Synthesis of Nitrogen Bridgehead Bicyclic Heterocycles via Ring-Closure of β-Ammonio 5-Hexenyl Radicals

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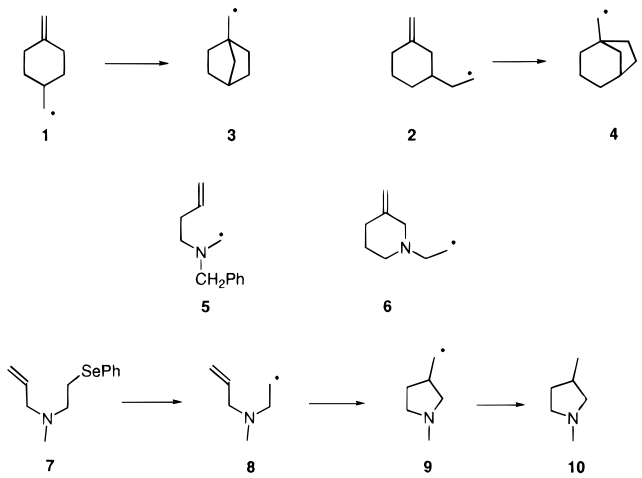
The 2-(3-methylenepiperidinyl)ethyl radical (**6**) displays considerable reluctance to ring-closure under conditions which its carbocyclic analog, the 2-(3-methylenecyclohexyl)ethyl radical (**2**), cyclizes essentially completely. Molecular mechanics calculations suggest that the increased activation barrier associated with ring-closure of **6** is the result of a higher than expected transition state energy. A study of the behavior of β-ammonio-substituted 5-hexenyl radicals, such as the 3,3-dimethyl-3-azonia-5-hexenyl radical (**22**), reveals that cyclization occurs readily. Treatment of 1-methyl-1-(2-(phenylselenyl)ethyl)-3-methylenepiperidinium iodide (**20**) with tributyltin hydride in *tert*-amyl alcohol yields the bridgehead nitrogen bicyclic heterocycle, 1,5-dimethyl-1-azoniabicyclo-[3.2.1]octane iodide (**26**), in excellent yield and without contamination, thus providing an attractive synthetic route to this hitherto unknown heterocyclic system.

Introduction

As part of a program of studies directed toward the synthesis of bridgehead-substituted bicycloalkanes, we recently reported[1−3] that the modified 5-hexenyl radicals **1** and **2** undergo facile ring-closure to the isomeric species **3** and **4** and that such cyclizations give very good yields of the bicycles with useful functionality at the bridgehead positions. One of the long-range objectives of this work was to determine whether this kind of transformation could be usefully employed for the synthesis of heterocyclic compounds, in particular bicyclic systems with nitrogen at the bridgehead.



Previous observations by Padwa and his colleagues[4] that impinge directly on this work reveal that α-amino radicals such as the 2-benzyl-2-aza-5-hexenyl radical (**5**) are reluctant to cyclize, presumably as a result of the stabilizing influence of the nitrogen atom on the radical center[5] which raises the expected barrier to rearrangement of **5** by lowering its ground-state energy. We decided from the outset, therefore, to commence with an examination of the 2-(3-methylenepiperidinyl)ethyl radical (**6**), the aza analog of the 2-(3-methylenecyclohexyl)-ethyl radical (**2**). As a member of the β-amino radical family, **6** was not expected to possess the same kind of stabilization displayed by **5** and thus be more amenable toward cyclization. In fact, it has been suggested[6] that 3-aza-5-hexenyl radicals are better suited to radical cyclization than the parent species.

We considered it essential to conduct a preliminary investigation of the behavior of the parent open-chain species, the 3-methyl-3-aza-5-hexenyl radical (**8**). It was found[7] that **8**, produced by treatment of the selenide **7** with Bu_3SnH, undergoes ring-closure with complete regioselectivity to give 1,3-dimethylpyrrolidine (**10**) via the *exo-trig* product **9**; significantly, the rate of cyclization is faster than the corresponding reaction of the 5-hexenyl radical. This result was encouraging for the planned extension of the investigation to a study of the 2-(3-methylenepiperidinyl)ethyl radical **6**. We now disclose the results of our work on this system.

