s, 2H), 3.95 (t, J = 7.8 Hz, 2H), 3.35 (s, 6H), 2.95 (t, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 138.6, 112.1, 68.9, 64.3, 50.8, 27.3. Anal. Calcd for $C_7H_{14}NI$: C, 35.16; H, 5.90; N, 5.86. Found: C, 35.22; H, 5.73; N, 5.91.

Note: Spectral analysis of the solution of 1-iodo-2,2-dimethyl-2-azonia-5-hexynyl iodide (**14**) after being heated to reflux in 2-methyl-2-butanol in the absence of tributyltin hydride showed that extensive decomposition had occurred.

2,2-Dimethyl-2-azonia-5-hexynyl Iodide (17). This salt, prepared from **13** (R = H) as described in the general procedure above, crystallized from ethanol as white needles: mp 218−220 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 3.49 (t, J = 7 Hz, 2H), 3.09 (s, 9H), 2.99 (dt, J = 2.7 Hz, 6.9 Hz, 2H), 2.73 (t, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 79.8, 74.3, 63.4, 53.0, 13.6.

2-Methyl-6-phenyl-2-aza-5-hexyne (13, R = Ph). 4-Phenylbut-3-ynol[30] (2 g, 13.7 mmol) was converted into the corresponding mesylate as described[27] and the ester (2.93 g, 13 mmol) stirred with 33% dimethylamine in ethanol (17.6 g, 130 mmol) overnight. The mixture was worked up as above and the product distilled to give the amine **13** (R = H) (2.16 g, 96%): bp 148 °C (15 mm); ^{1}H NMR ($CDCl_3$) δ 7.2−7.4 (m, 5H), 2.52 (s, 4H), 2.23 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 131.4, 128.0, 127.5, 123.7, 88.2, 81.0, 58.3, 45.1,18.2; HRMS calcd for $C_{12}H_{15}N$ 173.1204, found 173.1198.

1-Iodo-2,2-dimethyl-6-phenyl-2-azonia-5-hexynyl Iodide (18). 2-Methyl-6-phenyl-2-aza-5-hexyne (**13** R = H) (1.0 g, 5.8 mmol) was transformed into 1-iodo-2,2-dimethyl-6-phenyl-2-azonia-5-hexynyl iodide (**18**) via method A. The salt

(26) Kinnel, R. B.; Molloy, B. B.; Graham, D. W.; Harding, K. E. *Org. Prep. Proced. Int.* **1972**, *4*, 27.
(27) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.
(28) Clark, R. J. H.; Stockwell, J. A. *J. Chem. Soc., Dalton Trans.* **1975**, 468.
(29) Campbell, K. N.; Fatora, F. C.; Campbell, B. K. *J. Org. Chem.* **1952**, *17*, 1141.
(30) Collins, C. J.; Hanack, M.; Stutz, H.; Auchter, G.; Schoberth W. *J. Org. Chem.* **1983**, *48*, 5265.

crystallized from methanol as fine orange needles (1.76 g, 69%): mp 139−140 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 7.4 (m, 5H), 5.55 (s, 2H), 3.95 (t, J = 6.6 Hz, 2H), 3.42 (s, 6H), 3.1 (t, J = 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 129.3, 126.6, 126.4, 120.2, 82.3, 81.0, 60.4, 49.7, 32.9, 12.8. Anal. Calcd for $C_{13}H_{17}NI_2$: C, 35.39; H, 3.88; N, 3.17. Found: C, 35.31; H, 3.95; N, 3.17.

2,2-Dimethyl-1-phenyseleno-2-azonia-5-hexynyl Bromide (20). 2-Methyl-2-aza-5-hexyne (**13**, R = H) (0.1 g, 1 mmol) was treated with $PhSeCH_2Br$ as in the general procedure above to yield 1-phenylseleno-2,2-dimethyl-2-azonia-5-hexynyl bromide (**20**), which crystallized from ethanol/ether as white crystals (0.3 g, 87%): mp 120−121 °C; ^{1}H NMR ($CDCl_3$) δ 7.74−7.77 (m, 2H), 7.36−7.39 (m, 3H), 5.59 (s, 2H), 3.93 (t, J = 6.9 Hz, 2H), 3.46 (s, 6H), 2.72 (dt, J = 2.7 Hz, 6.9 Hz, 2H), 2.17 (t, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 133.9, 130.4, 129.4, 127.1, 78.1, 73.1, 64.8, 61.4, 51.2, 14.3. Anal. Calcd for $C_{13}H_{18}NSeBr$: C, 44.98, H, 5.23, N, 4.03. Found: C, 45.08, H, 5.35, N, 4.07.

