The role of the ester group in determining the regiochemistry of selected β-amino and β-ammonio radical cyclisations: generation of 1-azabicyclo[3.2.1]octyl- and -[2.2.2]octyl systems

Ernest W. Della * and Paul A. Smith

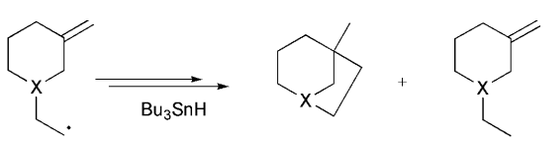
Department of Chemistry, Flinders University, Bedford Park, SA 5042, Australia

Received (in Cambridge, UK) 16th August 2000, Accepted 3rd January 2001
First published as an Advance Article on the web 1st February 2001

A comparison of the behaviour of the 2-(1,2,5,6-tetrahydro-3-methoxycarbonyl-1-pyridyl)ethyl radical and its quaternary *N*-methyl derivative shows that the latter is more conducive to cyclisation. These reactions display little regioselectivity, and significant quantities of both bicyclo[3.2.1]- and -[2.2.2]octanes are produced in each case. In contrast, an investigation of the quaternary 2-(4-ethoxycarbonylmethylene-1-pyridyl)ethyl radical, a modified hept-6-enyl-type radical, demonstrates that ring closure of this system provides a convenient, high-yielding route to quinuclidinium derivatives.

Introduction

The synthesis of bridged bicyclic systems *via* intramolecular radical cyclisation pathways has formed the basis of our research activities over recent years. Initially, our efforts were focused on the synthesis of bridgehead-substituted bicyclo-[3.2.1]octanes **2**[1] *via* intermediate radicals such as **1** (Scheme 1).



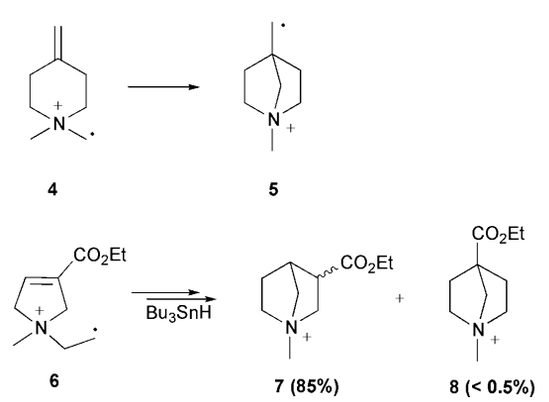
1 **2** **3**

a, X = CH; **b**, X = CCO_2Et; **c**, X = N; **d**, X = MeN^+

Scheme 1

As the data in Table 1 reveal, this transformation provides easy access to the target molecules and is particularly efficient in the case of the ester **2b**. The successful demonstration of such cyclisations then led to a program of studies directed towards the synthesis of bicyclic heterocycles substituted at the bridgehead position with nitrogen *via* β-amino- and β-ammonio radicals such as **1c** and **1d**. In the case of the latter, excellent yields of the 1-azoniabicyclo[3.2.1]octane **2d** were obtained.

The α-ammonio radical **4** has also been shown[2] to undergo smooth cyclisation and leads to excellent yields of the 1-azoniabicyclo[2.2.1]heptyl halides *via* the rearranged radical **5**. More recently, investigations[3] into the synthetic utility of the



4 **5**

6 **7 (85%)** **8 (< 0.5%)**

Table 1 Ratio of products from treatment of the radicals **1a**–**d** with tributyltin hydride[a]

Radical	Product (yield %)	
1a	**2a** (16)	**3a** (64)
1b	**2b** (81)	**3b** (7)
1c	**2c** (7)	**3c** (66)
1d	**2d** (87)	**3d** (nd)[b]

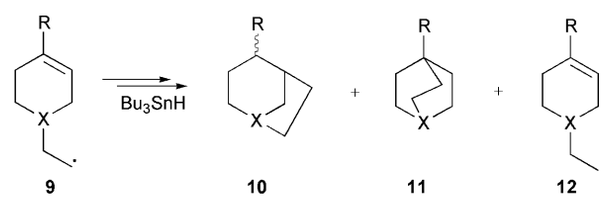
[a] Data taken from ref. 1. [b] nd = not detected.

Table 2 Products derived from treatment of the radicals **6** and **9a**–**d** with tributyltin hydride[a]

Radical	Product (yield %)		
6		**7** (85)	**8** (nd)[b]
9a	**10a** (nd)[b]	**11a** (nd)[b]	**12a** (83)
9b	**10b** (56)	**11b** (nd)[b]	**12b** (14)
9c	**10c** (93)	**11c** (nd)[b]	**12c** (nd)[b]
9d	**10d** (82)	**11d** (nd)[b]	**12d** (nd)[b]

[a] Data taken from ref. 2. [b] nd = not detected.

β-ammonio and β-amino radicals **6** and **9** have yielded practical routes to 1-azoniabicyclo[2.2.1]heptanes **7** and 1-azabicyclo-[3.2.1]octanes **10** incorporating substitution at ring carbons *other* than the bridgehead position (Scheme 2, Table 2). It is



9 **10** **11** **12**

a, X = N, R = H; **b**, X = N, R = CO_2Et
c, X = MeN^+, R = H; **d**, X = MeN^+, R = CO_2Et

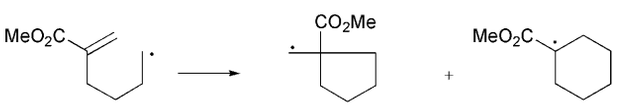
Scheme 2

noteworthy that in neither of these cases was the alternative isomeric ester **8** or **11** detected in the product.