Results and Discussion

We were precluded from employing the popular precursor for generating radicals, the organobromide or iodide, because of the lability of the required β-amino halide toward internal displacement of the halogen; accordingly we elected to use the phenylselenide **11** instead. The synthesis of **11** was accomplished (Scheme 1) using commercially-available 3-(hydroxymethyl)piperidine (**12**) as starting material. All the steps depicted in Scheme 1 represent essentially standard procedures; a noteworthy feature is that optimum yields of the amide **13** were obtained using the exchange process illustrated[8] rather than by selective acylation using acetic anhydride, for example, because the latter was found to give a product that was difficult to purify . The final step is a modification of the process of reductive amination described by Danishefsky and Panek.[9]

Treatment of 1-(2-(phenylselenyl)ethyl)-3-methylene-piperidine (**11**) with tributyltin hydride was attempted

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(1) Della, E. W.; Knill, A. M.; Pigou, P. E. *J. Org. Chem.* **1993**, *58*, 2110.
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(4) Padwa, A.; Nimmersgen, H.; Wong, G. S. K. *Tetrahedron Lett.* **1985**, *26*, 957. Padwa, A.; Nimmersgen, H.; Wong, G. S. K. *J. Org. Chem.* **1985**, *50*, 5620.
(5) Coolidge, M. B.; Borden, W. T. *J. Am. Chem. Soc.* **1988**, *110*, 2298.
(6) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.
(7) Della, E. W.; Knill, A. M. *Aust. J. Chem.* **1995**, *48*, 2047.
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(9) Danishefsky, S. J.; Panek, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 917.

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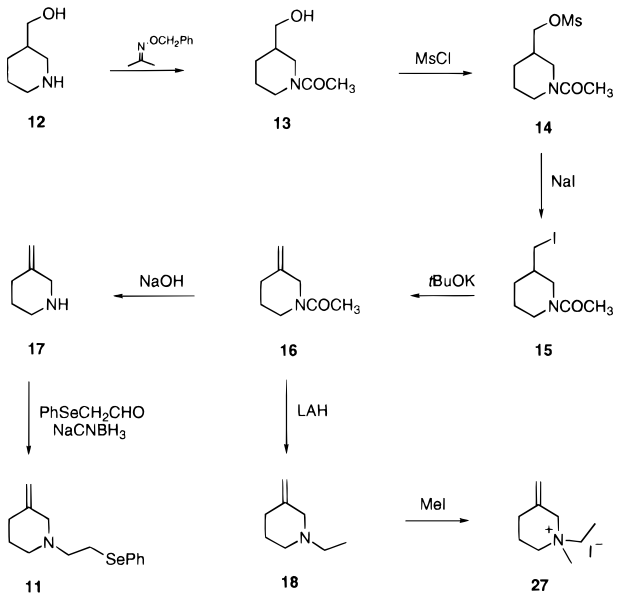
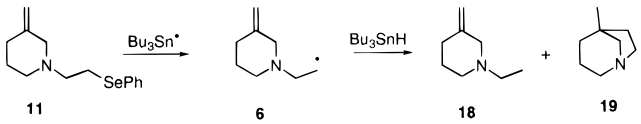
Scheme 1



under conditions (110 °C, AIBN, toluene) found earlier[3] to be conducive for cyclization of the carbocyclic analog, the 2-(3-methylenecyclohexyl)ethyl radical (**2**), in the expectation that the radical **6** would behave in a similar fashion. However, the extent of ring-closure in this case was disappointing; GC analysis of the product showed it to consist of a 9:1 mixture of the isomeric amines **18** and **19**. Modifying conditions, such as the rate of addition of the reagent, did not have any appreciable effect on the extent of cyclization; even under more drastic conditions (150 °C) an unacceptably large amount of reduced product was still evident. For assistance in identification of the products, an authentic specimen of the monocyclic amine **18** was prepared by reduction of the amide **16** with lithium aluminum hydride.



What is the explanation for the dramatic difference between the facility for ring-closure of the radicals **2** and **6**? Several possibilities were considered: (i) the presence of adventitious diphenyl diselenide, and (ii) an increased activation barrier to cyclization.