1,1-Dimethyl-3-methylene-1-azoniacyclopentyl Bromide (21). A 0.025 M solution of 2,2-dimethyl-1-phenylselenomethyl-2-azonia-5-hexynyl bromide (**20**) (0.65 g, 1.9 mmol) in 2-methyl-2-butanol was deoxygenated. The stirred solution was heated to 100 °C using a tungsten lamp, and tributyltin hydride (0.65 g, 2.3 mmol) in 2-methyl-2-butanol (1 mL) containing a catalytic amount of AIBN was added over 5 min. The reaction mixture was heated for 10 min, and then a further catalytic amount of AIBN was added and the mixture stirred for a further 30 min. The solvent was removed, and the resulting solid was washed with diethyl ether several times to furnish the title compound **21** as fine hygroscopic white crystals (0.33 g, 92%): ^{1}H NMR ($CDCl_3$) δ 5.3 (d, J = 23.7 Hz, 2H), 4.34 (s, 2H), 3.94 (t, J = 7.8 Hz, 2H), 3.34 (s, 6H), 2.91 (t, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 138.8, 112.3, 68.9, 64.3, 50.8, 27.7.

1,1-Dimethyl-3-phenylmethylene-1-azoniacyclopentyl Iodide (22). A 0.025 M solution of 1-iodo-2,2-dimethyl-6-phenyl-2-azonia-5-hexynyl iodide (**18**) (0.23 g, 0.52 mmol) in 2-methyl-2-butanol was deoxygenated and then heated to 80 °C using a tungsten lamp before being treated with tributyltin hydride (0.23 g, 0.78 mmol) as described above. After 15 min the reaction mixture was worked up to yield fine white crystals (0.14 g, 88%) shown by NMR analysis to be a mixture of the two diastereomers of the title compound **22**: mp 198−200 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 7.2−7.37 (m, 5H), 6.68 (s, 1H), 4.65 (s, 1H), 4.48 (s, 1H), 3.94 (t, J = 7.2 Hz, 1H), 3.84 (t, J = 7.2 Hz, 1H), 3.23 (d, J = 9 Hz, 6H), 3.1 (m, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 133.9, 133.7, 129.8, 129.7, 126.6, 126.5, 126.3, 126.0, 125.5, 125.4, 124.7, 123.6, 68.4, 65.4, 62.7, 61.0, 49.2, 48.7, 27.7, 25.2. Anal. Calcd for $C_{13}H_{18}NI$: C, 49.54; H, 5.76; N, 4.44. Found: C, 49.60; H, 5.65; N, 4.46.

2,2-Dimethyl-6-phenyl-2-azonia-5-hexynyl Iodide (23). This substance, prepared according to the general procedure from **13** (R = H), crystallized from ethanol/ether as colorless crystals: mp 218−220 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 7.35−7.45 (m, 5H), 3.85 (t, J = 7.2 Hz, 2H), 3.40 (s, 9H), 3.10 (t, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 130.3, 127.5, 127.3, 121.2, 82.8, 82.4, 62.9, 52.2, 13.7.

2,2-Dimethyl-6-phenyl-1-phenylseleno-2-azonia-5-hexynyl Bromide (24). Treatment of 2-methyl-6-phenyl-2-aza-5-hexyne (**13**, R = H) (0.23 g, 1.3 mmol) with $PhSeCH_2Br$ according to the general procedure above and recrystallization of the product from ethanol/ether afforded 1-phenylseleno-2,2-dimethyl-6-phenyl-2-azonia-5-hexynyl bromide (**24**) as white crystals (0.51 g, 90%): mp 86−88 °C: ^{1}H NMR ($CDCl_3$) δ 7.72−7.74 (m, 2H), 7.28−7.35 (m, 8H), 5.64 (s, 2H), 3.98 (t, J = 6.6 Hz, 2H), 3.51 (s, 6H), 2.93 (t, J = 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 133.9, 131.7, 130.3, 129.3, 128.7, 128.5, 127.1, 122.2, 84.5, 83.2, 64.6, 61.5, 51.3, 15.2. Anal. Calcd for $C_{19}H_{22}NSeBr\cdot H_2O$: C, 51.72, H, 5.48, N, 3.17. Found: C, 51.48, H, 5.37, N, 3.17.

