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The Synthesis of Indolizidine and Quinolizidine Ring Systems by Free Radical Cyclization of 4-Aza-6-methoxycarbonyl-5-hexenyl Radicals

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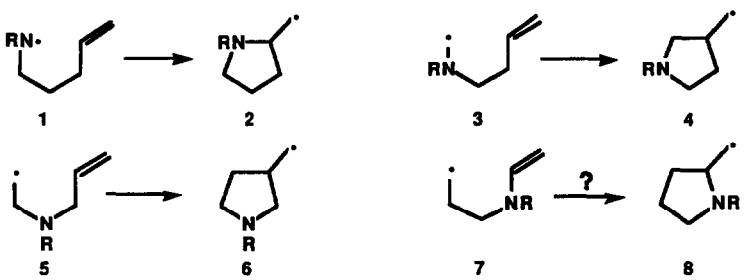
Abstract: *The formation of bicyclic amines by the intramolecular cyclization of 4-aza-6-methoxycarbonyl-5-hexenyl radicals is described. The direct attachment of a nitrogen atom to the double bond changes the electronic nature of the alkene such that the cyclization is less efficient than the all carbon analogue or the other aza-substituted 5-hexenyl cyclizations.The reaction has been used in a short, convenient synthesis of a variety of indolizidines from methyl nicotinate. In addition, the cyclization was used as the key step in a short synthesis of (±)-epilupinine from methyl nicotinate.*

Introduction

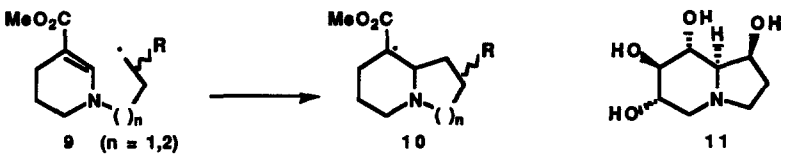
The last ten years have seen remarkable growth in the use of free radical reactions in synthetic organic chemistry for the formation of carbon-carbon bonds.[1] These developments have been inspired and greatly aided by the early pioneering fundamental studies on free radical chemistry which provided both a large body of kinetic data and related mechanistic information, and a detailed understanding of the factors affecting the reactivity of organic free radicals.[2] In particular the intramolecular cyclization of 5-hexenyl radical to give mainly cyclopentylmethyl radical by exo ring closure has been studied in great detail. Subsequently, the cyclization of radicals containing the 5-hexenyl system has been developed into a general method for the construction of cyclic compounds.[1] The utility of this method arises from the mildness of the reaction conditions and the predictable chemo-, regio- and stereo-selectivity of the cyclization process.[3] This approach has been used for the formation of nitrogen-containing heterocyclic systems, and examples of cyclizations of 1-aza-5-hexenyl radicals (**1**→**2**),[4] 2-aza-5-hexenyl radicals (**3**→**4**),[5] and 3-aza-5-hexenyl radicals (**5**→**6**),[6,7] have been reported.



The aim of the present work was to examine the susceptibility of 4-aza-5-hexenyl radicals to cyclization (**7** → **8**) involving radical addition to the *N*-terminus of an enamine double bond. Apart from their synthetic potential as a new route to pyrrolidines and related fused ring systems, cyclizations of 4-aza-5-hexenyl radicals are also of interest from a mechanistic viewpoint. As the nitrogen atom is directly attached to the alkene in radical **7**, the electronic properties of the double bond will be markedly different from those of the alkene in radicals **1**, **3**, and **5**. The affect this alteration in the electronic character of the alkene has on the course of radical cyclization should provide further information about the factors controlling intramolecular radical additions.

Since the simple enamines required as substrates for the formation of radical **7** were expected to be both difficult to prepare and unlikely to be stable under the conditions used for carrying out radical ring closure reactions, we chose to examine cyclizations of radicals onto vinylogous urethanes, in which the enamine is stabilized by conjugation with an ester. Some precedent for the viability of a cyclization of this type has been provided by the work of Ueda[8] who reported successful radical cyclizations onto the heterocyclic ring in suitable *N*-substituted uracils.

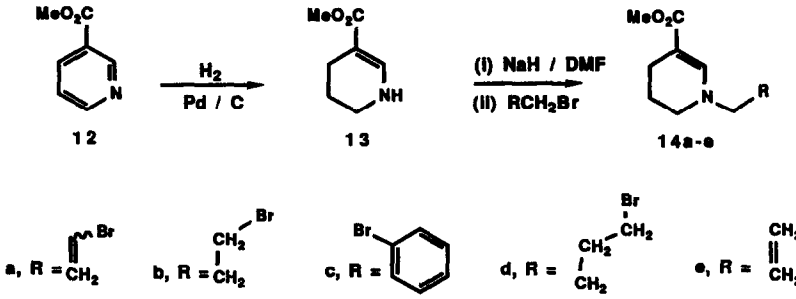
We have examined cyclizations of the cyclic 4-aza-6-methoxycarbonyl-5-hexenyl radicals, **9**. Successful intramolecular addition results in the formation of the indolizidine (**10**, **n=1**) and quinolizidine (**10**, **n=2**) ring systems, both of which contain a bridgehead nitrogen atom. Alkaloids containing these ring nuclei are widespread naturally, and are found in a number of compounds of considerable biological importance. Of particular interest at present is the indolizidine castanospermine, **11**, isolated from *Castanospermum australe*,[9] which demonstrates significant anti-cancer[10] and anti-HIV activity[11] in vitro.