Inspection of Tables 1 and 2 reveals that cyclisation occurs most readily in these types of systems when a quaternary

DOI: 10.1039/b006691p

carbon or nitrogen centre is located β to the radical site. As discussed previously,[1,2] such cyclisations are then driven strongly by a more favourable activation energy which results from an increase in the ground-state energy of the radical compared with that of its unsubstituted counterpart. In these substrates the cyclisation is more efficient because, unlike the unsubstituted radicals such as **1a**, **1c** and **9a** in which the radical has an equatorial configuration, there is essentially a 1 : 1 mixture of axial and equatorial radicals. While cyclisation of the β-ammonio substituted radicals **6**, **9c** and **9d** occurs readily, the free amine **9b** requires activation of the double bond by an attached ester group. The latter process provides an impressive demonstration of a two-pronged influence exerted by the ester function *via* a polar effect coupled with favourable allyl-like product stabilisation. This property of the ester group was found previously [3a] to assist 6-*endo* closure of the simpler hex-5-enyl radical **13** which gives a 15 : 85 mixture of the cyclic isomers **14** and **15**.



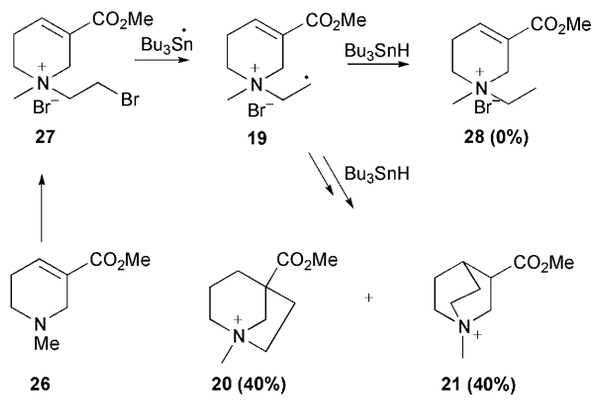
13 **14 (15%)** **15 (85%)**

It is seen that ring closure of these modified hex-5-enyl radicals occurs with great facility and with high regioselectivity and provides a valuable entry into bicyclo[3.2.1]octanes and bicyclo-[2.2.1]heptanes with little contamination by the products of reduction. It was of interest, then, to determine whether such cyclisation strategies could be applied to the synthesis of 1-azabicyclo[2.2.2]octyl systems from appropriate precursors. We now present the results of our investigations.

Results and discussion

We elected to investigate the behaviour of the radicals **16** and **19**. The questions under consideration were: (i) how influential is the polar effect/product stabilisation of the ester group in promoting ring closure of **16** compared with the unsubstituted radical **9a**, and (ii) if ring closure does occur, does it display any regioselectivity? It is not a simple matter to predict the likely course of reaction *a priori* because an interesting point concerning the radicals **16** and **19** is that ring closure at C3 to give the bicyclo[3.2.1]octyl systems **17** and **20**, respectively, is favoured stereoelectronically (as a 5-*exo* channel), whereas attack by the radical centre at C4 leading to the alternative bicyclo[2.2.2]octyl esters **18** and **21**, although normally a slower 6-*endo* mode, would be expected to be favoured according to frontier orbital considerations. Other relevant factors to be taken into consideration include the effect of allyl-like product stabilisation in the case of **18** and **21**, and the fact that, while closure at C3 would be disfavoured to some extent on steric grounds as observed in the rearrangement of the 5-methylhex-5-enyl radical,[4] cyclisation at C4 would also have unfavourable steric requirements because of the highly energetic boat-type transition state.

The relevant precursors **24** and **27** were synthesised from the commercially available esters **22** and **26**, respectively, as illustrated in Schemes 3 and 4; authentic specimens of the potential



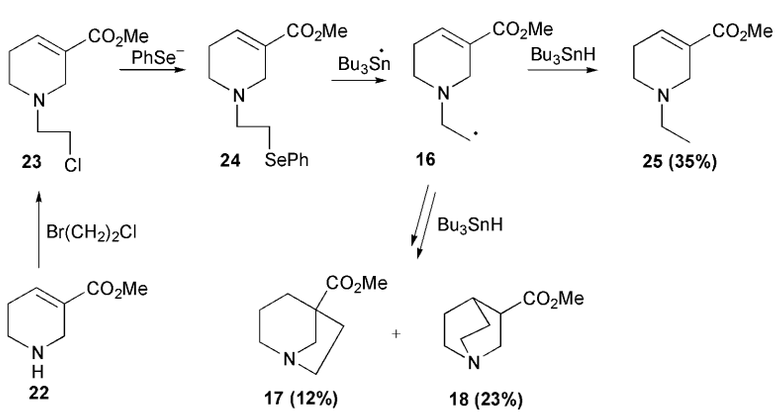
27 **19** **28 (0%)** **26** **20 (40%)** **21 (40%)**

Scheme 4

products of reaction, *viz.*, **17**, **18**, **20**, **21**, **25** and **28** were also prepared. In practice, it was found that reductive cyclisation of the selenide **24** with tributyltin hydride under standard conditions gave a 1 : 2 : 3 mixture of the esters **17**, **18** and **25**. This represents the first occasion in our work that formation of a product containing the bicyclo[2.2.2]octane skeleton has been observed and, furthermore, the 6-*endo* channel responsible for **17** is seen to be not only a competitive process, but a favoured one, demonstrating clearly once again the importance of the role of the ester group.

The combined yield of the bicyclic products was found to be increased when the quaternary salt **27** was employed, which is not surprising considering our earlier observations on systems **6**, **9c** and **9d**. Now, treatment of **27** with tributyltin hydride was observed to give a 1 : 1 mixture of the bicyclic esters **20** and **21** in good yield (79%); the product of reduction **28** was not detected in this case.

