Intramolecular Cyclization of β-Amino and β-Ammonio Radicals: A New Synthetic Route to the 1-Azabicyclo[3.2.1]octyl- and -[2.2.1]heptyl Systems

Ernest W. Della* and Paul A. Smith

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

ern.della@flinders.edu.au

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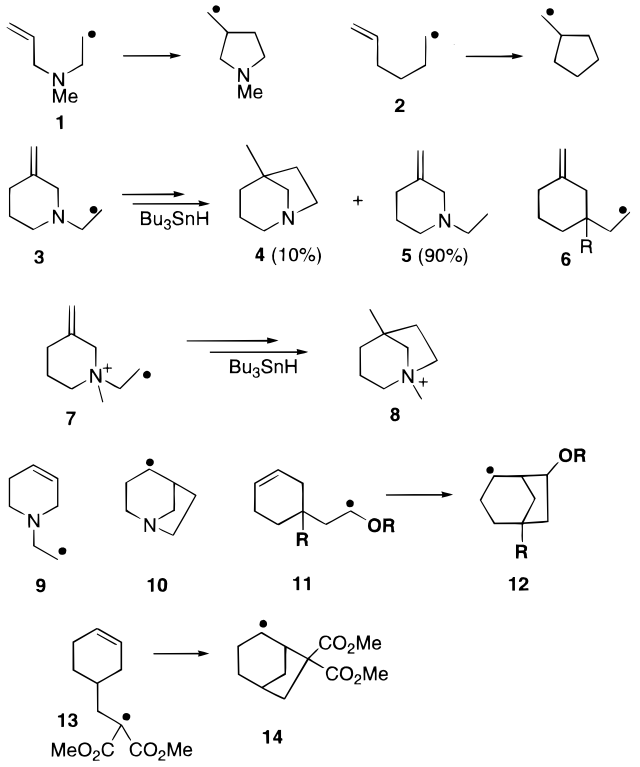
Treatment of 1-(2-phenylselenoethyl)-1,2,5,6-tetrahydropyridine (**15**) with tributyltin hydride affords only the product of reduction, demonstrating the reluctance of the 5-hexenyl radical **9** to undergo ring closure. When the nature of the radical is modified, either by introduction of an ester group at C4 or via its quaternary ammonium salt, cyclization occurs readily; while the radical **52** gives an excellent yield of 1-methyl-1-azoniabicyclo[3.2.1.]octyl bromide (**55**) uncontaminated with the product of reduction, the bicyclic product from **21** is accompanied by some reduced material. Production of the unwanted alkene can be eliminated in the latter by recourse to the quaternary ammonium ester 1-(2-bromoethyl)-4-carbethoxy-1-methyl-1,2,5,6-tetrahydropyridinium bromide (**35**) which, when exposed to tributyltin hydride, affords a 1:1 *endo/exo* mixture of 4-carbethoxy-1-methyl-1-azoniabicyclo[3.2.1]octyl bromide (**37**) exclusively. These results support the demonstration of the powerful polar effect of an ester function when attached to the double bond of a 5-hexenyl system, a property which can be exploited in the case of the radical **58**. Treatment of the precursor, 1-(2-bromoethyl)-3-carbethoxy-1-methyl-3-pyrrolinium bromide (**60**), with tributyltin hydride generates **58** which is found to cyclize with high regioselectivity, affording a convenient high-yielding synthesis of the *endo/exo* isomers of 3-carbethoxy-1-methyl-1-azoniabicyclo[2.2.1]heptyl bromide **57**. The isomeric bicyclo[2.2.1]heptyl ester **63** was not detected. These observations are in accordance with predictions based upon frontier molecular orbital considerations.

Introduction

As part of a program of studies directed toward the synthesis of heterocycles, we have demonstrated previously[1−3] that cyclization of β-amino and β-ammonium substituted 5-hexenyl radicals leads to excellent yields of heterocyclic compounds. A surprising observation, and one of synthetic significance, was that whereas the 3-methyl-3-aza-5-hexenyl radical **1** undergoes ring closure with a considerably enhanced rate compared with that of the corresponding carbon analogue **2**,[1] the modified 3-amino-5-hexenyl radical **3** was found[2] to give principally the product of reduction **5**. Despite the facility for ring closure of the all-carbon radical **6**[4] and its derivatives, a disappointing yield (ca. 10%) of cyclized product **4** was obtained from **3** under conditions found to be conducive for the cyclization of the carbocyclic analogue. In an attempt to obviate this problem, we transferred our attention to the behavior of the derived salt **7** in the expectation that a more favorable activation energy would be associated with its ring closure. It was believed[2] that the added methyl group would lead to an increase in the ground-state energy of **7** compared with that of the parent amine **3**, but would have little influence on the transition state energy of ring closure inasmuch as the alkyl group can adopt the equatorial position. In fact, the magnitude of this effect in facilitating ring-closure in the case of **7** turned out to be considerably larger than we had anticipated, and it was discovered that this process afforded excellent yields of the bicyclic heterocycle **8**.



* Corresponding author.

(1) Della, E. W.; Knill, A. M. *Aust. J. Chem.* **1995**, *48*, 2047.
(2) Della, E. W.; Knill, A. M. *J. Org. Chem.* **1996**, *61*, 7529.
(3) Della, E. W.; Knill, A. M. *Tetrahedron Lett.* **1996**, *37*, 5805.
(4) Della, E. W.; Knill, A. M. *J. Org. Chem.* **1995**, *60*, 3518.

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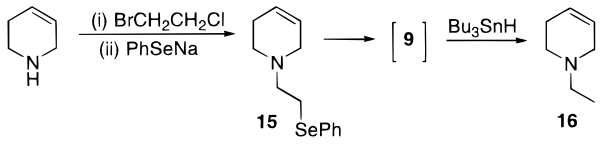
Scheme 1



Bearing in mind the difficulty of elaborating alkyl groups, one of our more recent objectives has been to adapt this procedure to the preparation of 1-azabicycloalkanes which lack the bridgehead methyl group. Our interest turned to the possibility of an intramolecular cyclization across an internal double bond, and we focused our investigation upon the behavior of the radical **9** as a potential precursor to the cyclized isomer **10**. The rationale for use of **9** was based on a precedent by Yadav and Fallis[5] who reported that cyclization of the radical **11** produced good yields of the bicyclo[3.2.1]octane derived from the rearranged radical **12**. This cyclization is especially interesting because it demonstrates that use of a stabilized radical, which would be associated with a relatively slow cyclization, is still possible using the tributyltin hydride method despite previous reports[6] that it is often unsuccessful for the formation of bridged bicyclic systems. Another interesting example of a system which would be expected to be reluctant to cyclize is reported by Curran and Chang[7] who showed that the alkene **13** can be induced to undergo cyclization to the substituted bicyclo[3.2.1]octane **14**. We report herein our observations.