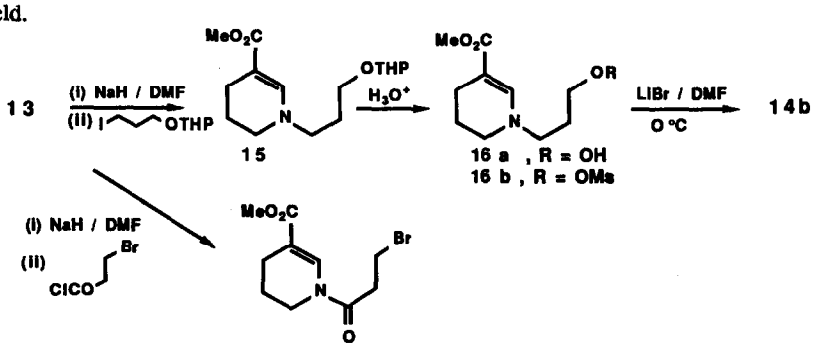
We describe herein the use of cyclizations of various cyclic 4-aza-6-methoxycarbonyl-5-hexenyl radicals for the formation of indolizidine systems, and of one 6-heptenyl homologue for the formation of a quinolizidine system. The stereochemical outcome of the cyclizations is discussed, as is the relative facility of the addition by comparison with related 5-hexenyl cyclizations.The synthetic utility of this approach is demonstrated in a short synthesis of (±)-epilupinine, a quinolizidine alkaloid.

Results and Discussion

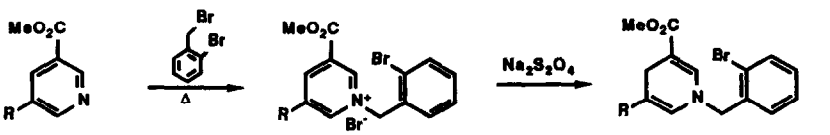
Precursors: Two routes were used for the preparation of the required substrates. In one approach, methyl nicotinate, **12**, was reduced to the tetrahydropyridine, **13**.[12] Careful addition of **13** to a suspension of sodium hydride, followed by alkylation of the resultant sodio-derivative of **13** with a suitable primary alkyl bromide, afforded substrates **14a**, **14c** and **14d** in moderate to good yield. However, direct alkylation of **13** with 1,3-dibromopropane afforded only a small amount of the expected *N*-(3-bromopropyl) adduct, **14b**, the main product being the *N*-allyl material, **14e**. It appears that **14b** is not stable under the reaction conditions, but undergoes ready dehydrobromination facilitated, presumably, by anchimeric assistance by the lone pair on nitrogen. Other alkylation protocols (1,3-dibromopropane and K_2CO_3 in CH_3CN or LDA in THF/HMPA) or the use of 1-bromo-3-chloropropane as alkylating agent all afforded similar results.



Attempted Mitsunobu coupling[13] of **13** with 3-bromo-1-propanol failed completely. However, **14b** could be prepared by an indirect route. Alkylation of **13** with 1-iodo-3-tetrahydropyranyloxypropane afforded the THP protected *N*-propyl derivative, **15**, which was converted into the bromide, **14b**, by sequential hydrolysis, conversion of alcohol, **16a**, to its mesylate, **16b**, and treatment of the latter with lithium bromide in DMF at 0 °C. The temperature of the final displacement had to be carefully controlled otherwise elimination was again a serious side reaction. The tetrahydropyridine, **13**, could also be acylated. Inverse addition of a DMF solution of the sodium salt of **13** to a cooled benzene solution of 3-bromopropionyl chloride afforded the acylated material, **17**, in 58% yield.



The second approach to the substrates involved initial formation of a pyridinium salt followed by sodium dithionite reduction to give a 1,4-dihydropyridine.[14] The dihydropyridines, **20a** and **20b**, were prepared from methyl nicotinate, **12**, and dimethyl dinicotinate, **18**, respectively by alkylation with *o*-bromobenzylbromide and reduction of the derived pyridinium salts. However, attempted catalytic hydrogenation of the pyridinium salt, **19a**, to give the tetrahydropyridine[12], **14c**, failed because hydrogenolysis of the aryl bromide bond occurred in serious competition with reduction of the pyridinium ring. In a related reaction, the dihydroisoquinoline, **22**, was prepared by alkylation of 4-cyanoisoquinoline with *o*-bromobenzylbromide and reduction of the derived isoquinolinium salt, **21**, with potassium borohydride.[15]



21 22

Products: Two methods were used for conducting radical cyclizations. Either the precursor was heated in degassed benzene with a slight excess of tributylstannane (Method A, $[Bu_3SnH]_0 = 0.05$ M) or a solution of tributylstannane in benzene (0.05 M) was added over several hours to a heated benzene solution of the substrate (Method B). The solvent was then removed and the residue was redissolved in ether and treated with 10% aqueous KF solution for several hours to precipitate most of the tin byproducts. The products were separated and isolated by column chromatography or medium pressure liquid chromatography (m.p.l.c.). Table 1 shows the products resulting from cyclization of the substrates **14a-d**, **17**, **20a**, and **20b**, the isolated yields of these products and the variation in product ratios with reaction method.

In all cases a significant amount (10 - 20%) of the simple reduction product was observed, even when the effective Bu_3SnH concentration was kept very low (Method B). The rate of cyclization of a 4-aza-6-methoxycarbonyl-5-hexenyl radical appears to be significantly slower than the rate of cyclization onto the corresponding simple αβ-unsaturated ester, as in analogous additions to unsaturated esters leading to hydrindane formation Stork reported almost exclusive formation of cyclized products at comparable Bu_3SnH concentrations.[16]

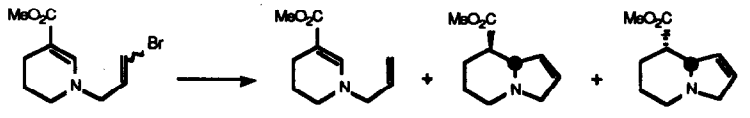
The ratios of reduced to cyclized material produced from reaction of substrates **14a** and **14c** show virtually no change with reaction method. This indicates that, in both these cases, the reduced material predominantly arises not by direct reduction of the initial radicals, but rather by initial 1,5 alkyl to aryl (or vinyl) hydrogen atom transfer followed by reduction of the rearranged radical. Such 1,5 transfers occur readily to an aryl or vinyl radical ($k \approx 10^7\ s^{-1}$)[17], and in this case the rearrangement results in the formation of a secondary alkyl radical stabilized by an adjacent nitrogen atom. When substrate **22** was treated with Bu_3SnH it failed to undergo any observable cyclization, even when slow addition of Bu_3SnH was used (Method B), and the only isolated product was reduced material. For this substrate there appears to be a complete preference for 1,5-hydrogen transfer resulting in the formation of a radical that is both benzylic and stabilized by an α-nitrogen atom.