Several aspects of the distribution of products observed in the reactions of Schemes 3 and 4 require comment. Firstly, why does the radical **16** isomerise readily to the bicyclo[3.2.1]octyl system, whereas the unsubstituted species **9a** is resistant to cyclisation? We believe that a rationale for this is provided by consideration of the frontier molecular orbitals involved. Both **16** and **9a** represent radicals of comparable nucleophilicity and the regioselectivity of ring closure is therefore expected to be determined by the dominant interaction of the radical SOMO with the alkene LUMO rather than its HOMO.[5] Frontier Molecular Orbital Theory predicts that attachment of a



23 **24** **16** **25 (35%)** **22** **17 (12%)** **18 (23%)**

Scheme 3

Table 3 Calculation of the atomic orbital coefficients of the alkene HOMO and LUMO in the radicals **16** and **19**

		LUMO		HOMO	
Method	Radical	C4	C3	C4	C3
AM1		0.66	0.47	0.51	0.61
MNDO	**16**	0.66	0.50	0.54	0.61
PM3		0.65	0.47	0.52	0.60
AM1		0.62	0.49	0.55	0.61
MNDO	**19**	0.61	0.46	0.51	0.58
PM3		0.62	0.49	0.55	0.62

powerful electron-withdrawing group, such as an ester, to an olefin lowers the energy of the LUMO relative to that in the unsubstituted alkene. Evidently, the strong interaction between the lower energy LUMO in **16** and the radical SOMO is conducive to rapid isomerisation, whereas the less favourable interaction of the radical centre in **9a** and the higher-energy alkene LUMO is not.

Secondly, why does the β-amino radical **16** give a 2:1 mixture of the bicyclo[2.2.2]- and -[3.2.1]octyl esters, yet the β-ammonio analogue **19** yields a 1:1 mixture of the corresponding esters? In an attempt to rationalise these observations we have calculated the orbital coefficients for the alkene carbons in the ground states of the radicals **16** and **19**. The results of the semi-empirical calculations are summarised in Table 3.

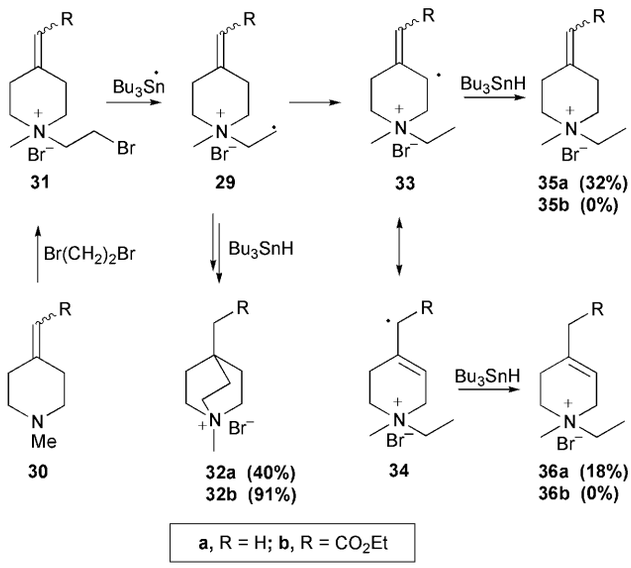
Inspection of the data in Table 3 reveals that in both radicals **16** and **19** the magnitude of the LUMO coefficients at C4 is larger than that at C3, but the reverse is true for the corresponding HOMO coefficients. It is proposed that the difference in product distribution is a function of the relative nucleophilicities of the β-amino and β-ammonio radicals. The former radical can be described as a nucleophilic species on the basis of the relatively weak electron-donating nature of the aminomethyl group (σ_p of $CH_2NH_2 = -0.11$[6]). On the other hand, because of the strongly electron-withdrawing effect of the ammoniomethyl substituent (σ_p value of $CH_2NH_3^+ = +0.53$[6]), the β-ammonio radical **19** possesses considerably more electrophilic character than **16**. As a result, the determination of regiochemistry in the case of the radical **19** is more biased towards a C3 HOMO–SOMO interaction compared with a C4 LUMO–SOMO interaction for the β-amino radical **16**. This would therefore reinforce the effect discussed above and lead to an increased ratio of 6-*endo* product **18** to 5-*exo* product **17** in the case of the radical **16** compared with the distribution of **21** to **20** derived from **19**.

Finally, it can be seen that the radical **16** produces a 1:2 mixture of the 5-*exo* (**17**) and 6-*endo* (**18**) isomers, whereas a 1:6 mixture of the corresponding *exo–endo* species **14** and **15** is obtained from the acyclic parent **13**. We ascribe the reduced quantity of 6-*endo* product **18** derived from **16** to steric retardation in the rate of its formation caused by the requirement of a highly energetic flexible conformation in the transition state *en route* to the bicyclo[2.2.2]octyl system. In the interconversion **13**→**15**, no such problem exists.

Modified hept-6-enyl radical systems: a novel route to 1-azabicyclo[2.2.2]octanes

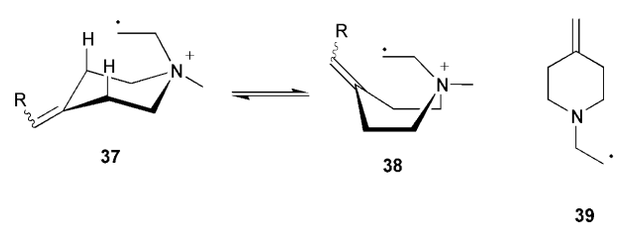
The results above proved to be interesting in their own right, but they do not provide an efficient synthetic route to the target ring-substituted 1-azabicyclo[2.2.2]octane because of contamination with reduced/isomeric products; these were found to be difficult to remove. We were, nevertheless, keen to try and develop a procedure for the synthesis of bridgehead-substituted quinuclidines by employing similar methodology and, in order to achieve this goal, we undertook an investigation of the radicals **29a** and **29b**.