1,1-Dimethyl-3-phenylmethylene-1-azoniacyclopentyl Bromide (25). A 0.025 M solution of 2,2-dimethyl-6-phenyl-1-phenylselenomethyl-2-azonia-5-hexynyl bromide (**24**) (0.20 g, 0.48 mmol) in 2-methyl-2-butanol was deoxygenated and then treated with a solution of tributyltin hydride (0.16 g, 0.56 mmol) and AIBN (cat.) as described above. Workup yielded fine hygroscopic white crystals (0.11 g, 89%) of **25**, the ^{1}H and ^{13}C NMR spectral data of which corresponded with those of the iodo analogue **22** synthesized previously. When **25** was dissolved in DMSO-d_6, the ^{13}C NMR signals for the two diastereomers were now separated: ^{1}H NMR ($CDCl_3$) δ 7.18−7.45 (m, 5H), 6.66 (s, 1H), 4.67 (s, 2H), 4.18 (t, J = 7.2 Hz, 2H), 3.51 (s, 6H), 3.11 (t, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 135.5, 130.0, 128.8, 128.7, 128.5, 128.1, 128.0, 127.6, 71.2, 68.2, 65.3, 63.5, 51.8, 51.3, 29.5, 27.0.

1-Methyl-4-methylene-1-azacyclohexane (30). A solution of 1.5 M butyllithium in hexane (7.0 mL, 11 mmol) was added dropwise to a stirred mixture of methyltriphenylphosphonium iodide (4.5 g, 11 mmol) in dry ether (55 mL) at room temperature. The mixture was allowed to stir for 2 h, after which a solution of 1-methyl-4-piperidone (**29**) (1.0 g, 8.9 mmol) in dry ether (45 mL) was added dropwise and the mixture was allowed to stir for a further 2 h. Triphenylphosphine oxide was removed by vacuum filtration and the volume of the filtrate reduced to 50 mL and then washed with H_2O (2 × 50 mL) and extracted with 5% HCl (2 × 50 mL). The aqueous layer was washed with ether (25 mL) and then basified (pH10) with 3 M NaOH before being extracted with dichloromethane (2 × 50 mL). The organic extracts were washed with H_2O (50 mL) and then dried (Na_2SO_4), and the solvent was evaporated to yield the amine **30** (0.51 g, 51%), which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 4.63 (s, 2H), 2.65 (m, 4H), 2.5 (m, 4H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.5, 107.7, 56.8, 45.8, 34.3; HRMS calcd for $C_7H_{13}N$ 111.1048, found 111.1041.

1-Iodomethyl-1-methyl-4-methylene-1-azoniacyclohexyl Iodide (31). 1-Methyl-4-methylene-1-azacyclohexane (**30**) (0.50 g, 4.5 mmol) was treated according to the conditions specified in method A to give the salt **31** (1.23 g, 72%) as fine white crystals from methanol: mp 178−179 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 5.35 (s, 2H), 4.95 (s, 2H), 3.2−3.4 (m, 7H), 2.45 (m, 4H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 136.26, 110.29, 59.44, 47.47, 30.99, 25.98. Anal. Calcd for $C_8H_{15}NI_2$: C, 25.35, H, 3.99, N, 3.69. Found: C, 25.29, H, 3.83, N, 3.63.

1,4-Dimethyl-1-azoniabicyclo[2.2.1]heptyl Iodide (33). A solution of 1-iodomethyl-1-methyl-4-methylene-1-azoniacyclohexyl iodide (**31**) (0.20 g, 0.53 mmol) in 2-methyl-2-butanol was deoxygenated and then heated to 90 °C with a tungsten lamp before being treated with Bu_3SnH (0.30 g, 0.53 mmol) as described above. Workup yielded the bicyclic salt **33** as hygroscopic orange crystals (0.12 g, 88%): mp 178−180 °C; ^{1}H NMR ($CDCl_3$/acetone-d_6) δ 4.05 (m, 4H), 3.72 (s, 2H), 3.51 (s, 3H), 2.15 (m, 4H), 1.4 (s, 3H); ^{13}C NMR ($CDCl_3$/acetone-d_6) δ 70.4, 62.5, 44.0, 43.6, 34.1, 15.4.