In contrast, the product ratios for cyclization of the less reactive alkyl radical derived from **14b** did vary with reaction method, thus indicating that for the radical **9** (n=1, R = H) generated from **14b** the main route to reduced material is by direct reduction rather than *via* 1,5-transfer. Thus the use of Method B, which increases the effective lifetime of the initial radical by keeping the concentration of stannane very low, results in the formation of increased amounts of cyclized material.

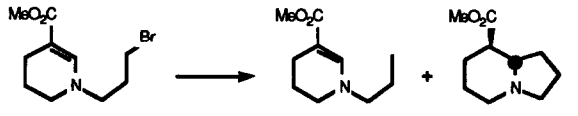
All of the cyclized products appeared to be *trans*-fused indolizidines, on the basis of the Bohlmann bands[18] at 2700 cm^{-1} in all their infrared spectra. Such bands are observed when two or more C-H bonds bear a *trans*-diaxial relationship to a nitrogen lone pair, and are diagnostic in this case for a *trans* ring fusion.[19] This was not unexpected as, due to the possibility of nitrogen inversion, *trans*- and *cis*-fused indolizidines have no separate identity and the *trans* form is known to be some 2.4 kcal mol^{-1} more stable than the *cis* in simple indolizidines.[20]

Table 1

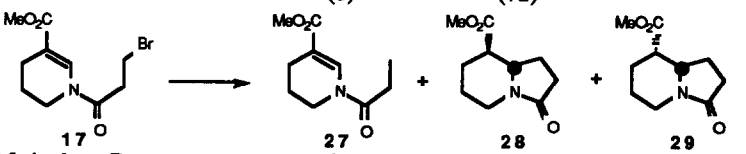
Products from radical cyclizations (% isolated yields)



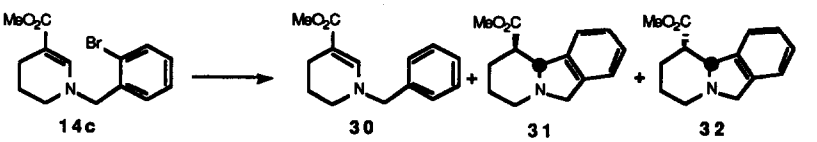
	14a	14e	23	24
Cyclization Method: A[a]		(15)	(48)	(15)
B[b]		(14)	(50)	(16)



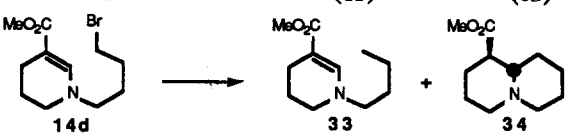
	14b	25	26
Cyclization Method: A		(21)	(63)
B		(8)	(72)



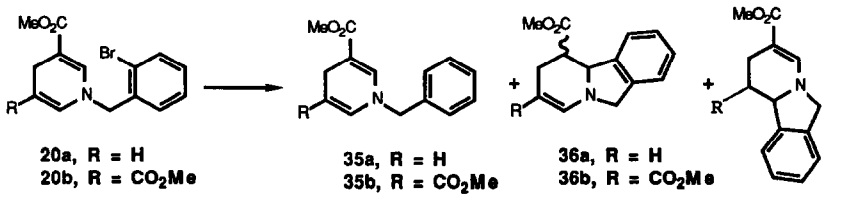
	17	27	28	29
Cyclization Method: B		(21)	(43)	(5)



	14c	30	31	29 32
Cyclization Method: A		(16)	(12)	(40)
B		(13)	(15)	(48)



	14d	33	34
Cyclization Method: A		(21)	(43)



	20a, R = H 20b, R = CO_2Me	35a, R = H 35b, R = CO_2Me	36a, R = H 36b, R = CO_2Me	37a, R = H
20a, Method A		(22)		(34)
20a, xs. Bu_3SnH		(32)		(24) [+ **32** (12)]
20b, Method B		(13)	(52)	

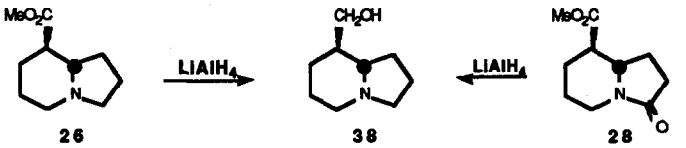
[a] Typical reaction conditions: AIBN/Bu_3SnH (ca. 0.05 M)/substrate in benzene at 80 °C for 1.5 h. Ratio AIBN/Bu_3SnH/substrate = 0.1/1.2/1.0 [b] Typical reaction conditions: AIBN/Bu_3SnH (ca. 0.05 M in benzene) added over 3 h. to substrate (ca. 0.1 M in benzene) at 80 °C. Ratio AIBN/Bu_3SnH/substrate = 0.1/1.2/1.0

Hence the possible cyclization products are all epimeric only with respect to the orientation of the methoxycarbonyl substituent. When this substituent is *anti* to the five membered ring it is in an equatorial orientation on the six membered ring, while if it is *syn* it is in an axial orientation.

Cyclization of vinyl bromide **14a** afforded, after purification by m.p.l.c. of the crude product, two epimeric bicyclic compounds in the ratio of 2.8:1. Comparison of their ^{13}C N.M.R. spectra revealed that the signals due to the carbons in the six-membered ring in the minor reaction product are shielded by 2-5 ppm relative to the position of the corresponding signals in the major product. In cyclohexanes which are isomeric only with respect to the axial-equatorial orientation of a substituent the interaction of an axial substituent with the cyclohexane ring carbons (and in particular the interaction with carbons in a 1,3 relationship with it, the so called γ-gauche effect)[21] results in a marked shielding of the ring carbons relative to the corresponding signals in the equatorial isomer. Hence the major product was identified as the *anti* isomer, **23** (equatorial methoxycarbonyl), and the minor product as the *syn* isomer, **24**. The stereochemistry of the other bicyclic indolizidine products was assigned by chemical correlation with **23**.