While we were cognizant of the *ca.* 100-fold decrease in rate for the 6-*exo* mode of cyclisation in the hept-6-enyl radical *versus* the analogous 5-*exo* closure in the hex-5-enyl system,[7] the rearrangement **29**→**32** (Scheme 5) was considered to be feasible



Scheme 5

despite the requirement of a boat-like transition structure **38**. Actually, the situation is further complicated by a potential problem arising from competition between internal hydrogen atom abstraction, *via* the conformer **37**, and ring closure, a feature we had not had to confront in our earlier work. It was felt that, by analogy with the results observed previously, the best chance for cyclisation lay with the β-ammonio radical **29a** rather than the β-amino analogue **39**. Accordingly, the selected



precursor **31a** was prepared[2b] by treatment of **30a** with 1,2-dibromoethane. Treatment of a 0.025 M solution of the salt **31a** with a solution of tributyltin hydride added over 15 minutes followed by heating for a further 15 minutes yielded, upon work-up, a colourless crystalline product (90%). NMR analysis showed it to consist of a mixture of cyclised material **32a** (40%), the reduced product **35a** (32%) and its isomer **36a** (18%). The latter is derived from internal H-abstraction in **29a** and subsequent delivery of hydrogen by tributyltin hydride to the exocyclic site of the allylic radical (**33a**↔**34a**) so produced. The reduced product **35a**, of course, arises from combined hydrogen atom abstraction by **29a** and by the internal site of the allylic radical from tributyltin hydride. In order to assist the NMR analysis, an authentic specimen of **35a** was prepared by treatment of the amine **30a** with bromoethane; a specimen of **36a** was synthesised in a two-step sequence involving reduction of 1,4-dimethylpyridinium iodide to 1,4-dimethyl-1,2,5,6-tetrahydropyridine followed by treatment with bromoethane. Alumina chromatography of the mixture was found to be effective in the separation of the bicyclo[2.2.2]octyl salt **32a** which was further purified by recrystallisation from chloroform. Modifications to the concentration of tributyltin hydride and/or its rate of addition had little effect on the product distribution.

Table 4 Calculated activation energies associated with cyclisation of the β-amino- and -ammonio-substituted radicals **6**, **9b**–**d**, **16** and **19**

Radical	Mode	Product	MNDO	AM1	PM3
6	5-*exo*	**7**	16.9	13.2	14.9
	5-*exo*	**8**	20.3	15.5	16.0
9b	5-*exo*	**10d**	16.2	9.6	10.8
	6-*endo*	**11d**	23.4	12.4	16.2
9c	5-*exo*	**10c**	12.3	8.4	9.1
	6-*endo*	**11c**	16.5	10.8	11.8
9d	5-*exo*	**10d**	6.1	9.6	4.7
	6-*endo*	**11d**	13.2	11.5	13.1
16	5-*exo*	**17**	24.0	21.3	12.1
	6-*endo*	**18**	23.5	18.1	11.6
19	5-*exo*	**20**	16.1	10.1	10.1
	6-*endo*	**21**	16.5	9.6	10.8

Bearing in mind the directional influence of the polar effect of the ester group referred to above, we felt that the introduction of an ester moiety at the terminal end of the double bond should facilitate ring closure and increase the yield of the bicyclo[2.2.2]octyl compound. The precursor **31b**, required as an entry point to the radical **29b** and ultimately **32b**, was prepared as described[2b] from **30b**. Treatment of **31b** with tributyltin hydride under the conditions described above gave an excellent yield (91%) of **32b** uncontaminated by either **35b** or **36b**. Evidently, ring closure is now promoted so readily that internal hydrogen abstraction is no longer competitive. Considering the small number of steps involved, we suggest that the synthetic sequence **30**→**31**→**32** depicted in Scheme 5 represents an alternative, high-yielding, easy route to the quinuclidinium system, which forms the core component of the important family of cinchona alkaloids.[8a] The amino ester derived from *N*-demethylation of **32b** has been shown to possess antimicrobial properties.[8b]

A semi-empirical theoretical study: predicting the regioselectivity of cyclisation

We decided to conduct a theoretical investigation of the activation energies associated with each mode of cyclisation of the radicals **6**, **9b**–**9d**, **16** and **19** at the semi-empirical level of calculation in order to determine to what extent such predictions of regioselectivity were a reasonable indicator of experimental data. Our focus was simply to provide a rapid qualitative assessment of the regioselectivity of ring closure of the radicals rather than determine quantitatively an absolute measure of the energies involved.

The heats of formation of the ground-state structure of each of the radicals and the energies of the optimised transition state structures leading to 1-azabicyclo[2.2.2]- and -[3.2.1]octanes, respectively, were calculated by each of the three common semi-empirical methods MNDO,[9] AM1[10] and PM3[11] to compare the methods. Although it is recognised that semi-empirical models are unreliable in their account of *absolute* energies, Hehre and Huang[12] suggest that these procedures properly account for activation energy *differences* among closely related reactions.