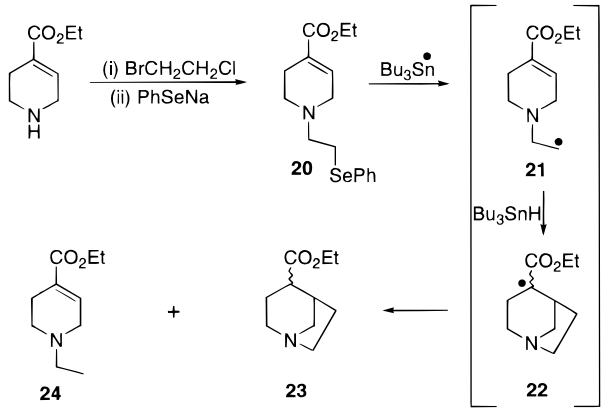
Results and Discussion

Consistent with our earlier goal of generating the target molecules as economically and as simply as possible, we employed the selenide **15** as the source of radical **9**. Synthesis of **15** could be achieved conveniently by alkylation of 1,2,5,6-tetrahydropyridine to give the *N*-(2-chloroethyl) derivative, followed by nucleophilic displacement of chlorine by the phenylseleno anion. Exposure of **15** to Bu_3SnH added slowly over 3 h in boiling benzene or toluene, however, yielded only **16**, the product of reduction (Scheme 1). There was no evidence for the formation of any cyclized material.

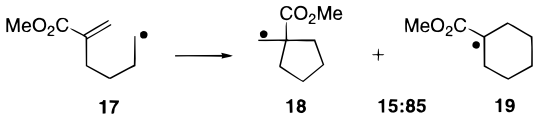
This observation is not totally surprising when the behavior of the exocyclic radical **3** is taken into consideration. Nevertheless, considering the relative ease of rearrangement of the analogues **11** and **13**, it was disappointing and it demonstrates once again that small changes in bond lengths and bond angles accompanying introduction of nitrogen in place of carbon appear to have a significant effect on the transition state, particularly, and so lead to an increase in activation energy.

In an attempt to devise an alternative strategy to the bicyclic system, we decided to exploit the recent observation[8] that attachment of an ester group to the double bond causes a rate enhancement in 6-*endo* mode of ring closure. Thus, we have found[8] that the regiochemistry of ring closure of the 5-carbomethoxy-5-hexenyl radical **17** is governed by a dominant polar effect associated with the presence of the ester group; frontier orbital interactions dominate both the stereoelectronic and steric effects

Scheme 2



and lead to a 15:85 mixture of 5-*exo* and 6-*endo* products derived from the cyclized radicals **18** and **19**. In view of the nucleophilic character of the radical **17**, it is expected that the regiochemistry of ring closure is determined by a SOMO/LUMO interaction;[9] accordingly, the predominance of 6-*endo* product is attributed to a highly attractive interaction between the radical center and the *β*-carbon of the α,*β*-unsaturated ester in the transition state because of the increased magnitude of the orbital coefficient at C6 compared with C5 in the LUMO frontier orbital of the alkene. Another important factor to be considered is the allyl-like thermodynamic stabilization present in radicals such as **19**, which complements the polar effect discussed above. The combination of both FMO theory and this allyl-like stabilization explain the recent observation concerning **17** that the 6-*endo* mode of ring closure is enhanced vs 5-*exo*. In related α,*β*-unsaturated cyclic systems, such as the radical **21**, the ester group would again be expected to play a prominent role in directing regioselectivity by promoting ring closure to the 5-*exo* species, the 1-azabicyclo[3.2.1]octyl isomer **22**, which would then give **23** at the expense of the reduced product **24**.

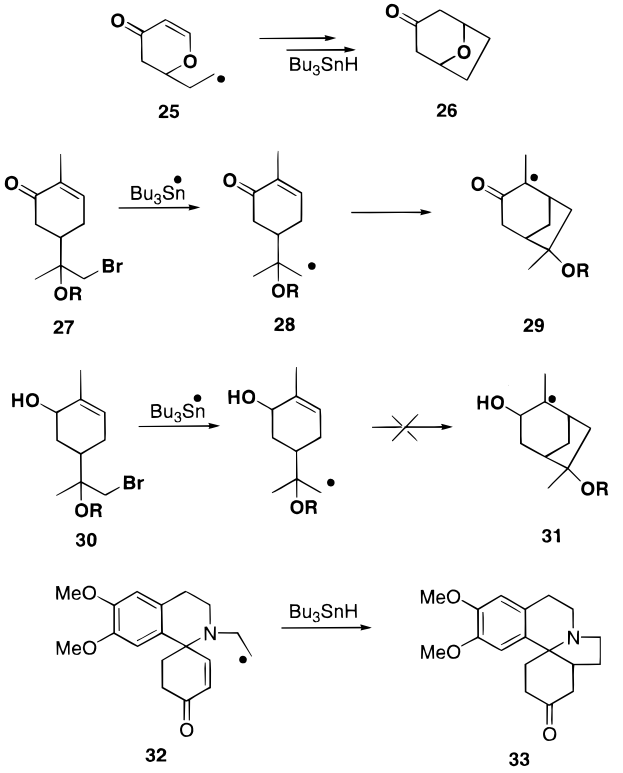


There are several noteworthy precedents for the importance of polar effects on bicyclic ring closure. For example, formation of the oxabicyclo[3.2.1]octane **26** from **25** is thought to be assisted this way[10] as was access to the bicyclo[3.2.1]octyl system from carvone precursors employed by the groups of Srikrishna[11] and Bonini.[12] The influence of a favorable polar effect was implicated in both of these reports and highlighted particularly by Srikrishna. Thus, it was observed that the radical derived from the allylic alcohol **30** failed to undergo cyclization to **31** under conditions which led to smooth ring closure (**28** → **29**) in the case of its α,*β*-unsaturated analogue.

Similarly, the *β*-amino radical species **32** has been

(5) Yadav, V.; Fallis, A. G. *Can. J. Chem*. **1991**, *69*, 779.
(6) Curran, D. P. *Synthesis* **1988**, *417*, 489.
(7) Curran, D. P.; Chang, C.-T. *J. Org. Chem*. **1989**, *54*, 3140.
(8) Della, E. W.; Kostakis, C.; Smith, P. A. *Org. Lett*. **1999**, *1*, 363.
(9) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: Chichester, 1976; Chapter 5.
(10) Clive, D. L.; Bergstra, R. J. *J. Org. Chem*. **1990**, *55*, 1786.
(11) (a) Srikrishna, A.; Hemamalini, P. *Tetrahedron*, **1992**, *42*, 9337. (b) Srikrishna, A.; Hemamalini, P. *J. Org. Chem*, **1990**, *55*, 4883.
(12) Bonini, C.; Fabio, R. D.; Mecozzi, S.; Righi, G. *Tetrahedron Lett*. **1990**, *31*, 5369.

shown[13] to undergo annulation via the α,β-unsaturated ketone to give the azabicycloalkane **33**. This cyclization is promoted by a favorable polar effect ascribed to the effect of the presence of the electron-withdrawing ketone function on the alkene LUMO as observed in the transformation **28** → **29**.