Initially, we felt that the use of the phenylselenyl functional group may have actually introduced an unwanted complication. For example, Crich and Yao[10] have demonstrated that in the tributyltin hydride reduction of oxygen-based heterocyclic substrates containing the phenylselenide group, the nature of the product is affected by the presence of diphenyl diselenide produced by decomposition of the substrate. Tributyltin hydride rapidly converts $(PhSe)_2$ into phenylselenol which is a far more effective hydrogen atom transfer agent than $(Bu)_3SnH$, and it therefore traps the initially-formed radical much more efficiently. Crich and Yao[10] have suggested that only a catalytic quantity of diphenyl diselenide is required as the phenylselenol is continually regenerated.

(10) Crich, D.; Yao, Q. *J. Org. Chem.* **1995**, *60*, 84.

Our experimental data do not appear to support this possibility. For example, in the earlier investigation[7] involving Bu_3SnH-mediated reduction of the acyclic amine **7**, we found no evidence for such an inhibiting effect toward ring-closure, and the product of cyclization, 1,3-dimethylpyrrolidine, was the sole constituent. Furthermore, when a sample of the precursor **11**, which had been purified by rigorous chromatography to remove any residual diphenyl diselenide, was treated under the above conditions, no improvement in the yield of bicyclic product was detected. Moreover, it was observed that heating the purified sample of **11** in the absence of Bu_3SnH did not lead to production of $(PhSe)_2$.

In connection with the alternative possibility, viz., an increase in activation energy to ring-closure, we began to suspect that the presence of a neighboring nitrogen atom may be responsible for conferring enhanced thermodynamic stability on the radical **6**. Although as mentioned above such stabilizing effects are well-known for radicals containing α-nitrogen substituents,[5] there has been no suggestion that *β*-nitrogen exerts a similar effect. There is, nevertheless, some precedence for this concept in the postulate by Barton[11] and Giese[12] that oxygen attached to a *β*-carbon exerts a marked stabilizing effect on a radical (termed[11] the "*β*-oxygen effect"). While this view has aroused some controversy,[13] it is now commonly accepted that the operation of such an effect is unlikely. Interestingly, Jenkins[14] has asserted that a *β*-oxygen can have either an activating or deactivating effect on the rate of radical formation, depending upon the mode of generation. Quite recently, a definitive article on the origin of the "*β*-oxygen effect" in radicals has appeared.[15]

In an attempt to shed some light on the possibility that a *β*-nitrogen might exert a similar effect, we[16] have performed *ab initio* calculations at the MP2/6-31G** level on the energy (ΔE) associated with the isodesmic reaction represented by eq 1. Unlike the situation encountered

$$^{\bullet}CH_2CH_2NH_2 + CH_3CH_2CH_3 \rightarrow CH_3CH_2NH_2 + CH_3CH_2CH_2^{\bullet} \quad (1)$$

with an α-amino-substituted radical,[5] the stability of which is enhanced as a result of interaction of the nitrogen lone pair with the radical center, the calculations predict that the reaction depicted in (eq 1) is essentially energy-neutral. Accordingly, in view of the lack of theoretical support for the concept of a *β*-nitrogen stabilizing effect, we are inclined to doubt its existence.

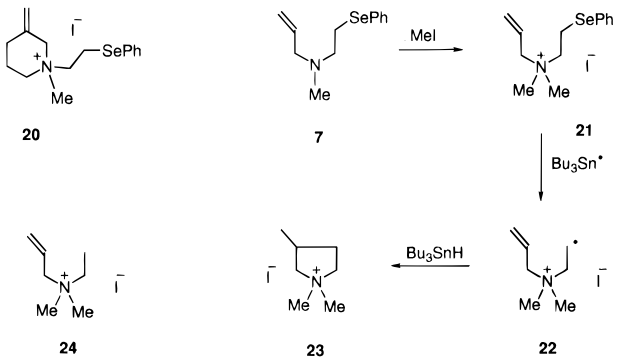
We believe that the underlying cause for the reluctance of radical **6** to undergo ring-closure compared with its carbocyclic analogue **2** is associated with an increased energy of the transition state for cyclization of the former. There is strong support for the larger activation barrier for reaction of **6** according to MM2 data we have obtained on the calculated energy profile for the two cyclizations.