Table 4 highlights the energy differences between the ground state energy and the transition state energy which are considered to parallel the E_{act} for the cyclisation process involving each of the radicals **6**, **9b**–**9d**, **16** and **19**. In the case of the β-ammonio substituted radicals, the experimental preference for formation of the bicyclo[3.2.1]octyl product from both the unsubstituted radical **9c** and the radical with ester substitution at C4, *viz.*, **9d**, is supported by the calculations, all of which predict a lower E_{act} for this (5-*exo*) mode of cyclisation. Calculations on the C3-ester radical **19**, on the other hand, predict very little difference between the activation energy leading to the bicyclo[3.2.1]octane **20** and that to the bicyclo[2.2.2]octane **21**; indeed, it is noteworthy that the calculated data support the 1 : 1 mixture of products observed experimentally. When considering the ammonio-substituted cyclopentenyl system **6**, the calculated activation energy associated with the transition structure leading to addition at the less substituted end of the alkene was favoured at all levels. This is also consistent with experimental observations.[3]

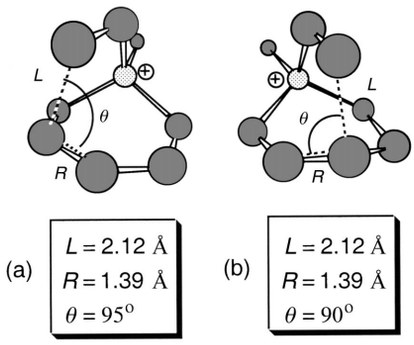


Fig. 1

In the case of the β-amino substituted radicals **9b** and **16**, the regiochemical preference for the bicyclo[3.2.1]octyl product from the C4-ester **9b** radical was correctly predicted at all three levels; however, the calculations do not work so well for the system **16**. These data demonstrate that it is prudent to exercise caution where differences in activation energy of the order of <1 kcal mol^{-1} such as those for **16** and **19** are involved.

It is also noteworthy that the magnitudes of the differences between the calculated energies for a given system correlate well with the combined favoured or disfavoured effects proposed to influence each transition structure. For example, the differences in E_{act} associated with formation of the isomeric bicyclooctanes are quite large for radical **9b** in which the combined stereoelectronic, polar and steric components provide a significant inducement to bicyclo[3.2.1]octane formation.

Further support for the proposition that a favourable stereoelectronic effect directs ring closure towards bicyclo[3.2.1]octyl product formation was gleaned from analysis of the calculated transition structures for the various systems. In general, the ground state structures of all of the radicals under study do not vary significantly in structure and resemble that of the unsubstituted radical shown below. Comparison of the calculated data (Fig. 1) shows that *L*, the distance between the radical centre and the respective trigonal carbons, is identical; however, the magnitude of the angle θ subtended by the three reactive centres for 5-*exo* attack (95°) is closer to that predicted (107°) in the transition state for cyclisation of the hex-5-enyl radical.[13]

In summary, while the calculated values of E_{act} are seen to be higher than would be feasible for practical ring closure, they parallel closely the experimental observations and thus provide a useful tool for predicting regiochemistry.

Conclusions

The results of this study highlight the lack of regioselectivity in the ring closure of the β-amino and β-ammonio radicals **16** and **19**; in neither case is the reaction synthetically useful as a route to 1-azabicyclo[2.2.2]octanes. By contrast, an investigation of the modified hept-6-enyl-type radical **29b** demonstrates that it provides convenient, high-yielding access to quinuclidinium derivatives. In a complementary study, the results of semi-empirical calculations are seen to be useful for predicting the regioselectivity of ring closure in these systems.

Experimental

Molecular orbital calculations were performed using MOPAC v7.0[14] or SPARTAN.[15] Vibrational frequencies were calculated

for each optimised transition structure but owing to the relatively low level of theory ZPE correction was not accounted. Values of $\langle S_2 \rangle$ were generally <1.0 and indicated low levels of higher-order spin contamination and all calculations used UHF methods for open shell systems. All calculations were performed on a Silicon Graphics Indigo workstation running OS IRIX 6.5.4 or an iMac running OS 8.6.

Elemental analyses were performed either by Microanalytical Services, University of Otago, New Zealand or Australian Microanalytical Services. Several ammonium salts were hygroscopic and were therefore unsuitable for elemental analysis by combustion. The purity of all volatile compounds was supported by GC analysis. Proton and carbon-13 NMR spectra were recorded at 300 and 75.462 MHz, respectively, on samples dissolved in deuterochloroform unless otherwise specified; chemical shifts are referenced to tetramethylsilane and *J* values are given in Hz. 3-Methoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridine and 3-methoxycarbonyl-1,2,5,6-tetrahydropyridine were commercially available. 3-Methoxycarbonyl-1-azabicyclo[2.2.2]octane **18** and 5-methoxycarbonyl-1-azabicyclo[3.2.1]octane **17** were synthesised as reported;[16] 1-methyl-4-methylene-1-azacyclohexane **30a** and 4-ethoxycarbonylmethylene-1-methyl-1-azacyclohexane **30b** were synthesised as described previously.[2b]

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 subsequently purified by recrystallisation.

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 cm^3 $mmol^{-1}$) for 24 h. The solvent was removed, water was added, and the solution extracted with ether (2×). The combined ether extracts were dried (Na_2SO_4) and the solvent removed *in vacuo*. If necessary, purification was effected by chromatography on silica (50 : 50 ether–hexane). A solution of sodium benzeneselenolate (PhSeNa), prepared by treatment of diphenyl diselenide in dry ethanol (5 cm^3 $mmol^{-1}$) with $NaBH_4$ (2.2 equiv.), was added to the 2-chloroethylamine and the solution heated under reflux for 2 h. The solvent was removed, 5% HCl was added, and the aqueous solution 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 evaporated.

General procedure for work-up of radical cyclisation reactions of quaternary ammonium salts

The solvent was removed *in vacuo* and the residue triturated with ether several times in order to facilitate removal of tin-containing residues. Particularly hygroscopic salts were purified using chromatography (alumina–chloroform) if trituration was not effective in the removal of all the tin residues.

1-(2-Chloroethyl)-3-methoxycarbonyl-1,2,5,6-tetrahydropyridine 23

3-Methoxycarbonyl-1,2,5,6-tetrahydropyridine **22** (1.5 g, 11 mmol) was treated with 1-bromo-2-chloroethane as described above. Column chromatography of the product furnished *1-(2-chloroethyl)-3-methoxycarbonyl-1,2,5,6-tetrahydropyridine* **23** (1.4 g, 62%) as an amber oil; δ_H 2.33–2.42 (2H, m), 2.63 (2H, t, *J* = 5.7), 2.86 (2H, t, *J* = 7.0), 3.26 (2H, q, *J* = 2.6), 3.64 (2H, t, *J* = 7.0), 3.74 (3H, s), 6.98–7.03 (1H, m); δ_C 26.2, 40.9, 48.9, 51.1, 51.4, 59.2, 128.5, 137.7, 166.0; *m/z* (EI) 203.0715 (M^+). Calc. for $C_9H_{14}NO_2Cl$: 203.0713.