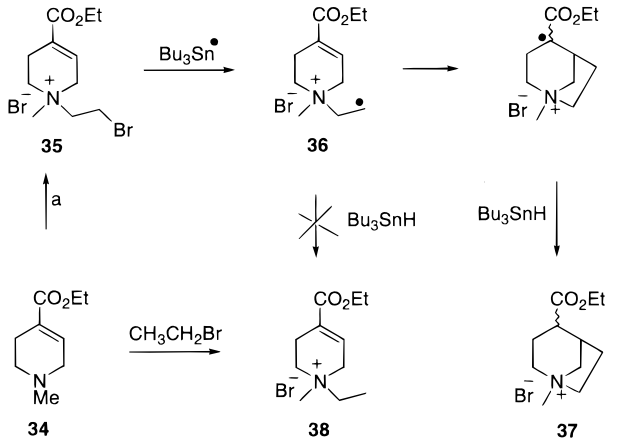


Access to the radical precursor **20** was provided by alkylation of 4-carbethoxy-1,2,5,6-tetrahydropyridine with 1-bromo-2-chloroethane, followed by treatment of the product with sodium benzeneselenolate. Exposure of **20** to tributyltin hydride under standard conditions gave a 80:20 mixture of the cyclized and reduced products **23** and **24**. In contrast with the behavior of the unsubstituted radical **9** which, as discussed above, shows little inclination to cyclize, the facility for ring closure of radical **21** provides another dramatic demonstration of the influence of the ester function on the rate of cyclization.

Although the enhanced amount of cyclized product derived from **20** was pleasing, the contamination of product by reduced material **24** was disappointing. In an attempt to further suppress formation of the latter, it was decided to examine the quaternized radical species **36**. Our expectation was that the added methyl group would play a similar favorable role on the rate of cyclization as disclosed above for the exocyclic alkene **6** and promote ring closure at the expense of reduction.

Synthesis of the required precursor **35** was achieved by treatment of 4-carbethoxy-1-methyl-1,2,5,6-tetrahydropyridine **34**[14] with an excess of 1,2-dibromoethane at 70 °C for 3 h. This conversion has the 2-fold effect of quaternization of nitrogen with concurrent introduction of the incipient radical center. Although difficulties such as proton abstraction and bromine elimination were

Scheme 3



encountered when this procedure was applied to the acyclic tertiary amine, triethylamine, less-hindered amines such as **34** were found to react to give the alkylated product in excellent yield. In any case, separation of possible protonated amines from the quaternary salts could be achieved simply by chromatography on alumina. The conversion **34** → **35** was achieved in 92% yield, and this procedure was therefore routinely applied to the preparation of quaternary salts employed in this work.

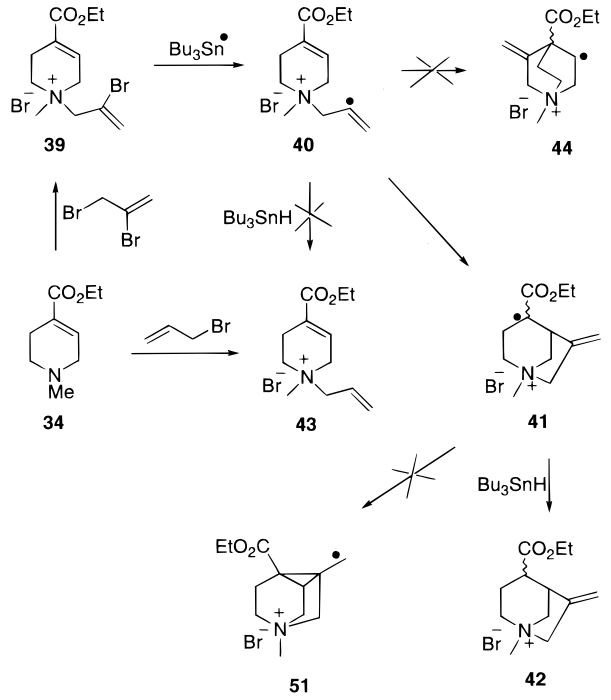
Under the modified conditions we had developed previously[2,15] for cyclization involving ammonium salts, a refluxing 0.025 M solution of **35** in *tert*-amyl alcohol was deoxygenated and treated with solution of Bu_3SnH (1.1 equiv) in *tert*-amyl alcohol containing a catalytic amount of AIBN over 15 min via a syringe pump. The solution was heated for a further 15 min and then worked up in the usual way. Analysis of the crude product by ^1H and ^{13}C NMR spectroscopy showed it to consist of the cyclized salt **37** (91%) as a 1:1 mixture of *exo* and *endo* esters. The product of reduction **38**, an authentic specimen of which was prepared as reported, was not detected. Clearly, the added methyl group is of paramount importance in determining the preferred pathway in the reaction.

In the interest of introducing increased functionality in the bicyclo[3.2.1]octane ring system, we considered extending the synthesis to include the species **42** which contains an exocyclic methylene at the 6 position. Retrosynthetically, C5−C6 bond dislocation in the precursor **41** implicates the quaternary ammonium vinyl radical **40** as the key intermediate in this synthesis. Preparation of its precursor **39**, by treatment of amine **34** with 1,2-dibromopropene as depicted in Scheme 4, is relatively simple and found to be high yielding.

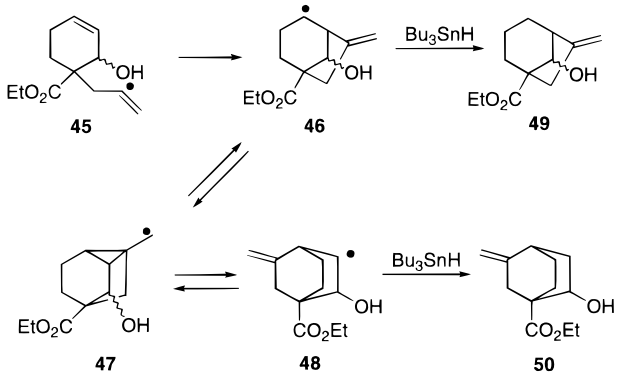
The salt **39** was exposed to tributyltin hydride under the usual conditions and, after workup, NMR analysis of the product indicated that ring closure of **40** had occurred in an exclusive 5-*exo* manner giving rise to a 12:88 mixture of the *exo* and *endo* isomers of **42** in excellent yield (90%). Separation of the mixture into the pure isomers was effected by chromatography on alumina. It is instructive to compare this result with the observation by Berkowitz and Wilson[16] on the behavior of the vinyl radical **45** which affords a mixture of the isomeric bicyclooctanes **49** and **50** (Scheme 5). It is

(13) Danishefsky, S. J.; Panek, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 917.
(14) Lyle, R. E.; Perlowski, E. F.; Troscianiec, H. J.; Lyle, G. G. *J. Org. Chem.* **1955**, *20*, 1761.
(15) Della, E. W.; Smith, P. A. *J. Org. Chem.* **1999**, *64*, 1798.
(16) Berkowitz, W. F.; Wilson W. J. *J. Org. Chem.* **1991**, *56*, 3097.