(11) Barton, D. H. R.; Hartwig, W.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1982**, 447.
(12) Dupois, J.; Giese, B.; Ruegge, D.; Fischer, H.; Korth, H.-G.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 896.
(13) (a) Beckwith, A. L. J.; Brumby, S. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1801. (b) Beckwith, A. L. J. *Chem. Soc. Rev.* **1993**, *22*, 144. (c) Motherwell, W. B.; Crich, D. In *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992; Chapter 3.
(14) Jenkins, I. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1227.
(15) Crich, D.; Beckwith, A. L. J.; Chen, C.; Yao, Q.; Davison, I. G. E.; Longmore, R. W.; de Parrodi, C. A.; Quintero-Cortes, L.; Sandoval-Ramirez, J. *J. Am. Chem. Soc.* **1995**, *117*, 8757.
(16) Della, E. W.; Elsey, G. M. Unpublished observations.

The force field calculations were performed following the procedure described by Beckwith and Schiesser[17] that we employed in earlier work.[1,3] They predict a barrier of 16.0 kcal mol^{-1} for ring-closure of radical **6** which is clearly larger than the value, 12.6 kcal mol^{-1}, derived previously[3] for cyclization of **2**. This observation was unexpected because it has been shown experimentally[7] in the case of the corresponding acyclic radicals that the activation energy for ring-closure of the 3-aza-5-hexenyl radical is lower than that for the 5-hexenyl radical as predicted.[6] We have no explanation for the increased barrier to ring-closure of the radical **6** and hence its reluctance to undergo cyclization. Undoubtedly, the use of 1-(2-(phenylselenyl)ethyl)-3-methylenepiperidine (**11**) as a precursor to the 1-azabicyclo[3.2.1]octyl system is impractical.

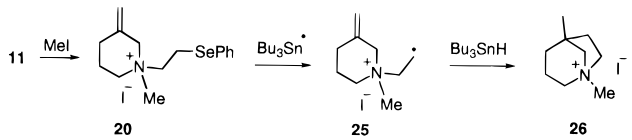
In an attempt to circumvent this problem, we decided to investigate the potential for ring-closure of the corresponding ammonium salt **20**. In this case, the expectation was that the extra substituent attached to nitrogen in **20** would enhance the rate of cyclization of the derived radical **25** by analogy with the beneficial effect[1−3] of added ester groups at C1, for example, in promoting ring-closure of radicals **1** and **2**. Thus, in the transition state associated with cyclization of **25**, the additional methyl group adopts the equatorial configuration and, accordingly, it is not expected to influence appreciably the energy of the transition state relative to that of the neutral species **6**. On the other hand, whereas radical **6** (through either nitrogen inversion or ring flip) can adopt a favorable ground state in which the substituent attached to nitrogen is equatorial, rotational interconversion in the case of the charged species **25** requires that it must always exist in a conformation in which one of the substituents attached to nitrogen has the axial orientation. The anticipated net effect of the increased ground state energy of radical **25** is a diminished activation barrier for its ring-closure relative to that of the neutral species **6**.

As far as we are aware, there are no reports in the literature on the use of ammonium salts in radical cyclizations of this type, and we therefore chose to initiate the study by an examination of the simpler acyclic system, 1-(phenylselenyl)-3,3-dimethyl-3-azonia-5-hexene iodide (**21**). We had access to 1-(phenylselenyl)-3-methyl-3-aza-5-hexene (**7**) previously,[7] and the synthesis of the salt **21** was accomplished simply by treating the amine with neat iodomethane.



In view of the limited solubility of the salt **21** in hydrocarbon solvents coupled with the expectation that temperatures in excess of 80 °C would be required for optimal cyclization, it was decided to employ *tert*-amyl alcohol as solvent; this alcohol is inexpensive and has the added requirement that it is expected to be inert to radicals. In the event, treatment of a solution of **21** in *tert*-amyl alcohol at 80 °C with Bu_3SnH gave a product which, by careful ^1H and ^{13}C NMR analysis, was found to consist of 1,1,3-trimethylpyrrolidinium iodide (**23**) exclusively. NMR signals that could be ascribed to other products were not detected and, in particular, there was no evidence for the formation of *N*-ethyl-*N*,*N*-dimethyl-*N*-allylammonium iodide (**24**), the product of reduction. The identity of the salt **23** was confirmed by demethylation with DABCO in DMF as described,[18] giving the known parent amine, 1,3-dimethylpyrrolidine (**10**).[7] The yield of cyclized material (92%) obtained under these conditions confirms that the presence of positively-charged nitrogen has no deleterious effect on the cyclization reaction. In fact, the intermediate radical **22** is seen to ring-close rapidly and at a rate comparable with that of the neutral species **8**. The real test, of course, was whether this situation could be duplicated in the case of the salt **20**.