3-Methoxycarbonyl-1-(2-phenylselenoethyl)-1,2,5,6-tetrahydropyridine 24

Treatment of 1-(2-chloroethyl)-3-methoxycarbonyl-1,2,5,6-tetrahydropyridine **23** (1.0 g, 4.9 mmol) with PhSeNa as described afforded *3-methoxycarbonyl-1-(2-phenylselenoethyl)-1,2,5,6-tetrahydropyridine* **24** as a colourless oil (1.2 g, 75%); δ_H 2.29–2.42 (2H, m), 2.56 (2H, t, *J* = 5.6), 2.81–2.85 (2H, m), 3.09 (2H, m), 3.23 (2H, q, *J* = 2.5), 3.73 (3H, s), 6.95–7.01 (1H, m), 7.20–7.24 (3H, m), 7.46–7.52 (2H, m); δ_C 24.9, 26.4, 51.0, 51.5, 57.9, 126.7, 128.7, 129.0, 130.1, 132.4, 137.9, 166.2; *m/z* (EI) 325.0581 (M^+). Calc. for $C_{15}H_{19}NO_2Se$: 325.0581.

1-Ethyl-3-methoxycarbonyl-1,2,5,6-tetrahydropyridine 25

3-Methoxycarbonyl-1,2,5,6-tetrahydropyridine **22** (0.5 g, 3.5 mmol) was stirred with K_2CO_3 (1.5 equiv.) and bromoethane (2.0 equiv.) in acetone (1.5 cm^3 $mmol^{-1}$) for 24 h. The solvent was removed, water was added, and the solution extracted with ether (2×), before being dried (Na_2SO_4) and evaporated *in vacuo*. Distillation of the product (Kugelrohr: 71 °C/0.5 mm) yielded *1-ethyl-3-methoxycarbonyl-1,2,5,6-tetrahydropyridine* **25** (0.4 g, 67%) as a colourless oil; δ_H 1.15 (3H, t, *J* = 6.9), 2.24–2.38 (2H, m), 2.48–2.58 (4H, m), 3.18–3.21 (2H, m), 3.74 (3H, s), 6.97–7.03 (1H, m); δ_C 12.0, 26.5, 48.5, 50.9, 51.4, 51.8, 128.8, 137.8, 166.0; *m/z* (EI) 169.1104 (M^+). Calc. for $C_9H_{15}NO_2$: 169.1103. The derived hydrobromide salt had identical NMR spectral data with those reported for the hydrochloride salt.[17]

Reduction of 3-methoxycarbonyl-1-(2-phenylselenoethyl)-1,2,5,6-tetrahydropyridine 24 with Bu_3SnH

A 0.025 M solution of 3-methoxycarbonyl-1-(2-phenylselenoethyl)-1,2,5,6-tetrahydropyridine **24** (0.1 g, 0.31 mmol) in toluene was deoxygenated and heated under reflux. A solution of Bu_3SnH (0.27 g, 0.93 mmol) in toluene (3 cm^3) containing AIBN (cat.) was added over 3 h while the reaction was monitored by GC. The solution was cooled, extracted with 5% HCl, and the aqueous extracts washed with hexane. The solution was basified (K_2CO_3), and extracted with dichloromethane. The combined extracts were dried (Na_2SO_4) and evaporated to give an amber oil (0.038 g, 70%) which was shown by GC and NMR comparison with authentic samples to consist of a 1 : 2 : 3 mixture of the isomers **17**, **18** and **25**.

1-(2-Bromoethyl)-3-methoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridinium bromide 27

3-Methoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridine **26** (1.5 g, 10 mmol) was treated with 1,2-dibromoethane as described above. Recrystallisation of the product from ethanol gave *1-(2-bromoethyl)-3-methoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridinium bromide* **27** (2.9 g, 83%) as colourless crystals; mp 211–213 °C (Found: C, 35.1; H, 5.1; N, 4.4. Calc. for $C_{10}H_{17}Br_2NO_2$: C, 35.0; H, 5.0; N, 4.1%); δ_H ($CDCl_3$/DMSO-d_6) 2.75 (2H, br s), 3.25 (3H, s), 3.65–3.76 (2H, m), 3.78 (3H, s), 3.89–4.03 (4H, m), 4.29 (1H, d, *J* = 16.0), 4.42 (1H, d, *J* = 16.0); δ_C ($CDCl_3$/DMSO-d_6) 21.3, 21.5, 47.2, 51.9, 55.4, 57.4, 63.0, 122.4, 135.7, 163.4.

Reduction of 1-(2-bromoethyl)-3-methoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridinium bromide 27 with Bu_3SnH

A 0.025 M solution of 1-(2-bromoethyl)-3-methoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridinium bromide **27** (0.2 g, 0.58 mmol) in 2-methylbutan-2-ol was deoxygenated and heated under reflux. A solution of Bu_3SnH (0.18 g, 0.64 mmol) in 2-methylbutan-2-ol (1 cm^3) containing AIBN (cat.) was added over 10 min and the solution heated for a further 5 min. Work-up as described yielded an amber residue which after purification by chromatography (neutral alumina–methanol)

afforded a colourless crystalline solid (0.12 g, 79%) shown by NMR analysis to consist of a 1:1 mixture of **20** and **21**. None of the reduced material **28** was detected.