Scheme 4



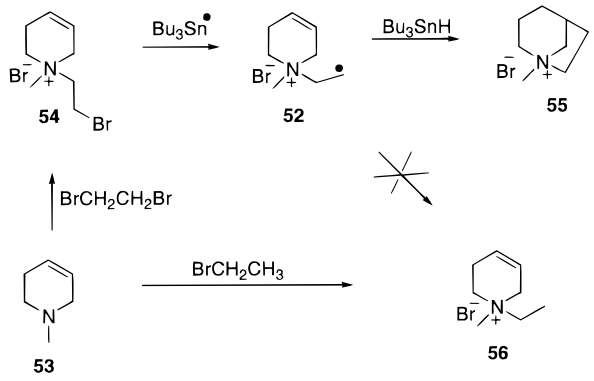
Scheme 5



claimed[16] that the bicyclo[2.2.2]octane **50** is not formed by 6-*endo* ring closure at C4 in the radical **45**, but rather it is derived exclusively via the intermediate **48**. The latter is produced by ring-opening of the cyclopropylmethyl radical **47** which occurs via rearrangement of the initially formed butenyl radical **46**. It is not surprising that a bicyclo[2.2.2]octyl derivative is not detected in our work; it would have had to arise either by an energetically unfavorable 6-*endo* closure at C4 in **40** or via the intermediacy of radical **51**, generated in an unlikely interconversion from the intermediate **41**. Normally, the position of equilibrium between 3-butenyl and cyclopropylmethyl radicals favors the former, a feature which would be enormously enhanced in the case of **41** because of resonance-stabilization by the ester group. Indeed, these observations support the proposal by Berkowitz and Wilson[16] that the precursor **48** to the bicyclo[2.2.2]octane **50** is not derived directly from the acyclic species **45**.

On the basis of the ease of ring closure of the radicals **36** and **40**, we focused our thoughts once more on the parent system **9** which, as discussed earlier, was found to be resistant to cyclization. We elected to reexamine the unsubstituted system in the form of its ammonium salt, viz., the radical **52**. It was felt that **52** would be

Scheme 6



rather more conducive to cyclization compared with the parent species **9** as a result of the added methyl group along the lines discussed earlier in connection with the quaternary system **7**. Treatment of commercially available 1-methyl-1,2,3,6-tetrahydropyridine **53** with an excess of 1,2 dibromoethane led to formation of the salt **54** (88% yield), which upon exposure to tributyltin hydride afforded the cyclized product **55** in an excellent yield. The product of reduction **56** was not detected (Scheme 6), demonstrating again that the added alkyl substituent has a dramatic effect on the kinetics and extent of ring closure.

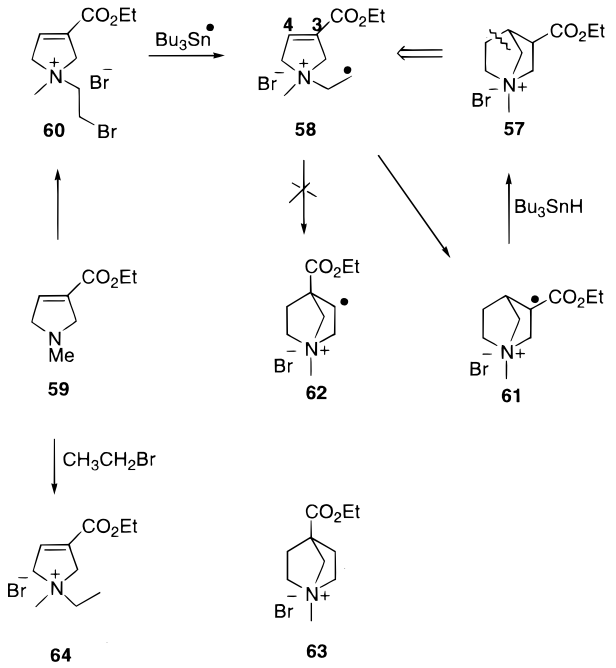
Finally, a synthetic target which has occupied our attention for some time is the bicyclo[2.2.1]heptyl salt **57**. This compound has been cited in the literature on a number of occasions, principally in connection with its reputed physiological activity.[17] Several recent reports[18] have described the synthesis of **57** via sequences involving ionic transformations. We were interested in devising an alternative radical-mediated route to the salt.

Retrosynthetically, on the basis of the observations made in the current investigation described herein, it seemed to us that ring closure of the β-ammonio radical **58** possessed considerable potential. In view of its symmetry, the species **58** is particularly interesting; it is unique among the systems under study in this work because no discrimination between ring closure at C3 or C4 is expected on stereoelectronic grounds. Each mode represents a 5-*exo* closure, that at C3 would lead to the bicycloheptyl radical **62** and hence **57**, whereas closure at C4 would give the isomeric species **61** en route to the ester **63**. However, in accordance with a highly effective polar factor associated with the presence of the ester function, cyclization at C4 would be expected to predominate over C3 closure; this would be reinforced by a favorable steric effect. Thus, it was anticipated that the radical **61**, rather than its isomer **62**, would be the preferred product of rearrangement of the monocyclic species **56**, and accordingly the bicyclic ester **57**, rather than its isomer **63**, should result from treatment of the bromide **60** with tributyltin hydride.

(17) See Jenkins, S. M.; Wadsworth, H. J.; Bromidge, S.; Orlek, B. S.; Wyman, P. A.; Riley, G. J.; Hawkins, J. *J. Med. Chem.* **1992**, *35*, 2392 for leading references.

(18) (a) Saunders, J.; MacLeod, A. M.; Merchant, K.; Showell, G. A.; Snow, R. J.; Street, L. J.; Baker, R. *J. Chem. Soc. Chem. Commun.* **1988**, 1618. (b) Street, L. J.; Baker, R.; Book, T.; Kneen, C. O.; MacLeod, A. M.; Merchant, K.; Showell, G. A.; Saunders, J.; Herbert, R. H.; Freedman, S. B.; Harley, E. A. *J. Med. Chem.* **1990**, *33*, 2690. (c) Cottrell, I. F.; Hands, D.; Kennedy, D. J.; Paul, K. J.; Wright, S. H. B.; Hoogsteen, K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1091. (d) Houghton, P. G.; Humphrey, G. R.; Kennedy, D. J.; Roberts, D. C.; Wright, S. H. B. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1421.

Scheme 7



To test these hypotheses, the precursor **60**, synthesized by treatment of the known[19] amine **59** with 1,2-dibromoethane, was exposed to tributyltin hydride in 2-methyl-2-butanol solution under the conditions specified above. It afforded an 85% yield of crude product, which was revealed by NMR analysis to consist almost exclusively of the desired 1-azoniabicyclo[2.2.1]heptyl ester **57**, contaminated with a small quantity of the product of reduction **64**. None of the isomeric species **63** was detected. Column chromatography enabled separation of the pure ester **57** (74%) as a 90:10 mixture of *endo* and *exo* isomers. The predominance of the *endo* ester in the product is consistent with the expected *exo* delivery of hydrogen by Bu_3SnH at a C2 trigonal carbon in the norbornyl system **61** and supports the suggested *exo*/*endo* assignments made in the parent amine.[20] This sequence then represents a useful alternative to the synthesis of the ester **57**.