1,1-Dimethyl-4-methylene-1-azoniacyclopentyl Iodide (34). The product obtained from reaction of the amine **30** with iodomethane as described in the general procedure was recrystallized from ethanol, furnishing the salt **34** as white crystals: mp 270−272 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 4.95 (s, 2H), 3.47 (m, 4H), 3.23 (s, 6H), 2.58 (m, 4H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 138.5, 112.8, 62.5, 51.3, 28.3.

1-Methyl-4-phenylmethylene-1-azacyclohexane (35). A 60% suspension of NaH in paraffin oil (0.21 g, 5.3 mmol) was washed with hexane (2 × 3 mL) and then treated with a solution of diethyl benzylphosphonate (1.1 g, 4.9 mmol), prepared from triethyl phosphite and benzyl chloride as reported.[31] 1-Methyl-4-piperidone (**29**) (0.50 g, 4.4 mmol) in DME (10 mL) was added all at once and the stirred mixture heated slowly to 85 °C and then refluxed for 1 h. The reaction mixture was added to water (50 mL) and extracted with ether (3 × 40 mL). The combined ether extracts were washed with saturated NaCl solution (2 × 25 mL) and dried (Na_2SO_4), and the solvent was removed. Distillation yielded the amine **35** (0.58 g, 70%): bp 86 °C (0.8 mm); ^{1}H NMR ($CDCl_3$) δ 7.27−7.4 (m, 5H), 6.38 (s, 1H), 2.6 (m, 4H), 2.4 (m, 4H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.7, 137.8, 128.8, 127.9, 125.9, 123.3, 57.1, 56.4, 46.0, 36.4, 29.0; HRMS calcd for $C_{13}H_{17}N$ 187.1361, found 187.1364.

(31) Kosolapoff, G. M. *J. Org. Chem.* **1946**, *11*, 3.

4-Carbethoxymethylene-1-methyl-1-azacyclohexane (36). A suspension of 60% NaH in paraffin oil (0.41 g, 10 mmol) was washed with hexane (2 × 3 mL), a solution of triethylphosphonoacetate[31] (2.2 g, 9.7 mmol) in DME (10 mL) was then added, and the reaction mixture was stirred for 1 h. A solution of 1-methyl-4-piperidone (**29**) (1.0 g, 8.9 mmol) in DME (1 mL) was added to the vigorously stirred mixture at such a rate as to maintain the temperature below 10 °C. After being stirred for 0.5 h, the reaction mixture was added to water (50 mL) and extracted with ether (3 × 50 mL). The ether extracts were washed with saturated NaCl (2 × 25 mL) and dried (Na_2SO_4), and the solvent was removed. Distillation of the residue yielded the ester **36** as a colorless oil (1.5 g, 92%): bp 65 °C (0.1 mm); ^{1}H NMR ($CDCl_3$) δ 5.65 (s, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.0 (m, 2H), 2.48 (m, 4H), 2.36 (m, 2H), 2.29 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.3, 158.5, 114.1, 59.2, 56.4, 55.8, 45.4, 36.4, 28.9,13.9; HRMS calcd for $C_{10}H_{17}NO_2$ 183.1259, found 183.1263.

1-Iodomethyl-1-methyl-4-phenylmethylene-1-azoniacyclohexyl Iodide (37). Treatment of 1-methyl-4-phenylmethylene-1-azacyclohexane (**35**) (1.0 g, 5.4 mmol) with CH_2I_2 as outlined under method B gave the salt **37** as fine off-white crystals (2.2 g, 91%) from methanol: mp 188−189 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 7.24−7.38 (m, 5H), 6.55 (s, 1H), 5.4 (s, 2H), 3.6 (m, 4H), 3.2 (s, 3H), 2.82 (m, 2H), 2.72 (m, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 134.3, 129.4, 126.9, 126.6, 125.1, 124.7, 59.7, 59.0, 47.8, 30.9, 26.7, 21.5. Anal. Calcd for $C_{14}H_{19}NI_2$: C, 36.95, H, 4.21, N, 3.08. Found: C, 36.78, H, 4.31, N, 3.02.