Conversion of the monocyclic amine **11** into 1-methyl-1-(2-(phenylselenyl)ethyl)-3-methylenepiperidinium iodide (**20**) was achieved by reaction with iodomethane. Exposure of a solution of **20** in *tert*-amyl alcohol to Bu_3SnH at 104 °C, but otherwise under conditions specified above, afforded a crystalline product whose identity was established by ^1H and ^{13}C NMR analysis as 1,5-dimethyl-1-azoniabicyclo[3.2.1]octane iodide (**26**). Signals attributable to other compounds, including 1-ethyl-1-methyl-3-



methylenepyrrolidinium iodide (**27**), the noncyclized product of reduction, were not detected in the NMR spectra.

This unprecedented transformation possesses several outstanding features. For example, it demonstrates conclusively that cyclization of these heterocyclic-based β-ammonio-substituted radicals occurs with relative ease, in contrast with their parent amines; presumably, as suggested above, the added methyl substituent does have the desired effect in terms of raising the ground state of the radical. Secondly, the reaction can be seen to proceed with high regioselectivity; as the sole product of the reaction, the salt **26** is seen to be produced in a high state of purity and in a spectacular yield (87%). Finally, as far as we are aware, this report represents the first disclosure of a synthesis of the 1-azoniabicyclo[3.2.1]-octane system, which can be achieved, significantly, via a route involving several relatively easy steps.

Experimental Section

Molecular mechanics calculations were performed as described previously;[1] spectral, chromatographic, and other standard experimental procedures adopted were as specified.[19]

1-Acetyl-3-(hydroxymethyl)piperidine (13). The procedure developed by Fernández and her colleagues[8] was used

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(18) Ho, T. L. *Synthesis* **1972**, 702.

(19) Della, E. W.; Pigou, P. E.; Schiesser, C. H.; Taylor, D. K. *J. Org. Chem.* **1991**, *56*, 4659.

to convert 3-(hydroxymethyl)piperidine (**12**) (10 g, 0.087 mol) into the title compound **13** (11.7 g, 86%) after distillation (Kugelrohr: 120 °C (0.01 mm)); its ^{1}H NMR spectrum was consistent with that reported;[20] ^{13}C NMR ($CDCl_3$) δ 169.12, 63.93, 63.83, 49.49, 47.20, 44.46, 42.14, 38.92, 37.87, 26.84, 26.63, 24.60, 23.83, 21.10.

1-Acetyl-3-methylenepiperidine (16). Treatment of 1-acetyl-3-(hydroxymethyl)piperidine (**13**) with mesyl chloride as described[21] gave the mesylate **14** (90%) which was used without further purification. Sodium iodide (25 g, 0.17 mol) was added to a stirred solution of **14** (13.7 g, 58 mmol) in dimethoxyethane (100 mL), and the mixture was heated at 65 °C for 4 h. Solvent was removed under vacuum and the residue taken up into CH_2Cl_2 (150 mL) which was washed twice with saturated sodium chloride. The organic layer was dried (Na_2SO_4) and evaporated leaving 1-acetyl-3-(iodomethyl)-piperidine (**15**) (15 g, 96%) as a light yellow oil; ^{1}H NMR ($CDCl_3$) δ 4.60−3.65 (m, 2H), 3.28−3.00 (m, 4H), 2.15 (d, 3H), 1.90−1.25 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 168.04, 167.97, 51.50, 46.49, 46.08, 41.27, 38.36, 36.81, 30.77, 30.48, 24.53, 23.30, 20.87, 9.59, 8.82. Potassium *tert*-butoxide (9.5 g, 0.84 mol) was introduced slowly into a solution of the iodide (**15**) (15 g, 0.56 mol) in dimethoxyethane (250 mL) and the mixture allowed to stir at room temperature for 2 h. The mixture was quenched with saturated ammonium chloride (20 mL) and extracted (3×) with CH_2Cl_2. The combined organic extracts were washed with water (2×) and dried ($MgSO_4$), and the solvent was removed under vacuum. The resulting light yellow residue was distilled (Kugelrohr: 100 °C (1 mm)) to give the title compound **16** (7.0 g, 90%): ^{1}H NMR ($CDCl_3$) δ 4.95−4.65 (s, 2H), 3.95 (d, 2H), 3.80−3.35 (m, 2H), 2.50−2.12 (m, 2H), 2.05 (s, 3H), 1.95−1.38 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 168.94, 168.84, 142.89, 142.21, 110.83, 110.21, 53.60, 48.30, 46.74, 42.22, 32.78, 27.27, 26.49, 21.71, 21.51. Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.97; H, 9.20; N, 10.19.