In conclusion, it is seen that ring closure of these modified 5-hexenyl radicals provides a valuable entry to bicyclo[3.2.1]octanes and bicyclo[2.2.1]heptanes. While cyclization of the β-ammonio substituted cyclohexene and cyclopentene radicals occurs readily, the free amine requires activation of the double bond by an attached ester group. Indeed, cyclization is driven strongly in all cases under study involving the α,β-unsaturated esters by a combination of the polar effect of the ester function and the effect of allyl-like product stabilization such that these ring closures occur with high regioselectivity.

Experimental Section

3-Carbethoxy-1-methyl-3-pyrroline[19] and 4-carbethoxy-1-methyl-1,2,5,6-tetrahydropyridine[14] were synthesized as reported. 4-Carbethoxy-1,2,5,6-tetrahydropyridine was prepared from 4-carbethoxy-1-methyl-1,2,5,6-tetrahydropyridine as described[21] except that demethylation was effected by use of ethyl chloroformate or phenyl chloroformate instead of vinyl chloroformate. 1-Ethyl-1,2,5,6-tetrahydropyridine was synthesized as reported previously[22] in order to record its NMR data. 4-Carbethoxy-1-ethyl-1,2,5,6-tetrahydropyridine was prepared via a modification of the procedure described.[23] 1,2,5,6-Tetrahydropyridine, 1-methyl-1,2,5,6-tetrahydropyridinium chloride, and 4-carbethoxypyridine (ethyl isonicotinate) were available commercially.

General Procedure for Generation of 2-Bromoethylammonium Salts. The free amine was heated at 70 °C for 3 h with 1,2-dibromoethane (5.0 equiv). The reaction mixture was cooled, and excess ether was added to precipitate the quaternary ammonium salt which was isolated by filtration. The salt was then purified by recrystallization or by chromatography on alumina.

General Procedure for Generation of 2-Phenylselenoethylamines. The secondary amine was stirred with K_2CO_3 (1.5 equiv) and 1-bromo-2-chloroethane (2 equiv) in acetone (1.5 mL/mmol) for 24 h. The solvent was removed, water was added, and the solution was extracted with ether (2×). The combined ether extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. If necessary, purification was effected by chromatography on silica (50:50 diethyl ether: hexane). A solution of sodium benzeneselenolate (PhSeNa) was prepared by treatment of diphenyldiselenide in dry ethanol (5 mL/mmol) with $NaBH_4$ (2.2 equiv). The 2-chloroethylamine was added and the solution heated under reflux for 2 h. The solvent was removed, 5% HCl was added, and the aqueous solution was washed with hexane (2×). The aqueous layer was basified (K_2CO_3) and extracted with CH_2Cl_2 (2×). The combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated.

General Procedure for Workup of Radical Cyclization Reactions of Quaternary Ammonium Salts. The solvent was removed in vacuo and the residue triturated with ether several times to facilitate removal of tin-containing residues. Particularly hygroscopic salts were chromatographed (alumina/chloroform) if trituration was not effective in the removal of all the tin residues.

Characterization of Ammonium Salts. Elemental analyses were performed by Microanalytical Services, University of Otago, New Zealand, or Australian Microanalytical Services. Hygroscopic ammonium salts were unsuitable for elemental analysis by combustion. HRMS of the ammonium moiety of a number of these salts were determined by FAB using the Fisons Instruments VG Autospec facility located at the Australian National University (Dr. J. MacLeod, director).

1-(2-Phenylselenoethyl)-1,2,5,6-tetrahydropyridine (15). 1,2,5,6-Tetrahydropyridine (1 g, 12.0 mmol) was treated with 1-bromo-2-chlorethane as described in the general procedure to give 1-(2-chloroethyl)-1,2,5,6-tetrahydropyridine (1.3 g, 74%) as an amber oil after purification of the product by column chromatography: ^{1}H NMR ($CDCl_3$) δ 3.62 (t, J = 7.2 Hz, 2H), 3.05 (m, 2H), 2.8 (t, J = 7.2 Hz, 2H), 2.64 (t, J = 5.7 Hz, 2H), 2.19 (bs, 2H); ^{13}C NMR ($CDCl_3$) δ 125.1, 124.8, 59.7, 52.5, 50.0, 41.0, 25.9; HRMS calcd for $C_7H_{12}NCl$ 145.0658, found 145.0660. 1-(2-Chloroethyl)-1,2,5,6-tetrahydropyridine (1.0 g, 6.9 mmol) was exposed to PhSeNa as described above giving 1-(2-phenylselenoethyl)-1,2,5,6-tetrahydropyridine (**15**) (1.6 g, 84%) as a colorless oil after distillation (Kugelrohr: 120 °C (0.5 mm)); ^{1}H NMR ($CDCl_3$) δ 7.51 (m, 2H), 7.25 (m, 3H), 5.77−5.63 (m, 2H), 3.08 (t, J = 7.9 Hz, 2H), 3.0 (bs, 2H), 2.76 (t, J = 7.9 Hz, 2H), 2.59 (t, J = 5.7 Hz, 2H), 2.18 (bs, 2H); ^{13}C NMR ($CDCl_3$) δ 132.2, 130.2, 128.9, 126.6, 125.1, 124.9, 58.4, 52.3, 49.7, 26.0, 24.7; HRMS calcd for $C_{13}H_{17}NSe$ 267.0526, found 267.0528.

1-Ethyl-1,2,5,6-tetrahydropyridine (16). 1,2,5,6-Tetrahydropyridine was stirred with K_2CO_3 (1.5 equiv) and bromoethane (2.0 equiv) in acetone (1.5 mL/mmol) for 24 h. The solvent was removed, water was added, and the solution was

(19) Mattocks, A. R. *J. Chem. Soc., Perkins Trans. 1* **1978**, 896.
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extracted with ether (2×). The combined ether extracts were dried (Na_2SO_4), and the solvent was removed in vacuo to yield 1-ethyl-1,2,5,6-tetrahydropyridine (**16**) as an amber oil: ^{1}H NMR ($CDCl_3$) δ 5.8−5.64 (m, 2H), 2.95 (m, 2H), 2.55 (t, J = 5.7 Hz, 2H), 2.46 (t, J = 7.2 Hz, 2H), 2.19 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 125.2, 125.1, 52.2, 49.7, 26.2, 12.1. HRMS calcd for $C_7H_{13}N$ 111.1048, found 111.1051.