4-Carbethoxymethylene-1-iodomethyl-1-methyl-1-azoniacyclohexyl Iodide (38). Treatment of 4-carbethoxymethylene-1-methyl-1-azacyclohexane (**36**) (1.0 g, 5.4 mmol) under method A conditions and recrystallization of the crude product from methanol gave the salt **38** as fine white crystals (1.74 g, 71%): mp 155−156 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 5.9 (s, 1H), 5.58 (s, 2H), 5.14 (q, J = 7.1 Hz, 2H), 3.8 (m, 4H), 3.4 (s, 3H), 3.3 (m, 2H), 2.79 (s, 2H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 163.7, 147.4, 116.2, 59.5, 59.3, 58.4, 48.5, 32.1, 28.4, 12.7. Anal. Calcd for $C_{11}H_{19}NO_2I_2$: C, 27.36, H, 4.36, N, 3.19. Found: C, 27.35, H, 4.36, N, 3.07.

4-Benzyl-1-methyl-1-azoniabicyclo[2.2.1]heptyl Iodide (39). A 0.02 M solution of 1-iodomethyl-1-methyl-4-phenylmethylene-1-azoniacyclohexyl iodide (**37**) (0.2 0 g, 0.44 mmol) in 2-methyl-2-butanol was deoxygenated and then, after being heated to reflux, was treated with a solution of tributyltin hydride (0.18 g, 0.66 mmol) in 2-methyl-2-butanol (1 mL) as described above. After workup, the product was washed with dry ether (3 × 5 mL) to yield **39** as white crystals (0.13 g, 93%): mp 164−166 °C; ^{1}H NMR ($CDCl_3$) δ 7.16−7.32 (m, 5H), 3.74−3.88 (m, 4H), 3.55 (s, 2H), 3.37 (s, 3H), 3.04 (s, 2H), 2.21 (m, 2H), 1.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 135.5, 128.2, 127.4, 125.7, 68.7, 61.9, 48.0, 43.8, 36.2, 31.8. Anal. Calcd for $C_{14}H_{20}NI$: C, 51.08; H, 6.12; N, 4.25. Found: C, 50.82; H, 5.82; N, 3.98.

4-Carbethoxymethyl-1-methyl-1-azoniabicyclo[2.2.1]heptyl Iodide (40). A 0.025 M solution of 4-carbethoxymethylene-1-iodomethyl-1-methyl-1-azoniacyclohexyl iodide (**38**) (0.20 g, 0.44 mmol) in 2-methyl-2-butanol was deoxygenated, heated to 90 °C and then treated with a solution of tributyltin hydride (0.19 g, 0.66 mmol) in 2-methyl-2-butanol (1 mL) under irradiation as above. Workup yielded the salt **40** as orange crystals (0.12 g, 87%) which crystallized from ethanol/ether: mp 112−114 °C; ^{1}H NMR ($CDCl_3$) δ 4.12 (q, J = 7.1 Hz, 2H), 3.75 (m, 2H), 3.63 (m, 2H), 3.55 (s, 2H), 3.28 (s, 3H), 2.78 (s, 2H), 1.96−2.08 (m, 4H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.1, 70.3, 63.5, 61.2, 45.7, 45.6, 35.8, 35.6, 33.4, 14.3. Anal. Calcd for $C_{11}H_{20}NO_2I$: C, 38.35, H, 6.44, N, 4.47. Found: C, 38.69, H, 6.31, N, 4.19.

1,1-Dimethyl-4-phenylmethylene-1-azoniacyclohexyl iodide (41) was prepared from **35** as described in the general procedure and recrystallized from ethanol as fine white crystals: mp 219−220 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 7.19−7.36 (m, 5H), 6.56 (s, 1H), 3.73 (m, 2H), 3.59 (m, 2H), 3.48 (s, 6H), 2.85 (m, 2H), 2.77 (m, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ_134.3, 129.1, 126.9, 126.6, 125.2, 60.5, 59.8, 49.3, 27.9, 21.5.

4-Carbethoxymethylene-1,1-dimethyl-1-azoniacyclohexyl iodide (42) was prepared according to the general procedure and recrystallized from ethanol as fine white crystals: mp 129−131 °C; ^{1}H NMR ($CDCl_3$) δ 5.90 (s, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.90 (t, J = 6.3 Hz, 2H), 3.78 (t, J = 6.3 Hz, 2H), 3.66 (s, 6H), 3.40 (t, J = 5.7 Hz, 2H), 2.81 (t, J = 5.7 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 163.6, 147.7, 116.0, 115.9, 60.2, 59.9, 58.2, 28.3, 21.7, 12.5.