3-Methylenepiperidine (17). 1-Acetyl-3-methylenepiperidine (**16**) (1 g, 7.2 mmol) was added to 10% NaOH (10 mL) and heated under reflux for 3 h. The cooled solution was diluted with saturated sodium chloride and extracted with ether (3x). The combined organic extracts were washed with water and then dried (Na_2SO_4). Removal of the solvent afforded the title product **17** as a clear liquid (0.5 g, 71%): ^{1}H NMR ($CDCl_3$) δ 4.65 (d, 2H), 3.30 (s, 2H), 2.90−2.85 (m, 2H), 2.25 (t, 2H), 1.78 (s, 1H), 1.70−1.60 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 146.36, 107.24, 52.96, 46.15, 32.98, 29.30. The amine was converted into its hydrochloride salt which crystallized from ether/CH_2Cl_2 as colorless needles, mp 210−213 °C. Anal. Calcd for $C_6H_{12}NCl$: C, 53.90; H, 9.05; N, 10.48. Found: C, 53.54; H, 8.72; N, 10.30.

1-(2-(Phenylselenyl)ethyl)-3-methylenepiperidine (11). (Phenylselenyl)acetaldehyde (2.0 g, 10.3 mmol) was added to a solution of 3-methylenepiperidine (**17**) (0.5 g, 5.15 mmol) in a 50:50 mixture of methanol and tetrahydrofuran (25 mL) and the mixture left to stir for 15 min at room temperature. Sodium cyanoborohydride (0.65 g, 10.3 mmol) was then added, and stirring was continued for 24 h after which the mixture was quenched with saturated ammonium chloride (20 mL) and extracted (3x) with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), and solvent was removed under vacuum. The residue was dissolved in ether (40 mL) which was extracted (2×) with 5% HCl. The combined acid washes were basified (pH 10) with NaOH and then extracted with CH_2Cl_2. The organic extract was washed with saturated sodium chloride and then dried ($MgSO_4$) and evaporated. The resulting yellow oil was distilled (Kugelrohr: 125 °C (0.1 mm)) to yield the selenide **11** (0.61 g, 42%) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.53−7.46 (m, 2H), 7.35−7.20 (m, 3H), 4.75 (s, 2H), 3.10−3.00 (m, 2H). 2.95 (s, 2H), 2.77−2.66 (m, 2H), 2.53 (t, 2H), 2.15 (t, 2H), 1.70−1.60 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 143.91, 133.44, 131.97, 128.73, 126.4, 109.04, 59.88, 58.14, 53.1, 32.45, 25.97, 24.49; mass spectrum *m*/*z* (relative intensity); 202 (12.5), 110 (85), 69 (100); HRMS calcd for $C_{14}H_{19}N^{78}Se$ 279.0690, found 279.0680.

1-Ethyl 3-methylenepiperidine (18). A solution of 1-acetyl-3-methylenepiperidine (**16**) (1 g, 7.2 mmol) in ether (2 mL) was slowly added to a stirred solution of $LiAlH_4$ (1.09g, 0.029 mol) in dry ether (20 mL), and the solution was heated under reflux for 3 h. The cooled mixture was quenched with saturated aqueous sodium sulfate and then filtered, and the solids were washed thoroughly with ether. The combined filtrate was dried (Na_2SO_4) and the solvent carefully removed to afford the amine **18** (0.77g, 86%) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 4.78 (d, 2H), 2.95 (s, 2H), 2.56−2.48 (m, 2H), 2.45 (t, 2H), 2.2−2.12 (m, 2H), 1.75−1.65 (m, 2H), 1.1 (t, 3H), ^{13}C NMR ($CDCl_3$) δ 144.16, 109.50, 59.95, 53.10, 52.18, 32.73, 26.14, 11.97. The amine was converted into its picrate salt mp: 121−123 °C. Anal. Calcd for $C_{14}H_{18}N_4O_7$: C, 47.46; H, 5.12; N, 15.81. Found: C, 47.46; H, 5.09; N, 15.84.