Attempted Cyclization of 1-(2-Phenylselenoethyl)-1,2,5,6-tetrahydropyridine (15). A 0.025 M solution of **15** (0.2 g, 0.75 mmol) in toluene was deoxygenated and heated under reflux. A solution of Bu_3SnH (0.66 g, 2.3 mmol) in toluene (3 mL) containing AIBN (cat.) was added over 3 h. The progress of reaction was monitored by GC and, upon completion, the solution was cooled and extracted with 5% HCl. The aqueous extracts were washed with hexane, and the solution was basified (K_2CO_3) and extracted with dichloromethane. The organic extract was dried (Na_2SO_4) and evaporated to give an amber oil (0.07 g, 83%) which was identified as 1-ethyl-1,2,5,6-tetrahydropyridine **16**.

4-Carbethoxy-1-(2-phenylselenoethyl)-1,2,5,6-tetrahydropyridine (20). Treatment of 4-carbethoxy-1,2,5,6-tetrahydropyridine (7.0 g, 45 mmol) with $BrCH_2CH_2Cl$ as described above afforded 4-carbethoxy-1-(2-chloroethyl)-1,2,5,6-tetrahydropyridine (5.3 g, 54%) as an amber oil: ^{1}H NMR ($CDCl_3$) δ 6.83 (m, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.57 (t, J = 6.9 Hz, 2H), 3.19 (q, J = 3.1 Hz, 2H), 2.79 (t, J = 6.9 Hz, 2H), 2.63 (t, J = 5.7 Hz, 2H), 2.4 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.3, 135.8, 128.8, 60.3, 59.0, 52.4, 49.5, 41.0, 24.9, 14.1; HRMS calcd for $C_{10}H_{16}ClNO_2$ 217.0870, found 217.0874. Exposure of 4-carbethoxy-1-(2-chloroethyl)-1,2,5,6-tetrahydropyridine (1.9 g, 8.8 mmol) to PhSeNa as outlined above yielded 4-carbethoxy-1-(2-phenylselenoethyl)-1,2,5,6-tetrahydropyridine (**20**) (2.5 g, 84%) as a colorless oil after column chromatography of the crude product on alumina (20% ether/hexane): ^{1}H NMR ($CDCl_3$) δ 7.51−7.48 (m, 2H), 7.28−7.22 (m, 3H), 6.86 (sept, J = 1.8 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.17 (q, J = 3.0 Hz, 2H), 3.06 (m, 2H), 2.78 (m, 2H), 2.6 (t, J = 5.7 Hz, 2H), 2.41 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.4, 136.0, 132.3, 130.1, 128.9, 128.8, 126.7, 60.2, 57.6, 52.2, 49.1, 25.0, 24.9, 14.2; HRMS calcd for $C_{16}H_{21}NO_2Se$ 339.0738, found 339.0739.

4-Carbethoxy-1-ethyl-1,2,5,6-tetrahydropyridine (24). Ethyl isonicotinate (2.0 g, 13 mmol) was treated with bromoethane and the resulting pyridinium salt reduced with $NaBH_4$.[23] Distillation of the product (Kugelrohr: 80 °C (0.5 mm)) yielded 1-ethyl-4-carbethoxy-1,2,5,6-tetrahydropyridine (**24**) (1.8 g, 75%) as a colorless oil: ^{1}H NMR[22] ($CDCl_3$) δ 6.9 (m, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.15 (q, J = 3.1 Hz, 2H), 2.6 (q, J = 5.6 Hz, 2H), 2.5 (q, J = 7.2 Hz, 2H), 2.43 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.5, 136.3, 128.8, 60.2, 52.2, 51.7, 49.2, 25.2, 14.1, 12.1; HRMS calcd for $C_{10}H_{17}NO_2$ 183.1259, found 183.1260.

Treatment of 4-Carbethoxy-1-(2-phenylselenoethyl)-1,2,5,6-tetrahydropyridine (20) with Bu_3SnH. A 0.025 M solution of 4-carbethoxy-1-(2-phenylselenoethyl)-1,2,5,6-tetrahydropyridine (**20**) (0.1 g, 0.29 mmol) in toluene was deoxygenated and heated under reflux. A solution of Bu_3SnH (0.26 g, 0.87 mmol) in toluene (3 mL) containing AIBN (cat.) was added over 3 h, and the progress of the reaction was monitored by GC. The solution was cooled and extracted with 5% HCl, and the aqueous extracts were washed with hexane. The solution was basified (K_2CO_3), and extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and evaporated to give an amber oil (0.038 g, 70%) which by NMR analysis was found to consist of a 80:20 mixture of the amines **23** and **24**. Attempts to separate the components (column chromatography, distillation (80 °C (0.5 mm)), selective bromination, or oxidation of the double bond in the reduced material followed by distillation) were unsuccessful. The product was found to decompose readily and must be treated with care. Treatment of the mixture with methyl iodide gave a product whose NMR spectrum was identical with that of **37**: ^{1}H NMR ($CDCl_3$) δ 4.19 (m, 2H), 3.05−2.2 (m, 8H), 2.0−1.7 (m, 4H), 1.25 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 174.4, 174.0, 60.4, 60.3, 56.3, 54.0, 52.7, 51.5, 50.8, 45.2, 44.5, 36.6, 36.2, 30.8, 28.2, 27.5, 21.3, 20.3, 14.2, 14.1.; HRMS calcd for $C_{10}H_{17}NO_2$+ 183.1259, found 183.1258.

1-(2-Bromoethyl)-4-carbethoxy-1-methyl-1,2,5,6-tetrahydropyridinium Bromide (35). 4-Carbethoxy-1-methyl-1,2,5,6-tetrahydropyridine (**34**) (1.0 g, 5.9 mmol) was treated with $BrCH_2CH_2Cl$ as described in the general procedure and the product recrystallized from ethanol/ether to furnish the salt **35** (1.9 g, 92%) as colorless crystals: mp 156−158 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 6.80 (s, 1H), 4.40 (m, 2H), 4.21 (q, J = 7.2 Hz, 2H), 3.98−3.93 (m, 5H), 3.77 (m, 1H), 3.25 (s, 3H), 2.69 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 164.0, 127.2, 62.6, 60.8, 58.7, 56.2, 47.1, 22.2, 20.2, 14.0. Anal. Calcd for $C_{11}H_{19}Br_2NO_2$: C, 37.1; H 5.36; N, 3.92. Found: C, 36.70; H, 5.32; N, 3.95.

1-Ethyl-4-carbethoxy-1-methyl-1,2,5,6-tetrahydropyridinium Bromide (38). 4-Carbethoxy-1-methyl-1,2,5,6-tetrahydropyridine (**34**) (0.5 g, 3.0 mmol) was stirred with bromoethane at room temp for 12 h, after which the solvent was removed and the residue triturated with ether. Recrystallization of the product from ethanol/ether gave **38** as colorless crystals (0.75 g, 90%): mp 158−160 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 6.84 (s, 1H), 4.48 (m, 2H), 4.24 (q, J = 7.2 Hz, 2H), 3.90 (m, 1H), 3.74 (m, 3H), 3.23 (s, 3H), 2.72 (bs, 2H), 1.45 (t, J = 7.0 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 164, 129.2, 127.4, 60.8, 58.7, 58.4, 55.5, 46.5, 20.2, 13.8, 7.6. Anal. Calcd for $C_{11}H_{20}BrNO_2$: C, 47.49; H, 7.25; N, 5.03. Found: C, 47.47; H, 7.35; N, 4.85.