Dequaternization of 1,1,3-Trimethyl-1-azoniacyclopentyl Iodide (11). A solution of **11** (0.20 g, 0.83 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.19 g, 1.6 mmol) in DMF (4 mL) was added to a thick wall glass reaction vessel that was sealed and then was stirred for 4 h at 170 °C. The cooled reaction mixture was added to water (10 mL) and extracted with benzene (2 × 10 mL). The organic layer was extracted with a solution of 5% HCl (20 mL) and the aqueous layer basified (pH 10) with 3 M NaOH and then extracted with dichloromethane (2 × 15 mL). The solvent was evaporated to give 1,3-dimethyl-1-azacyclopentane (**43**) (0.06 g, 77%), which had physical properties identical with those reported:[29] ^{13}C NMR ($CDCl_3$) δ 64.3, 56.2, 42.5, 33.5, 32.7, 20.5.

Dequaternization of 1,1-Dimethyl-3-phenylmethylene-1-azoniacyclopentyl Iodide (16). The diastereomeric mixture of salts **16** (0.20 g, 0.64 mmol) was treated with 1,4-diazabicyclo[2.2.2]octane (0.14 g, 1.3 mmol) as outlined above for the salt **11**. Workup gave 1-methyl-3-phenylmethylene-1-azacyclopentane (**44**) (0.08 g, 72%) as a mixture of diastereoisomers: ^{1}H NMR ($CDCl_3$) δ 7.1−7.3 (m, 5H), 6.35 (s, 1H), 3.4 (m, 1H), 3.28 (m, 1H), 2.65 (m, 1H), 2.58 (m, 1H), 2.37 (s) and 2.4 (s, total = 3H), 2.29 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 142.1, 137.8, 128.0, 127.9, 127.5, 127.6, 125.8, 125.8, 120.9, 120.1, 63.0, 59.7, 56.7, 55.1,42.2, 42.0, 34.2; HRMS calcd for $C_{12}H_{15}N$ 173.1204, found 173.1199.

Dequaternization of 1-Ethyl-1-methyl-1-azoniacyclohexyl Iodide (47). (a) With DABCO. When 1-ethyl-1-methyl-1-azoniacyclohexyl iodide was treated with DABCO under the conditions specified above, it was converted in high yield to 1-ethyl-1-azacyclohexane (**48**), which was identified by comparison of its physical properties with those of an authentic specimen prepared as described above.

(b) With $PhSe^-$. HMPA (1.5 mL) was added to NaH (0.15 g, 3.7 mmol) prepared from a hexane-washed 60% dispersion in paraffin oil. Phenylselenol (0.42 mL, 3.9 mmol) was added to the stirred mixture followed by a solution of 1-ethyl-1-methyl-1-azoniacyclohexyl iodide (0.50 g, 1.9 mmol) in DMSO (0.5 mL) The resultant mixture was heated at 110 °C. The progress of the reaction was monitored by ^{13}C NMR and found to be complete after 4 h. Water (10 mL) was added to the cooled reaction mixture, which was then extracted with ether (3 × 5 mL). The combined organic extracts were washed several times with saturated NaCl solution and extracted with 5% HCl. The aqueous layer was basified (pH 10) and extracted with dichloromethane, and the combined extracts was dried (Na_2SO_4) and evaporated. The ^{1}H and ^{13}C NMR spectra of the resulting brown oil (0.19 g, 85%) were identical with those of authentic 1-ethyl-1-azacyclohexane.

Dequaternization of 4-Benzyl-1-methyl-1-azoniabicyclo-[2.2.1]heptyl Iodide (39). (a) With DABCO. The salt **39** was recovered unchanged when treated with DABCO under the conditions specified above.