Cyclization of **14b** afforded primarily one cyclized product (>95% one isomer by ^{13}C N.M.R., G.L.C.) found to be identical with the saturated indolizidine obtained by hydrogenation of **23**; hence it was identified as the *anti* isomer, **26**.

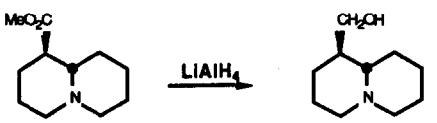
Cyclization of the acylated material, **17**, afforded two cyclized products in the ratio 9:1. The major product was identified as the *anti* isomer, **28**, by chemical correlation with **26**. Reduction of **26** or **28** with $LiAlH_4$ afforded the same amino alcohol, **38**, thus confirming that the orientation of the methoxycarbonyl group is the same in both substrates.



26 **38** **28**

Treatment of **14c** with Bu_3SnH gave two tricyclic products in a 3:1 ratio. These were separated by m.p.l.c., and their stereochemistry was again assigned from their ^{13}C N.M.R. spectra. On the basis of the expected shielding affect of an axial substituent on the position of the signals due to the cyclohexane ring carbons relative to the affect of an equatorial substituent, it appeared that the major product is the *syn* isomer, **33**, in which the methoxycarbonyl substituent is axial, in contrast to the case for the other cyclizations leading to bicyclic products. A rationale for the stereochemical outcome of all the cyclizations is given later.

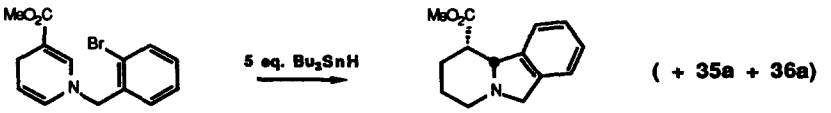
Cyclization of the 4-bromobutyl substrate **14d**, resulting in the formation of a quinolizidine ring system, afforded only one cyclization product. It was unambiguously determined to be the *anti* isomer **34** by correlation with the natural product epilupinine, **39**,[22] which was obtained when **34** was reduced with $LiAlH_4$. This constitutes a four-step synthesis of epilupinine from methyl nicotinate, unusual in that no specific protection-deprotection steps are required for the bridgehead amine functionality.



34 **39**

Upon treatment with Bu_3SnH the dihydropyridine, **20a**, afforded two isolable products, the direct reduction product, **35a**, in 22% isolated yield and the vinylogous urethane, **37a**, resulting from cyclization onto

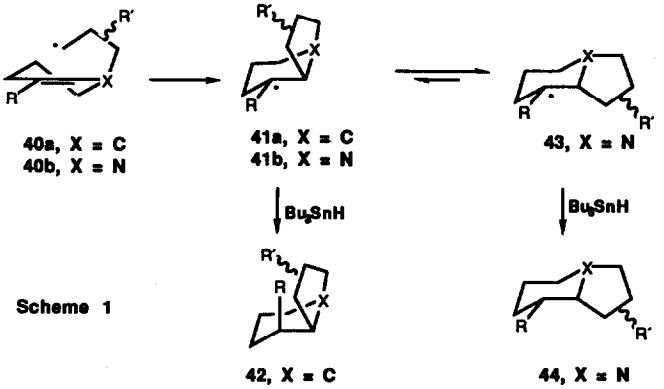
the "unsubstituted" double bond of the substrate, in 34% yield. The remainder of the mass balance was accounted for by highly polar material derived, presumably, from decomposition of the simple enamine, **36a**, expected to result from cyclization onto the "vinylogous urethane". We attempted to trap this intermediate by carrying out the cyclization with sodium cyanoborohydride and tributyltin chloride as a source of Bu_3SnH.[23] It was hoped that the cyanoborohydride would both regenerate the stannane as it was consumed and would also reduce the enamine, **36a**, as it was formed to one or both of the amines, **32** or **33**. Unfortunately, the reaction under these conditions was very sluggish and afforded only small amounts of reaction products, in roughly the same proportions as previously observed. As Bu_3SnH itself is able to reduce iminium salts to amines,[24] and as enamines readily react with Lewis acids to form iminium salts, we hoped that the simple use of an excess of Bu_3SnH would result in the trapping of the reactive enamine, **36a**. When the reduction was carried out in the presence of five equivalents of Bu_3SnH, **32** was isolated in 12% yield, in addition to the usual products. This result indicates that the enamine, **36a**, was at least present in the reaction mixture. If we assume that the bulk of the non-polar material is derived from decomposition of **36a** under the reaction conditions, it then appears that cyclization of the intermediate radical shows no strong preference for addition to either of the non-equivalent double bonds. This is despite the fact that addition to the ester substituted alkene would result in formation of an ester stabilised radical.



20a **32**

The reaction of the symmetrical substrate, **20b**, proceeded cleanly, giving a mixture of the two possible isomers of **36b** as well as some direct reduction product. The major product again appeared to be the *cis* isomer (axial carbomethoxy group) from comparison of the ^{13}C n.m.r. spectra of the two products. Note that in both these cases relatively little direct reduction product is formed, as 1,5-hydrogen transfer is not possible for these substrates.