Reduction of 1-(2-(Phenylselenyl)ethyl)-3-methylenepiperidine (11) with Bu_3SnH. (i) At 110 °C. A solution of tributyltin hydride (0.62 g, 2.1 mmol) in dry toluene (3 mL) containing a few crystals of AIBN was slowly added over a 3 h period to 1-(2-(phenylselenyl)ethyl)-3-methylenepiperidine (0.2 g, 0.71 mmol) (**11**) in refluxing toluene (25 mL).The extent of the reaction was monitored by GC/MS analysis and, upon completion, the mixture was cooled and extracted with 5% HCl (3x). The combined aqueous extracts were washed with hexane before being basified (pH10) and reextracted with CH_2Cl_2 (2×). The combined organic extracts were dried (Na_2SO_4) and concentrated carefully. GC/MS analysis of the residue (0.065 g, 73%) showed it to consist of a 9:1 mixture of 1-ethyl 3-methylenepiperidine (**18**) and 1-aza-5-methylbicyclo(3.2.1)-octane (**19**).

(ii) At 150 °C. Analysis of the product obtained from treatment of the selenide **11** with a solution of Bu_3SnH in *tert*-butylbenzene at reflux under conditions described above showed the amines **18** and **19** to be formed as a 3:1 mixture.

3,3-Dimethyl-1-(phenylselenyl)-3-azoniahex-5-ene Iodide (21). 1-Allyl-1-methyl-1-(2-(phenylselenyl)ethyl)amine (**7**) (0.2 g, 0.78 mmol)[7] was stirred with iodomethane (2 mL) overnight. Removal of excess MeI under vacuum afforded a yellow solid which upon recrystallization (benzene/CH_2Cl_2) gave colorless needles (0.27 g, 86%) of the ammonium salt **21**; mp 85−87 °C; ^{1}H NMR (acetone-d_6) δ 7.75−7.65 (m, 2H), 7.40−7.30 (m, 3H), 6.20−6.05 (m, 1H), 5.88−5.61 (m, 2H), 4.48 (d, 2H), 3.93−3.83 (m, 2H), 3.60−3.52 (m, 2H), 3.41 (s, 6H); ^{13}C NMR (acetone-d_6) δ 133.85, 130.29, 128.88, 128.97, 128.43, 126.28, 66.16, 64.73, 50.72, 19.70. Anal. Calcd for $C_{13}H_{20}INSe$: C, 39.41; H, 5.09; N, 3.54. Found: C, 39.29; H, 4.80; N, 3.37.

Reduction of 3,3-Dimethyl-1-(phenylselenyl)-3-azoniahex-5-ene Iodide (21) with Bu_3SnH:1,1,3-Trimethylpyrrolidinium Iodide (23). A solution of 3,3-dimethyl-1-(phenylselenyl)-3-azoniahex-5-ene iodide (**21**) (0.25 g, 0.63 mmol) in dry *tert*-amyl alcohol (25 mL) was maintained at 80 °C and treated with a solution of tributyltin hydride (0.22 g, 0.75 mmol) and a few crystals of AIBN in dry *tert*-amyl alcohol (2 mL). After addition was complete, heating was continued for a further 30 min after which the mixture was cooled and the solvent removed *in vacuo* leaving a light yellow liquid. Trituration with dry ether and filtration afforded 1,1,3-trimethylpyrrolidinium iodide (**23**) as a colorless solid (0.13 g, 92%): mp 180−182 °C; ^{1}H NMR (DMSO-d_6) δ 3.71−3.61 (m, 1H), 3.58−3.50 (m, 2H), 3.18 (s, 3H), 3.10−3.02 (m, 1H), 3.08 (s, 3H), 2.69−2.52 (m, 1H), 2.38−2.21 (m, 1H), 1.78−1.63 (m, 1H), 1.08 (d, 3H). ^{13}C NMR (DMSO-d_6) δ 70.92, 70.88, 65.12, 65.08, 52.73, 52.68, 51.73, 51.62, 30.44, 30.23, 17.77.