1-Ethyl-3-methoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridinium bromide 28

3-Methoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridine **26** (0.5 g, 3.2 mmol) was stirred with excess bromoethane at room temp. for 12 h, after which the solvent was removed, and the residue triturated with ether. Recrystallisation of the product (methanol–ether) afforded *1-ethyl-3-methoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridinium bromide* **28** (0.72 g, 85%) as colourless crystals; mp 168–170 °C (Found: C, 45.6; H, 6.7; N, 5.4. Calc. for $C_{10}H_{18}BrNO_2$: C, 45.5; H, 6.9; N, 5.3%); δ_H 1.49 (3H, t, J = 7.2), 2.82 (2H, br s), 3.39 (3H, s), 3.78 (3H, s), 3.84–3.97 (3H, m), 4.08–4.18 (1H, m), 4.43 (2H, q, J = 15.2), 7.21 (1H, s); δ_C 7.9, 21.8, 47.1, 52.1, 55.4, 57.0, 58.9, 122.8, 135.9, 163.5.

3-Methoxycarbonyl-1-methyl-1-azoniabicyclo[2.2.2]octyl iodide 21

3-Methoxycarbonyl-1-azabicyclo[2.2.2]octane[16] was treated with excess iodomethane in ether to give a quantitative yield of *3-methoxycarbonyl-1-methyl-1-azoniabicyclo[2.2.2]octyl iodide* **21** which was recrystallised from methanol–ether; mp 162–163 °C (Found: C, 38.85; H, 6.1; N, 4.5. Calc. for $C_{10}H_{17}Br_2NO_2$: C, 38.6; H, 5.8; N, 4.5%); δ_H 1.80–1.90 (1H, m), 2.03–2.32 (3H, m), 2.63 (1H, q, J = 3.1), 3.36 (3H, s), 3.38–3.40 (2H, m), 3.78 (3H, s), 3.75–3.82 (1H, m), 3.97–4.10 (3H, m), 4.26–4.35 (1H, m); δ_C 20.8, 22.8, 23.7, 39.9, 52.5, 52.9, 56.1, 57.1, 58.1, 171.8.

5-Methoxycarbonyl-1-methyl-1-azoniabicyclo[3.2.1]octyl iodide 20

5-Methoxycarbonyl-1-azabicyclo[3.2.1]octane[16] was treated with excess iodomethane and furnished *5-methoxycarbonyl-1-methyl-1-azoniabicyclo[3.2.1]octyl iodide* **20** which crystallised from methanol–ether; mp 162–164 °C (Found: C, 38.8; H, 5.7; N, 4.5. Calc. for $C_{10}H_{18}INO_2$: C, 38.6; H, 5.8; N, 4.5%); δ_H ($CDCl_3$/DMSO-d_6) 2.02–2.33 (5H, m), 2.65 (1H, dt, J = 5.4, 12.3), 3.55 (3H, s), 3.76 (3H, s), 3.82–4.21 (6H, m); δ_C ($CDCl_3$/DMSO-d_6) 17.5, 28.8, 30.2, 48.5, 50.6, 51.7, 60.1, 61.9, 66.6, 170.5.

1-(2-Bromoethyl)-1-methyl-4-methylene-1-azoniacyclohexyl bromide 31a

1-Methyl-4-methylene-1-azacyclohexane **30a** was treated with 1,2-dibromoethane as outlined above; recrystallisation of the product from ethanol–ether gave *1-(2-bromoethyl)-1-methyl-4-methylene-1-azoniacyclohexyl bromide* **31a** as white plates; mp 187–188 °C (Found: C, 36.3; H, 5.4; N, 5.0. Calc. for $C_9H_{17}Br_2N$: C, 36.15; H, 5.7; N, 4.7%); δ_H ($CDCl_3$/DMSO-d_6) 2.56–2.64 (4H, m), 3.43 (3H, s), 3.62–3.71 (2H, m), 3.74 (2H, sept, J = 6.0), 3.92 (2H, t, J = 7.5), 4.13 (2H, t, J = 7.5), 4.98 (2H, s); δ_C ($CDCl_3$/DMSO-d_6) 20.6, 27.1, 46.1, 60.3, 62.2, 112.3, 135.7.

1-Ethyl-1-methyl-4-methylene-1-azoniacyclohexyl bromide 35a

1-Methyl-4-methylene-1-azacyclohexane **30a** was stirred with excess ethyl bromide at room temp. for 12 h, after which the solvent was removed and the residue triturated with ether. The product was recrystallised from ethanol–ether and gave *1-ethyl-1-methyl-4-methylene-1-azoniacyclohexyl bromide* **35a** as colourless crystals; mp 225–227 °C (Found: C, 49.3; H, 8.1; N, 6.6. Calc. for $C_9H_{18}BrN$: C, 49.1; H, 8.2; N, 6.4%); δ_H ($CDCl_3$/DMSO-d_6) 1.39 (3H, t, J = 6.8), 2.52–2.71 (4H, m), 3.26 (3H, s), 3.48–3.58 (2H, m), 3.62–3.72 (2H, m), 3.73 (2H, q, J = 6.8), 4.96 (2H, s); δ_C ($CDCl_3$/DMSO-d_6) 7.5, 27.7, 46.3, 58.0, 59.9, 112.4, 137.4.