Stereochemistry: Simple 5-hexenyl radical cyclizations leading to fused carbocyclic compounds usually afford *cis*-fused products.[25] The steric and stereoelectronic factors which make the transition structure leading to *cis*-fused products significantly lower in energy than the transition structure for *trans* fusion have been previously discussed.[26] Thus, as outlined in Scheme 1 for cyclization of the simple cyclic 6-substitiuted-5-hexenyl radical, **40a**, initial addition affords the *cis*-fused radical, **41a**. Subsequent hydrogen atom transfer from Bu_3SnH to **41a** preferentially occurs from the less hindered *exo*-face, giving rise to an *endo* substituted product, **42**, in which the substituent on the six membered ring is *syn* to the fused ring (Scheme 1, $R \neq H$). By contrast, the cyclizations of vinylogous urethanes leading to *bicyclic* products all afforded predominantly and sometimes exclusively *trans*-fused products in which the substituent was *anti* to the fused ring. Presumably, the initial cyclization of the 4-aza-6-methoxycarbonyl-5-hexenyl radical, **40b**, affords the *cis*-fused radical, **41b**, but this intermediate is not configurationally stable due to nitrogen inversion and rapidly isomerizes to the more stable *trans*-fused radical, **43**. Axial transfer of a hydrogen atom from Bu_3SnH to **43** should be preferred on steric and stereoelectronic grounds,[27] leading to the observed preference for formation of a *trans*-fused indolizidine product, **44**, in which the carbomethoxy group is *anti* to the fused ring and in an equatorial orientation with respect to the six-membered ring. When the five-membered fused ring is flattened by the incorporation of an sp2 centre into the ring the steric preference for formation of an equatorial substituent is reduced, thus accounting for the increase in the amount of the (axial) *syn* isomer observed in the case of cyclization of **14a**, and to a lesser extent of **17**.



Scheme 1

The cyclizations leading to *tricyclic* benzo-fused indolizidines show a more "normal" preference for formation of products with the substituent *syn* to the fused ring. One possible explanation for this result is that in the benzo-fused substrates there is a decrease in the rate of isomerization of the initial radical addition product, **41b**, to **43** after the initial *cis* cyclization. Inspection of models show that the ortho hydrogen of the aromatic ring adjacent to the bridgehead carbon is very close in space to the methoxycarbonyl group. If steric interactions between these groups slow the rate of nitrogen inversion sufficiently to allow hydrogen transfer to **41b** to occur prior to inversion, then the *syn* (axial) isomer would be expected to predominate in the final product.

Kinetics: Although these experiments were not intended to provide kinetic data, the results do afford some further insights into the factors affecting the rates of intramolecular radical addition processes. Thus, application in the usual way of the appropriate rate equation[28] to the results of the reaction of **14b** with 0.05M Bu_3SnH (method A) gives an approximate value of $k_c/k_H \sim 0.06\ M^{-1}$ at 80 °C where k_c and k_H are the respective rate constants for cyclization of **9** (n=1, R=H) and hydrogen atom transfer from tributylstannane. Since $k_H = 6.4 \times 10^6\ s^{-1}$ at this temperature[29] it follows that k_c must have an approximate value of $4 \times 10^5\ s^{-1}$. This is somewhat smaller than that ($k_c = 1.4 \times 10^6\ s^{-1}$ at 80 °C) for cyclization of the 5-hexenyl radical; thus it appears that the electron donating nitrogen atom in the vinylogous amide system of **9** (n=1, R = H) completely counteracts the usual activating effect of the ester group.[30]

The fact that reasonable yields of products were obtained from **14d** and **17** only when Method B was used indicate that the radicals derived from them undergo ring closure considerably more slowly than does the radical **9** (n=1, R=H) derived from **14b**. This is as expected. The radical **9** (n=2, R=H) derived from **14d**, like other radicals containing the 6-heptenyl system,[28] should have a low value of k_c, while the cyclization of the radical derived from **17** is probably disfavoured both by hindrance to rotation about the N-CO bond and by the effect of the C=O group on the strain energy of the transition structure.

The competition between cyclization and intramolecular hydrogen atom transfer in radicals derived from **14a**, **14c** and **22** precludes the determination of k_c. Like other intramolecular reactions of aryl and vinyl radicals these cyclizations are expected to have relatively large rate constants.

Experimental Section

General Methods. ^{1}H N.M.R. spectra were recorded on a Varian XL-200 spectrometer operating at 200 MHz. ^{13}C N.M.R. spectra were recorded on a Varian XL-300 spectrometer operating at 75.4 MHz. The following abbreviations are used in describing n.m.r. spectra: br (broad), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Infrared spectra were measured on a Perkin-Elmer 683 spectrophotometer and were obtained as liquid films on sodium chloride plates or as chloroform solutions in 0.5 mm path length sodium chloride cells. Mass spectra were recorded on a VG-Micromass 7070F medium-resolution mass spectrometer operating at 70 eV. High-resolution mass spectrometry was carried out on an MS-902 high-resolution mass spectrometer. Gas-liquid chromatographic (G.L.C.) analyses were performed on a Varian 6000 chromatograph equipped with a flame ionisation detector using a 25m x 0.2 mm vitreous silica capillary column (SGE25QC2/BPI-1.0) with helium as the carrier gas.

Ajax Grade 923 (0.07-0.15 mm) silica gel was used for column chromatography. Merck Kieselgel 60 (230-400 mesh) silica gel was used for flash chromatography. Medium-pressure chromatography (m.p.l.c.) was carried out with Merck pre-packed LiChroprep Si 60 (40-60 μm) columns.

3-Methoxycarbonyl-1,4,5,6-tetrahydropyridine, **13**, was prepared from methyl nicotinate, by use of the procedure of Wenkert.[12] Other starting materials were commercially available. Organic solutions that had been in contact with water were dried over anhydrous magnesium sulphate. Concentration under reduced pressure implies the removal of solvent on a Büchi rotary evaporator operating at water pump pressure.

General Procedure for the *N*-Alkylation of 3-Methoxycarbonyl-1,4,5,6-tetrahydropyridine (13). 1-[(E) or (Z) 3-Bromo-2-propenyl]-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine (14a). A solution of vinylogous urethane **13** (420 mg, 3 mmol) in DMF (5 mL) was added dropwise to hexane-washed NaH (240 mg, 5 mmol) suspended in DMF (5 mL) and the reaction mixture was stirred at room temperature for 30 min. A solution of (*E* or *Z*) 1,3-dibromopropene (450 μL, 3.5 mmol) in DMF (2 mL) was added and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with water (50 mL) and was extracted with ether (50 mL, 2 x 25 mL). The combined extracts were dried and concentrated under reduced pressure. The residue was purified by flash chromatography (20% ethyl acetate/hexane) to give 385 mg (49%) of the alkylation product **14a** as a yellow oil: IR ($CHCl_3$) 3040, 1730, 1670, 1620 cm^{-1}; ^{1}H N.M.R. δ 7.4 (br s, 1H), 6.1-6.6 (m, 2H), 4.05 (br d, 2H), 3.65 (s, 3H), 3.05 (br t, 2H), 2.26 (m, 2H), 1.6-1.9 (m, 2H); *m/e* 261/259 (M+, 100), 246/244, 230/228, 202/200. HRMS calcd. for $C_{10}H_{14}NO_2Br^{79}$: 259.0208. Found: 259.0189.