4-Carbethoxy-1-methyl-1-azoniabicyclo[3.2.1]octyl Bromide (37). A 0.025 M solution of 1-(2-bromoethyl)-4-carbethoxy-1-methyl-1,2,5,6-tetrahydropyridinium bromide (**35**) (0.2 g, 0.56 mmol) in 2-methyl-2-butanol was deoxygenated and heated under reflux. A solution of Bu_3SnH (0.18 g, 0.62 mmol) in 2-methyl-2-butanol (1 mL) containing AIBN (cat.) was added over 15 min and the solution heated for a further 15 min. Workup in the usual mannner yielded a very hygroscopic product which by NMR analysis was found to consist of 4-carbethoxy-1-methyl-1-azoniabicyclo[3.2.1]octyl bromide (**37**) (ca. 50:50 *endo:exo*) only: ^{1}H NMR ($CDCl_3$) δ 4.3−3.9 (m, 14H), 3.75 (d, J = 17.0 Hz, 1H), 3.56 (s, 3H), 3.54 (s, 3H), 3.45 (m, 1H), 3.15−3.0 (m, 3H), 2.75 (m, 2H), 2.54−2.36 (m, 2H), 2.2 (m, 3H), 2.1−1.9 (m, 2H), 1.26 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 171.6, 171.0, 66.6, 64.1, 61.7, 61.3, 60.9, 60.7, 60.5, 59.7, 50.8, 50.5, 40.8, 40.1, 36.4, 36.2, 28.0, 25.3, 20.4, 19.7, 13.51, 13.48; HRMS calcd for $C_{11}H_{20}NO_2^+$ 198.1494, found 198.1489.

1-(2-Bromopropenyl)-4-carbethoxy-1-methyl-1,2,5,6-tetrahydropyridinium Bromide (39). Excess 1,2-dibromo-2-propene was added to 1-methyl-4-carbethoxy-1,2,3,6-tetrahydropyridine (**34**) in ether and the solution stirred for 1 h. The precipitate was filtered off and recrystallized (ethanol/ethyl acetate) to yield **39** as colorless needles (0.4 g, 90%): mp 168−170 °C; ^{1}H NMR ($CDCl_3$) δ 6.98 (d, J = 1.8 Hz, 1H), 6.87 (m, 1H), 6.26 (d, J = 1.8 Hz, 1H), 5.14 (d, J = 13.6 Hz, 1H), 5.08 (d, J = 13.6 Hz, 1H), 4.96 (m, 1H), 4.7 (m, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.16 (m, 2H), 3.49 (s, 3H), 2.8 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 163.8, 135.1, 128.4, 127.5, 116.3, 68.4, 61.3, 59.0, 56.8, 47.4, 20.5, 13.9. Anal. Calcd for $C_{12}H_{19}Br_2NO_2$: C, 39.05; H, 5.19; N, 3.79. Found: C,39.31; H, 5.33; N,3.78.

4-Carbethoxy-1-methyl-1-(2-propenyl)-1,2,5,6-tetrahydropyridinium Bromide (43). Excess allyl bromide was added to a solution of 1-methyl-4-carbethoxy-1,2,3,6-tetrahydropyridine (**34**) in ether and the mixture stirred for 1 h. The precipitate was isolated by filtration and recrystallized (ethanol/ethyl acetate) to yield **43** as colorless needles (0.3 g, 86%): mp 200−202 °C; ^{1}H NMR ($CDCl_3$) δ 6.87 (m, 1H), 6.1 0(m, 1H), 5.85 (m, 2H), 4.73 (m, 1H), 4.60 (m, 2H), 4.48 (m, 1H), 4.24 (q, J = 7.1 Hz, 2H), 4.05 (m, 1H), 3.85 (m, 1H), 3.38 (s, 3H), 2.75 (m, 2H), 1.32 (t, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) 163.8, 130.2, 128.7, 127.5, 123.6, 64.9, 61.1, 58.2, 55.7, 47.2, 20.4, 13.8. Anal. Calcd for $C_{12}H_{20}BrNO_2$: C, 49.67; H,6.95; N,4.83. Found: C,49.81; H,7.05; N,4.86.

Cyclization of 1-(2-Bromopropenyl)-1-methyl-4-carbethoxy-1,2,5,6-tetrahydropyridinium Bromide (39). A 0.025 M solution of 1-(2-bromopropenyl)-1-methyl-4-carbethoxy-1,2,5,6-tetrahydropyridinium bromide (**39**) (0.2 g, 0.54

mmol) in 2-methyl-2-butanol was deoxygenated and heated under reflux. A solution of Bu_3SnH (0.19 g, 0.65 mmol) in 2-methyl-2-butanol (1 mL) containing AIBN (cat.) was added over 30 min and the solution heated for a further 15 min. Workup in the usual manner yielded an amber residue shown by NMR analysis to consist of a 12:88 mixture of *exo*/*endo* isomers of ester **42** (0.14 g, 90%) which were separated by column chromatography (neutral alumina; 10% ethanol/dichloromethane. *exo*-**42**: ^{1}H NMR ($CDCl_3$) 5.3 (d, J = 9.3 Hz, 2H), 5.04 (d, J = 16.2 Hz, 1H), 4.55 (d, J = 16.2 Hz, 1H), 4.3 (m, 2H), 4.17 (q, J = 7.2 Hz, 2H), 4.05 (m, 1H), 3.64 (s, 3H), 3.6 (m, 1H), 3.48 (m, 1H), 2.77 (m, 1H), 2.2 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H);); ^{13}C NMR ($CDCl_3$) 171.5, 141.0, 111.2, 64.6, 61.7, 61.5, 58.0, 51.7, 42.6, 41.9, 20.2, 14.1. *endo* **42**: ^{1}H NMR ($CDCl_3$) 5.17 (d, J = 9.3 Hz, 2H), 4.7 (d, J = 15.6 Hz, 1H), 4.43 (d, J = 10.5 Hz, 1H), 4.32 (d, J = 15.6 Hz, 1H), 4.23 (m, 1H), 4.17 (q, J = 7.2 Hz, 2H), 4.04 (m, 1H), 3.8 (m, 1H), 3.64 (s, 3H), 3.6 (m, 1H), 3.15 (m, 1H), 2.2 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H);); ^{13}C NMR ($CDCl_3$) 170.3, 139.5, 111.0, 67.3, 65.5, 62.0, 60.9, 51.3, 42.4, 42.3, 20.6, 14.0. Anal. Calcd for $C_{12}H_{20}BrNO_2$: C, 49.67; H,6.95; N,4.83. Found: C,49.53; H,6.67; N,4.98.