1-Ethyl-1,4-dimethyl-1,2,5,6-tetrahydropyridinium bromide 36a

1,4-Dimethyl-1,2,5,6-tetrahydropyridine[18] (0.5 g, 4.5 mmol) was treated overnight with excess bromoethane in ether (5 cm^3). The resulting solid was isolated by vacuum filtration and recrystallised from EtOH–EtAc to furnish *1-ethyl-1,4-dimethyl-1,2,5,6-tetrahydropyridinium bromide* **36a** as colourless platelets; mp 161–163 °C (Found: C, 48.9; H, 8.2; N, 6.4. Calc. for $C_9H_{18}BrN$: C, 49.1; H, 8.2; N, 6.4%); δ_H 1.38 (3H, t, J = 7.2), 1.74 (3H, s), 2.30–2.54 (2H, m), 3.27 (3H, s), 3.65 (1H, quin, J = 6.3), 3.76 (2H, q, J = 7.2), 3.86 (1H, quin, J = 6.3), 3.88–4.42 (2H, m), 5.33 (1H, s); δ_C 132.8, 112.9, 59.0, 58.5, 56.5, 46.9, 25.8, 22.2, 8.1.

1,4-Dimethyl-1-azoniabicyclo[2.2.2]octyl bromide 32a

A 0.025 M solution of 1-methyl-1-(2-bromoethyl)-4-methylene-1-azoniacyclohexyl bromide **31a** (0.2 g, 0.67 mmol) in 2-methylbutan-2-ol was deoxygenated and heated under reflux by irradiation with a 300 W tungsten lamp. A solution of Bu_3SnH (0.21 g, 0.74 mmol) in 2-methylbutan-2-ol (1 cm^3) containing a catalytic amount of AIBN was added over 15 min and the solution heated for a further 15 min. Work-up as described yielded a product (0.13 g, 90%) which by NMR analysis was shown to be a mixture of the salt **32a** (45%), and the alkenes **35a** (35%) and **36a** (20%). Recrystallisation of the product from chloroform gave a sample of *1,4-dimethyl-1-azoniabicyclo[2.2.2]octyl bromide* **32a** (20%) as colourless crystals; mp >300 °C (Found: C, 48.2; H, 8.2; N, 6.2. Calc. for $C_9H_{18}BrN{\cdot}0.25H_2O$: C, 48.1; H, 8.3; N, 6.2%); δ_H 1.16 (3H, s), 1.95 (6H, t, J = 8.0), 3.46 (3H, s), 3.92 (6H, t, J = 8.0); δ_C 25.0, 26.2, 30.8, 52.3, 57.5.

1-(2-Bromoethyl)-4-ethoxycarbonylmethylene-1-methyl-1-azoniacyclohexyl bromide 31b

4-Ethoxycarbonylmethylene-1-methyl-1-azacyclohexane **30b** was treated with 1,2-dibromoethane as described above to furnish *1-(2-bromoethyl)-4-ethoxycarbonylmethylene-1-methyl-1-azoniacyclohexyl bromide* **31b** which crystallised from ethanol–ethyl acetate as hygroscopic white crystals: δ_H 1.31 (3H, t, J = 7.2), 2.65–2.81 (2H, m), 3.14–3.30 (1H, m), 3.48–3.58 (1H, m), 3.73 (3H, s), 3.84–4.10 (6H, m), 4.19 (2H, q, J = 7.2), 4.32–4.48 (2H, m), 5.92 (1H, s); δ_C 14.2, 22.2, 23.4, 29.9, 48.2, 60.4, 60.9, 61.3, 63.6, 118.7, 147.6, 165.5.

4-Ethoxycarbonylmethylene-1-ethyl-1-methyl-1-azoniacyclohexyl bromide 35b

4-Ethoxycarbonylmethylene-1-methyl-1-azacyclohexane **30b** was stirred with excess bromoethane at room temp. for 12 h, after which the solvent was removed and the residue triturated with ether; recrystallisation of the product from ethanol–ethyl acetate gave the *4-ethoxycarbonylmethylene-1-ethyl-1-methyl-1-azoniacyclohexyl bromide* **35b** as colourless crystals; mp 170–172 °C; δ_H 1.23 (3H, t, J = 7.2), 1.43 (3H, t, J = 7.2), 2.62–2.88 (2H, m), 3.22–3.24 (1H, m), 3.47 (3H, s), 3.52–3.68 (1H, m), 3.70–3.84 (2H, m), 3.88–4.02 (3H, m), 4.11 (2H, q, J = 7.2), 5.82 (1H, s); δ_C 8.1, 14.1, 23.2, 29.8, 47.4, 59.0, 59.6, 60.1, 60.2, 118.6, 147.6, 165.3.

4-(Ethoxycarbonylmethyl)-1-methyl-1-azoniabicyclo[2.2.2]octyl bromide 32b

A 0.025 M solution of 1-(2-bromoethyl)-4-ethoxycarbonylmethylene-1-methyl-1-azoniacyclohexyl bromide **31b** (0.1 g, 0.27 mmol) in 2-methylbutan-2-ol was deoxygenated and heated under reflux by irradiation with a 300 W tungsten lamp. A solution of Bu_3SnH (0.09 g, 0.3 mmol) in 2-methylbutan-2-ol (1 cm^3) containing a catalytic amount of AIBN was added over

30 min and the solution heated for a further 15 min. Work-up as described yielded colourless crystals (0.07 g, 91%) which by NMR analysis were shown to be *4-(ethoxycarbonylmethyl)-1-methyl-1-azoniabicyclo[2.2.2]octyl bromide* **32b**; mp 176–178 °C (Found: C, 48.55; H, 7.5; N, 4.7. Calc. for $C_{12}H_{22}BrNO_2 \cdot 0.25H_2O$: C, 48.6; H, 7.6; N, 4.7%); δ_H 1.26 (3H, t, J = 7.2), 2.04 (6H, t, J = 8.0), 2.35 (2H, s), 3.46 (3H, s), 3.87 (6H, t, J = 8.0), 4.12 (2H, q, J = 7.2); δ_C 14.1, 27.3, 28.5, 43.2, 52.2, 56.9, 60.6, 170.0.

Acknowledgements

We thank the Australian Research Council for financial support; we are indebted to Professor Carl H. Schiesser for assistance with the calculations.

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