1-(3-Bromopropyl)-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine (14b). Following the general *N*-alkylation procedure, vinylogous urethane **13** (420 mg, 3 mmol) in DMF (2 mL) was added to a suspension of NaH (170 mg, 3.5 mmol) in DMF (5 mL). The derived sodium salt of **13** was treated with 1,3-dibromopropane (1 mL, 7.5 mmol). The crude product isolated after workup was purified by flash chromatography. Initial elution with 10% ethyl acetate/hexane afforded 110 mg (20%) of **1-allyl-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine (14e)** as a clear oil: IR (film) 1730, 1680, 1615 cm^{-1}; ^{1}H N.M.R. δ 7.29 (br s, 1H), 5.6-5.8 (m, 1H), 5.05-5.2 (m, 2H), 3.62 (br d, 2H), 3.58 (s, 3H), 2.99 (br t, 2H), 2.20 (br t, 2H), 1.75 (m, 2H); *m/e* 181, 166, 154, 150, 122 (100). Further elution with 20% ethyl acetate/hexane afforded 105 mg (12%) of the *N*-bromopropyl adduct **14b** as a clear oil: IR (film) 1735, 1675, 1610 cm^{-1}; ^{1}H N.M.R. δ 7.29 (br s, 1H), 3.59 (s, 3H), 3.33 (t, 2H, *J* = 6.4 Hz), 3.22 (t, 2H, *J* = 6.5 Hz), 3.03 (br t, 2H), 1.2-2.3 (m, 6H); *m/e* 263/261, 248/246, 232/230, 204/202, 182, 181, 154 (100); HRMS calcd. for $C_{10}H_{16}NO_2Br^{79}$: 261.0364. Found: 261.0365. Further elution afforded 125 mg (30%) of unreacted starting material.

1-(2-Bromobenzyl)-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine (14c). Following the general *N*-alkylation procedure, vinylogous urethane **13** (420 mg, 3 mmol) was added to a suspension of NaH (170 mg, 3.5 mmol) in DMF (5 mL). The derived sodium salt of **13** was treated with 2-bromobenzylbromide (820 mg, 3.3 mmol) in DMF (2 mL). The crude product isolated after workup was purified by flash chromatography. Elution with 15% ethyl acetate/hexane afforded 690 mg (74%) of the *N*-alkylation product **14c** as a clear oil: IR ($CHCl_3$) 3060, 1730, 1670, 1620 cm^{-1}; ^{1}H N.M.R. δ 7.58 (br s, 1H), 7.3 (m, 4H), 4.38 (s, 2H), 3.67 (s, 3H), 3.07 (m, 2H), 2.34 (m, 2H), 1.82 (m, 2H); *m/e* 311 (M+), 309, 296, 294, 280, 278, 171, 169, 83 (100). HRMS calcd. for $C_{14}H_{16}NO_2Br^{79}$: 309.0364. Found: 309.0363.

1-(4-Bromobutyl)-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine (14d). Following the general *N*-alkylation procedure, vinylogous urethane **13** (700 mg, 5 mmol) in DMF (5 mL) was added to a suspension of NaH (260 mg, 5.5 mmol) in DMF (5 mL). The derived sodium salt of **13** was treated with 1,4-dibromobutane (1.2 mL, 10 mmol) in DMF (5 mL). The crude product isolated after workup was purified by flash chromatography (30% ethyl acetate/hexane) to give 670 mg (49%) of the *N*-alkylation product **14d** as a clear oil: IR 1735, 1680, 1610 cm^{-1}; ^{1}H N.M.R. δ 7.32 (br s, 1H), 3.60 (s, 3H), 3.40 (t, 2H, *J* = 6.0 Hz), 3.29 (t, 2H, *J* = 6.3 Hz), 2.98 (br t, 2H), 1.1-2.3 (m, 8H); *m/e* 277/275 (M+), 262/260, 246/244, 196, 154 (100).

HRMS calcd. for $C_{11}H_{18}NO_2Br^{79}$: 275.0521. Found: 275.0521. Further elution afforded 110 mg (16%) of unreacted starting material.

3-Methoxycarbonyl-1,4,5,6-tetrahydro-1-(3-tetrahydropyranyloxypropyl)pyridine (15). Following the general *N*-alkylation procedure, vinylogous urethane **13** (700 mg, 5 mmol) in DMF (5 mL) was added to a suspension of NaH (720 mg, 3.5 mmol) in DMF (5 mL). The derived sodium salt of **13** was treated with 1-iodo-3-tetrahydropyranyloxypropane (2 g, 7.5 mmol) in DMF (5 mL). The crude product isolated after workup was purified by flash chromatography (20% ethyl acetate/hexane) to give 930 mg (66%) of the *N*-alkylation product **15** as a yellow oil: IR ($CHCl_3$) 1730, 1670, 1610 cm^{-1}; ^{1}H N.M.R. δ 7.30 (br s, 1H), 3.65 (s, 3H), 3.0-3.8 (m, 9H), 1.4-2.8 (m, 10H).