1-(2-Bromoethyl)-1-methyl-1,2,5,6-tetrahydropyridinium Bromide (54). 1-Methyl-1,2,5,6-tetrahydropyridine (**53**) (1 g, 10 mmol), generated from an aqueous solution of commercially available 1-methyl-1,2,5,6-tetrahydropyridine hydrochloride by addition of saturated K_2CO_3 solution followed by extraction with ether, was converted into the title compound **54** (2.6 g, 88%) by treatment with 1,2-dibromoethane as described in the general procedure above. The salt crystallized from ethanol/ether as colorless crystals: mp 188−190 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 6.04 (d, J = 10 Hz, 1H), 5.72 (d, J = 10 Hz, 1H), 4.26 (d, J = 16.8 Hz, 1H), 4.10 (d, J = 16.8 Hz, 1H), 4.05−3.95 (m, 4H), 3.83 (m, 1H), 3.71 (m, 1H), 3.29 (s, 3H), 2.52 (bs, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 124.1, 118.7, 62.8, 58.8, 56.7, 46.8, 21.5, 20.8. Anal. Calcd for $C_8H_{15}Br_2N$: C, 33.71; H, 5.30; N, 4.91. Found: C, 33.85; H, 5.51; N, 5.15.

1-Methyl-1-azoniabicyclo[3.2.1]octyl Bromide (55). A 0.025 M solution of 1-(2-bromoethyl)-1-methyl-1,2,5,6-tetrahydropyridinium bromide (**54**) (0.2 g, 0.7 mmol) in 2-methyl-2-butanol was deoxygenated and heated under reflux. A solution of Bu_3SnH (0.2 g, 0.7 mmol) in 2-methyl-2-butanol (1 mL) containing AIBN (cat.) was added over 10 min and the solution heated for a further 10 min. Workup as described above yielded the salt **55** (0.13 g, 93%) as slightly hygroscopic colorless crystals, ^{1}H and ^{13}C NMR analysis of which revealed the absence of **56**. The product was recrystallized from ethanol/ether: mp > 300 °C; ^{1}H NMR ($CDCl_3$) δ 4.04 (m, 1H), 3.83 (m, 5H), 3.55 (s, 3H), 2.79 (bs, 1H), 2.57 (sept, J = 6.4 Hz, 1H), 2.10 (m, 1H), 1.93 (m, 2H), 1.80 (m, 1H), 1.70 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 68.2, 63.7, 61.3, 51.5, 34.4, 28.3, 26.7, 18.4; Anal. Calcd for $C_8H_{16}BrN$: C, 46.62; H, 7.82; N, 6.87. Found: C, 46.33; H, 7.88; N, 6.80.

1-Ethyl-1-methyl-1,2,5,6-tetrahydropyridinium Bromide (56). 1-Methyl-1,2,5,6-tetrahydropyridine (**53**) (0.5 g, 5 mmol) was stirred with an excess of bromoethane at room temp for 12 h. The solvent was removed and the residue triturated with ether causing separation of a solid the which was purified by recrystallization from ethanol/ether to give salt **56** (0.9 g, 88%) as colorless, very hygroscopic crystals: ^{1}H NMR ($CDCl_3$) δ 6.00 (m, 1H), 5.74 (m, 1H), 4.27 (m, 2H), 3.94 (sept, J = 6.0 Hz, 1H), 3.87 (m, 2H), 3.73 (m, 1H), 3.37 (s, 3H), 2.55 (m, 2H), 1.47 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 124.5, 119.1, 58.9, 58.8, 56.3, 47.2, 21.4, 8.1.

1-(2-Bromoethyl)-3-carbethoxy-1-methyl-3-pyrrolinium Bromide (60). 3-Carbethoxy-1-methyl-3-pyrroline (**59**) (0.4 g, 2.9 mmol) was treated with 1,2-dibromoethane as described in the general procedure above, and the product was purified on alumina (dichloromethane) to give **60** (0.75 g, 80%) as a hygroscopic oil: ^{1}H NMR ($CDCl_3$) δ 6.91 (s, 1H), 5.29 (d, 1H), 5.05 (m, 2H), 4.78 (d, J = 15.0 Hz, 1H), 4.61 (t, J = 7.1 Hz, 2H), 4.25 (q, J = 7.1 Hz, 2H), 3.98 (t, J = 7.1 Hz, 2H), 3.69 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 160.8, 134.0, 129.9, 71.8, 69.3, 64.6, 61.6, 52.0, 29.3, 23.2, 13.8; HRMS calcd for $C_{10}H_{17}BrNO_2^+$ 262.0443, found 262.0453.

3-Carbethoxy-1-ethyl-1-methyl-3-pyrrolinium Bromide (64). 3-Carbethoxy-1-methyl-3-pyrroline (**59**) (0.1 g, 0.7 mmol) was stirred with excess bromoethane at room temp for 12 h, after which the solvent was removed and the residue triturated with ether. Purification of the product on alumina (dichloromethane) gave **64** as an hygroscopic amber oil (0.14 g, 82%): ^{1}H NMR ($CDCl_3$) δ 6.88 (s, 1H), 5.09 (d, J = 17 Hz, 1H), 4.96 (d, J = 15.9 Hz, 1H), 4.78 (d, J = 15.0 Hz, 1H), 4.58 (d, J = 14.7 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.56 (s, 2H), 1.48 (t, J = 7.2 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 160.8, 134.2, 129.8, 70.9, 68.2, 61.5, 60.7, 51.4, 13.8, 9.6; HRMS calcd for $C_{10}H_{17}NO_2^+$ 183.1259, found 183.1256.

3-Carbethoxy-1-methyl-1-azoniabicyclo[2.2.1]heptyl Bromide (57). A 0.025 M solution of 1-(2-bromoethyl)-3-carbethoxy-1-methyl-3-pyrrolinium bromide (**60**) (0.1 g, 0.3 mmol) in 2-methyl-2-butanol was deoxygenated and heated under reflux. A solution of Bu_3SnH (0.1 g, 0.33 mmol) in 2-methyl-2-butanol (1 mL) containing AIBN (cat.) was added over 15 min and the solution then heated for a further 15 min. The product obtained after the customary workup procedure was shown by NMR analysis to consist of the salt **57** (ca.9:1 *endo*:*exo*) contaminated with 3−5% of the reduced product **64**. The mixture was separated by column chromatography on alumina (10% methanol/dichloromethane) which gave *endo*/*exo* **57** (0.056 g, 74%) as very hygroscopic colorless crystals: ^{1}H NMR ($CDCl_3$) δ 4.37 (m, 2H), 4.24 (m, 2H), 4.12 (m, 2H), 3.78 (m, 2H), 3.63 (s, 3H), 3.45 (m, 1H), 3.22 (m, 1H), 2.39 (m, 1H), 1.76 (m, 1H), 1.29 (m, 3H).^{13}C NMR ($CDCl_3$) (major component: *endo*) δ 170.1, 68.2, 63.7, 62.5, 61.8, 45.0, 44.8, 39.5, 25.1, 13.9, (minor component: *exo*) δ 171.2, 66.4, 64.7, 62.1, 61.8, 45.7, 44.7, 40.9, 28.5, 13.8; HRMS calcd for $C_{10}H_{18}NO_2^+$ 184.1338, found 184.1335.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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