(b) With $PhSe^-$. Generation of a slurry of sodium benzeneselenide in HMPA was performed as described above from a 60% dispersion of NaH in paraffin oil (0.02 g, 0.5 mmol), HMPA (0.4 mL), and benzeneselenol (0.56 mL, 0.26 mmol). A solution of 1-methyl-4-benzyl-1-azoniabicyclo[2.2.1]heptyl iodide (**39**) (0.10 g, 0.26 mmol) in DMSO (0.1 mL) was added and the reaction mixture heated at 110 °C and worked up as above. The oily product (0.04 g, 42%) was identified by NMR spectral analysis as 3-benzyl-1-methyl-3-(2-phenylselenoethyl)-azacyclopentane (**45**): ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 7.05−7.5 (m, 10H), 2.9−3.0 (m, 2H), 2.73 (d, 2H), 2.5−2.6 (m, 4H), 2.31 (s, 3H), 2.29 (m, 2H), 1.74−1.84 (m, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 138.6, 133.0, 130.3, 129.1, 128.1, 128.0, 126.9, 126.2, 66.9, 56.0, 46.9, 44.3, 42.5, 39.3, 36.4, 23.4; HRMS calcd for $C_{20}H_{25}NSe$ 359.1152, found 359.1140.

1-(2-Phenylethyl)-4-phenylmethylene-1-azacyclohexane (50). NaH (60%) in paraffin oil (0.24 g, 5.9 mmol) was washed with hexane (2 × 3 mL) and the hexane removed carefully. A solution of diethyl benzylphosphonate (1.1 g, 4.8 mmol) and 1-(2-phenylethyl)-4-piperidone (**49**) (1 g, 4.9 mmol) in DME (10 mL) was added all at once and the stirred mixture heated slowly to 85 °C and then refluxed for 1 h. The reaction mixture was added to water (50 mL) and then extracted with diethyl ether (3 × 40 mL). The combined ether extracts were washed with saturated NaCl solution (2 × 25 mL) and dried (Na_2SO_4), and the solvent was evaporated. Chromatography on alumina (20% dichloromethane/hexane) yielded the amine **50** as an amber oil (0.88 g, 65%): bp 170 °C (0.3 mm); ^{1}H NMR ($CDCl_3$) δ 7.15−7.27 (m, 10H), 6.27 (s, 1H), 2.8 (dt, J = 3 Hz, 8.4 Hz, 2H), 2.53−2.6 (m, 6H), 2.46 (t, J = 4.8 Hz, 2H), 2.4 (t, J = 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 140.4, 139.4, 137.7, 128.9, 128.6, 128.3, 128.0, 126.0, 125.9, 123.2, 60.3, 55.0, 54.3, 36.2, 33.6, 28.9; HRMS calcd for $C_{20}H_{23}N$ 277.1830, found 277.1842.

1-Iodomethyl-1-(2-phenylethyl)-4-phenylmethylene-1-azoniacyclohexyl Iodide (51). This compound was prepared via method A and purified by column chromatography on alumina (dichloromethane/methanol): ^{1}H NMR ($CDCl_3$) δ 7.15−7.32 (m, 10H), 6.48 (s, 1H), 5.26 (s, 2H), 3.72 (t, J = 5.7 Hz, 2H), 3.49−3.55 (m, 4H), 2.98−3.04 (m, 2H), 2.74 (t, J = 5.7 Hz, 2H), 2.84−2.75 (m, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 135.6, 134.7, 129.5, 129.0, 128.8, 128.5, 128.3, 127.7, 127.3, 127.0, 62.1, 60.1, 59.4, 29.2, 28.7, 27.8, 23.0.

Attempted Synthesis of 4-Benzyl-1-(2-phenylethyl)-1-azoniabicyclo[2.2.1]heptyl Iodide (52). The salt **51** exhibited very low solubility in 2-methyl-2-butanol; treatment of the resulting mixture with tributyltin hydride and AIBN (cat.) at reflux under irradiation as discussed followed by workup of the reaction mixture yielded a complex mixture of products containing starting material (**51**), cyclized product, and reduced product (**53**).

1-Methyl-1-(2-phenylethyl)-4-phenylmethylene-1-azoniacyclohexyl Iodide (53). 1-(2-Phenylethyl)-4-phenylmethylene-1-azacyclohexane (**50**) was converted into the salt **53** as described in the general procedure above. The latter crystallized from ethanol/ether as white crystals: mp 165−167 °C; ^{1}H NMR ($CDCl_3$) δ 7.15−7.43 (m, 10H), 6.5 (s, 1H), 3.95 (t, 2H), 3.82 (m, 1H), 3.7 (m, 2H), 3.55 (m, 1H), 3.5 (s, 3H), 3.17 (m, 2H), 2.77(m, 3H), 2.66 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 135.7, 134.9, 129.4, 129.0, 128.8, 128.8, 128.6, 128.5, 127.5, 127.3, 64.1, 61.5, 60.9, 47.9, 29.5, 28.6, 23.2. Anal. Calcd for $C_{21}H_{26}NI$: C, 60.15, H, 6.25, N, 3.34. Found: C, 60.18, H, 6.49, N, 3.34.