1-(3-Hydroxypropyl)-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine (16a). The THP-protected ether **15** (900 mg, 3.2 mmol) was taken up in methanol (20 mL) and *p*-toluenesulphonic acid (1.2 g, 6.5 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was taken up in CH_2Cl_2 (10 mL). The organic phase was dried and concentrated and the residue was purified by column chromatography. Initial elution with 2% MeOH/CH_2Cl_2, increasing to 5% MeOH/CH_2Cl_2, afforded 605 mg (95%) of the alcohol **16a** as a clear oil: IR 3440, 1740, 1670, 1600 cm^{-1}; ^{1}H N.M.R. δ 7.25 (br s, 1H), 3.68 (s, 3H), 3.18 (t, 2H, J = 6 Hz), 3.0-3.2 (m, 4H), 2.26 (t, 2H, J = 6 Hz), 1.5-1.9 (m, 5 H); *m/e* 199 (M+), 184, 168, 154 (100). HRMS calcd. for $C_{10}H_{17}NO_3$: 199.1208. Found: 199.1208.

1-(3-Bromopropyl)-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine (14b) from (16a). The alcohol **16a** (480 mg, 2.4 mmol) and triethylamine (560 μL, 3.6 mmol) were taken up in CH_2Cl_2 (2 mL). The solution was cooled in an ice-bath and methanesulphonyl chloride (200 μL, 2.6 mmol) was added dropwise to the stirred solution. The solution was stirred at 0 °C for 10 min. The reaction mixture was diluted to a volume of 10 mL with CH_2Cl_2 and the solution was washed successively with ice-water (5 mL), dilute HCl (5 mL), saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The organic phase was dried and concentrated under reduced pressure and the crude mesylate was taken up in DMF (3 mL). The solution was cooled in an ice-bath and lithium bromide (500 mg, 5.8 mmol) was added. The reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with water (10 mL) and was extracted with ether (10 mL, 2 x 5 mL). The organic phase was washed with brine (10 mL) and was dried. The solvent was removed under reduced pressure and the residue was purified by column chromatography (20% ethyl acetate/hexane) to give 510 mg (80%) of the *N*-(3-bromopropyl) adduct **14b** (spectral data given previously).

3-Methoxycarbonyl-1-(1-oxo-3-bromopropyl)-1,4,5,6-tetrahydropyridine (17). 3-Bromopropionic acid (3.25 g, 21 mmol) was taken up in benzene (20 mL) and oxalyl chloride (2 mL, 23 mmol) and a catalytic amount of DMF were added. The solution was stirred at room temperature until evolution of CO_2 had ceased. The solvent was removed under reduced pressure and the residue was twice redissolved in benzene (5 mL) and concentrated under reduced pressure. The residual acid chloride was taken up in benzene (10 mL) and the solution was cooled in an ice-bath. In a separate flask vinylogous urethane **13** (2g, 14.2 mmol) in DMF (10 mL) was slowly added to a suspension of NaH (640 mg, 16 mmol) in DMF (5 mL). The reaction mixture was stirred for 1 h at room temperature and was transferred dropwise by cannula to the stirred solution of the acid chloride. The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with saturated aqueous $NaHCO_3$ solution (20 mL) and was diluted with water (80 mL). The aqueous mixture was extracted with ether (2 x 100 mL, 2 x 50 mL) and the combined extracts were washed with brine and dried. The solvent was removed under reduced pressure and the solid residue was recrystallised from ethyl acetate/hexane to give a first crop of 1.89 g (49%) of the amide **17** as colourless crystals. Reworking the mother liquor afforded a further 390 mg (9%) of **17**, m. p. 79-80 °C: IR ($CHCl_3$) 1750, 1730, 1680 cm^{-1}; ^{1}H N.M.R. δ 7.65 (br s, 1H), 3.65 (s, 3H), 3.4-3.6 (m, 4H), 3.0 (br t, 2H), 2.25 (br t, 2H), 1.5-1.8 (m, 2H); *m/e* 277/275, 246/244, 141 (100). Calcd. for $C_{10}H_{14}NO_3Br$: C, 43.50; H, 5.11; N, 5.07; Br, 28.94. Found: C, 43.53; H, 5.15; N, 5.01; Br, 29.01.

1-(2-Bromobenzyl)-3-methoxycarbonylpyridinium bromide (19a). Methyl nicotinate (2.8 g, 20 mmol) and 2-bromobenzylbromide (5.25 g, 21 mmol) were taken up in methanol (25 mL) and the solution was heated at reflux for 2.5 h. The bulk of the solvent was removed under reduced pressure and the residual syrup was washed with ether (3 x 10 mL). The residue was dried in a vacuum dessicator for three days, during which time it crystallised to form a pink solid. The crude product was recrystallised from methanol/ethyl acetate to afford 5.5 g (71%) of the pyridinium salt **19a** as a white solid, m. p. 131-132 °C. Calcd. for $C_{14}H_{13}NO_2Br_2$: C, 43.08; H, 3.33; N, 3.50; Br, 41.05. Found: C, 43.44; H, 3.39; N, 3.62; Br, 41.29.

1-(2-Bromobenzyl)-1,4-dihydro-3-methoxycarbonylpyridine (20a). A solution of $Na_2S_2O_4$ (8 g, 46 mmol) and Na_2CO_3 (4g, 38 mmol) in water (100 mL) was heated to 50 °C in an oil bath. A solution of pyridinium bromide **19a** (4 g, 10.3 mmol) in water (20 mL) was added dropwise over 10 min. to the stirred dithionite solution. When the addition was complete the reaction mixture was stirred at 50 °C for 10 min. and for a further 30 min. at room temperature. A yellow precipitate formed which was collected and washed with water (2 x 10 mL). The air-dried product was recrystallised from methanol/water to give 2.4 g (76%) of the dihydropyridine **20a** as yellow needles, m. p. 73-76 °C: IR ($CHCl_3$) 3060, 3000, 1680, 1600 cm^{-1}; ^{1}H N.M.R.

δ 7.1-7.7 (m, 4H), 7.38 (br s, 1H), 5.71 (dt, 1H, J = 6.5, 2 Hz), 4.75-4.9 (m, 1H), 4.37 (s, 2H), 3.70 (s, 3H), 3.2 (br s, 2H); *m/e* 308/306, 294/292, 169 (100). Calcd. for $C_{14}H_{14}NO_2Br$: C, 54.56; H, 4.58; N, 4.55; Br 25.93. Found: C, 54.72; H, 4.73; N, 4.53; Br, 26.04.