1,3-Dimethylpyrrolidine (10). Heating 1,1,3-trimethylpyrrolidinium iodide (**23**) (0.1 g), with DABCO in DMF as described by Ho[18] yielded the amine **10** almost quantitatively. The product was identical with an authentic specimen.[7]

1-Methyl-1-(2-(phenylselenyl)ethyl)-3-methylenepiperidinium Iodide (20). 1-(2-(Phenylselenyl)ethyl)-3-methylenepiperidine (**11**) (0.5 g, 1.78 mmol) was allowed to stir with iodomethane (5 mL) overnight. Removal of the excess iodomethane under vacuum and recrystallization (benzene/CH_2Cl_2) of the residue afforded the ammonium salt **20** (0.68 g, 90%) as a pale yellow solid: mp 102−104 °C; ^{1}H NMR ($CDCl_3$) δ 7.69−7.58 (m, 2H), 7.39−7.25 (m, 3H), 5.15 (d, 2H), 4.37−4.13 (m, 2H), 3.95−3.65 (m, 4H), 3.42−3.20 (m, 2H), 3.31 (s, 3H),

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2.50−2.30, (m, 2H), 2.02−1.63 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 134.06, 133.24, 129.26, 127.81, 127.0, 118.82, 65.51, 61.95, 59.93, 48.01, 29.10, 20.26, 18.78. Anal. Calcd for $C_{15}H_{22}$-INSe: C, 42.67; H, 5.25; N, 3.32. Found: C, 41.92; H, 5.31; N, 3.21.

1-Ethyl-1-methyl-3-methylenepiperidinium iodide (27). 1-Ethyl-3-methylenepiperidine (**18**) (0.5 g, 4.0 mmol) was allowed to stir with iodomethane (5 mL) overnight. Removal of the excess iodomethane under vacuum and recrystallization (benzene/CH_2Cl_2) of the residual solid afforded 1-ethyl-1-methyl-3-methylenepiperidinium iodide (**27**) as a pale yellow solid (0.98 g, 92%): mp 116−118 °C; ^{1}H NMR ($CDCl_3$) δ 5.3 (d, 2H), 4.3 (s, 2H), 3.95−3.70 (m, 4H), 3.25 (s, 3H), 2.52 (t, 2H), 2.10−1.96 (m, 2H), 1.43 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 134.37, 118.54, 65.14, 58.76, 57.56, 46.54, 28.75, 20.02, 7.45. Anal. Calcd for C_9H_{18}IN: C, 40.46; H, 6.79; N, 5.24. Found: C, 40.09; H, 6.99; N, 5.13.

Reduction of 1-Methyl-1-(2-(phenylselenyl)ethyl)-3-methylenepiperidinium Iodide (20) with Bu_3SnH:1,5-Dimethyl-1-azoniabicyclo[3.2.1]octane Iodide (26). A solution of 1-methyl-1-(2-(phenylselenyl)ethyl)-3-methylenepiperidinium iodide (**20**) (0.2 g, 0.47 mmol) in dry *tert*-amyl alcohol (18 mL) was maintained at 104 °C while a solution of tributyltin hydride (0.16 g, 0.58 mmol) and a few crystals of AIBN in dry *tert*-amyl alcohol (2 mL) was added over 15 min. After addition, heating was continued for a further 30 min after which the mixture was cooled and the solvent removed *in vacuo*. Trituration of the light residue with dry ether afforded a white solid which was filtered and washed with ether. Recrystallization from benzene/CH_2Cl_2 yielded 1,5-dimethyl-1-azoniabicyclo[3.2.1]octane iodide (**26**) (0.11 g, 87%); ^{1}H NMR ($CDCl_3$) δ 4.08−3.65 (m, 6H), 3.55 (s, 3H), 2.30−1.89 (m, 4H), 1.78−1.55 (m, 2H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 72.43, 63.50, 62.35, 51.19, 41.06, 35.03, 34.37, 22.84, 19.54. Anal. Calcd for C_9H_{18}NI: C, 40.46; H, 6.79; N, 5.24. Found: C, 40.35; H, 7.02; N, 5.15.

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