1-(2-Phenylethyl)-4-phenylmethylene-1-phenylselenomethyl-1-azoniacyclohexyl Bromide (54). Treatment of 1-(2-phenylethyl)-4-phenylmethylene-1-azacyclohexane (**50**) (1.0 g, 3.8 mmol) with $PhSeCH_2Br$ as outlined above converted it into the title salt **54**, which crystallized from ethanol/ether as colorless crystals (1.7 g, 86%): mp 201−202 °C; ^{1}H NMR ($CDCl_3$) δ 7.79 (d, 2H), 7.07−7.4 (m, 13H), 6.4 (s, 1H), 5.69 (s, 2H), 3.7−4.0 (m, 6H), 3.01 (m, 2H), 2.67 (s, 2H), 2.54 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 135.5, 134.8, 134.0, 130.0, 129.1, 128.8, 128.7, 128.6, 128.1, 127.0, 126.9, 126.6, 125.5, 59.4, 59.2, 59.0, 58.4, 29.1, 28.1, 22.9. Anal. Calcd for $C_{27}H_{30}NSeBr$: C, 61.49, H, 5.73, N, 2.66. Found: C, 61.44, H, 5.64, N, 2.74.

4-Benzyl-1-(2-phenylethyl)-1-azoniabicyclo[2.2.1]heptyl Bromide (55). A 0.025 M solution of 1-(2-phenylethyl)-1-phenylselenomethyl-4-phenylmethylene-1-azoniacyclohexyl bromide (**54**) (0.4 g, 0.76 mmol) in 2-methyl-2-butanol was deoxygenated and treated with a solution of tributyltin hydride (0.33 g, 1.1 mmol) and AIBN (cat.) in 2-methyl-2-butanol (1 mL) under irradiation at reflux as discussed earlier. Workup and recrystallization of the product from ethanol/ether yielded the title compound **55** as white crystals (0.26 g, 92%): mp 198−200 °C; ^{1}H NMR ($CDCl_3$) δ 7.08−7.34 (m, 10H), 3.8−4.0 (m, 6H), 3.6 (s, 2H), 3.08 (t, J = 8.1 Hz, 2H), 2.95 (s, 2H), 2.19 (s, 2H), 1.75 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 136.2, 135.1, 128.9, 128.5, 128.4, 128.2, 126.8, 126.5, 68.8, 60.4, 58.0, 47.7, 36.9, 32.0, 30.1. Anal. Calcd for $C_{21}H_{26}NBr$: C, 67.74, H, 7.04, N, 3.76. Found: C, 67.75, H, 7.00, N, 3.80.

4-Benzyl-1-azabicyclo[2.2.1]heptane (57). Potassium *tert*-butoxide (0.60 g, 5.6 mmol) was added to a solution of 4-benzyl-1-(2-phenylethyl)-1-azoniabicyclo[2.2.1]heptyl bromide (**55**) (0.20 g, 0.56 mmol) in DMF (4 mL) and the solution stirred for 12 h. Diethyl ether (10 mL) was added and the mixture washed with water (3 × 10 mL). The ether extracts were then extracted with 5% HCl, which was basified (pH 10) with NaOH (3 M), and then extracted with dichloromethane. After being dried (Na_2SO_4), the solvent was evaporated yielding the title amine **57** (60 mg, 60%) as an amber solid: ^{1}H NMR ($CDCl_3$) δ 7.13−7.31 (m, 5H), 2.97 (s, 2H), 2.88 (m, 2H), 2.55 (m, 2H), 2.28 (s, 2H), 1.54 (m, 2H), 1.18 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 140.0, 129.7, 128.2, 126.0, 63.8, 55.4, 50.5, 38.9, 35.3; HRMS calcd for $C_{13}H_{17}N$ 187.1361, found 187.1363.

Supporting Information Available: NMR data for obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9813538