1-(2-Bromobenzyl)-3,5-dimethoxycarbonylpyridinium bromide (19b). Dimethyl dinicotinate (2.0 g, 10 mmol) and 2-bromobenzyl bromide (2.75 g, 11 mmol) were heated under reflux in methanol (20 mL) for 12 h. The bulk of the solvent was removed under reduced pressure and the residual oil was crystallised from methanol/ethyl acetate to give 2.1 g (47%) of the pyridinium bromide **19b** as a white solid, m. p. 145 °C (dec.). Calcd. for $C_{16}H_{15}NO_4Br_2$: C, 43.18; H, 3.40; N, 3.15; Br, 35.90. Found: C, 43.16; H, 3.19; N, 3.05; Br, 36.34.

1-(2-Bromobenzyl)-1,4-dihydro-3,5-dimethoxycarbonylpyridine (20b). Pyridinium bromide **19b** (1.5 g, 3.4 mmol) was taken up in water (10 mL). A solution of sodium dithionite (2.3 g, 13.4 mmol) and sodium carbonate (1.5 g, 14 mmol) in water (25 mL) was added dropwise to the stirred reaction mixture. The solution initially became dark red and after a few minutes an orange precipitate began to form. The reaction mixture was left to stir overnight at room temperature, during which time the precipitate acquired a yellow colour. The product was collected at the pump and was recrystallised from methanol to give 605 mg of the dihydropyridine **20b** as yellow needles, m. p. 129-130 °C: I.R. ($CHCl_3$) 3000, 1710, 1595 cm^{-1}; ^1H N.M.R. δ 7.2-7.7 (m, 4H), 7.03 (s, 2H), 4.50 (s, 2H), 3.71 (s, 6H), 3.31 (s, 2H); *m/e* 367/365, 366/364, 352/350, 169/171 (100). Calcd. for $C_{16}H_{16}NO_4Br$: C, 52.48; H, 4.40; N, 3.82; Br, 21.82. Found: C, 52.50; H, 4.50; N, 3.80; Br, 21.53. Reworking the mother liquor afforded a further 100 mg of product. The combined yield of **20b** was 57%

2-(2-Bromobenzyl)-4-cyano-1,2-dihydroisoquinoline, (22). 4-Cyanoisoquinoline (1 g, 6.5 mmol) and 2-bromobenzylbromide (1.7g, 6.8 mmol) were heated under reflux in ethanol (10 mL) for 2 h. The clear yellow solution was allowed to cool at 4 °C for 12 h. The intermediate isoquinolinium salt **21** crystallised from the reaction mixture. The product was collected and was dried under vacuum dessication to give 1.7 g (65%) of the isoquinolinium salt **21**. A sample of **21** (1.0 g, 2.5 mmol) was taken up in methanol (15 mL) and KBH_4 (1 g, 18 mmol) was added portionwise over 30 min. The reaction mixture was stirred at room temperature for a further 30 min. The bulk of the solvent was removed under reduced pressure and the residue was treated with water (20 mL). The aqueous suspension was extracted with $CHCl_3$ (2 x 20 mL) and the combined extracts were dried and concentrated under reduced pressure. The residue was recrystallised from ethanol to give the dihydroisoquinoline **22** as a yellow crystalline solid, m. p. 90-93 °C: IR 3060, 2200, 1670, 1620 cm^{-1}; ^1H N.M.R. δ 7.08 (s, 1H), 6.85-7.70 (m, 4H), 4.52 (s, 2H), 4.41 (s, 2H); *m/e* 326/324 (100), 325/323, 171/169, 154 . Calcd. for $C_{17}H_{13}N_2Br$: C, 62.79; H, 4.03; N, 8.61; Br, 24.57. Found: C, 62.59; H, 3.94; N, 8.51; Br, 24.52.

Cyclization of 1-[(E) or (Z) 3-Bromo-2-propenyl]-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine (14a). *(a) Using cyclization method A.* A deoxygenated solution of vinyl bromide **14a** (130 mg, 0.5 mmol), Bu_3SnH (150 μL, 0.6 mmol) and AIBN (5 mg, 0.03 mmol) in benzene (10 mL) was heated under reflux for 1h. The solvent was removed under reduced pressure and the residue was redissolved in ether (5 mL). 10% aqueous KF solution (5 mL) was added and the biphasic mixture was stirred for 1h. The organic layer was isolated from the precipitate of polymeric tin residues and was dried and concentrated under reduced pressure. G.L.C. analysis (column temp. = 200 °C) showed the formation of three products, two of similar retention time (4.9 and 5.0 min.) and one of longer retention time (5.8 min.). The products were formed, in order of increasing G.L.C. retention time, in the ratio 60:21:19. The longer retention time product corresponded by G.L.C. with an authentic sample of *N*-allyl tetrahydropyridine **14e**. The crude mixture was purified by flash chromatography (5% MeOH/CH_2Cl_2). Initial elution afforded 12 mg (15%) of **14e** [Spectral data given previously]. Further elution afforded 43 mg (48%) of ***rel*-(8*R*, 8a*S*)-8-methoxycarbonyl-3,5,6,7,8,8a-hexahydroindolizine (23)** as a yellow oil: IR ($CHCl_3$) 3000, 2780, 1730, 1620 cm^{-1}; ^1H N.M.R. δ 5.8-6.0 (m, 2H), 3.62 (s, 3H), 2.8-3.1 (m, 2H), 1.2-2.6 (m, 7H); ^{13}C N.M.R. δ 174.5 (s), 131.8 (d), 128.9 (d), 68.2 (d), 57.3 (t), 51.5 (q), 48.9 (t), 46.0 (t), 27.8 (t), 25.9 (t); *m/e* 181 (M^+), 180, 150, 120, 83 (100). HRMS calcd. for $C_{10}H_{15}NO_2$: 181.1103. Found: 181.1101. Further elution afforded 14 mg (15%) of ***rel*-(8*S*, 8a*S*)-8-methoxycarbonyl-3,5,6,7,8,8a-hexahydroindolizine (24)** as a yellow oil: IR ($CHCl_3$) 3000, 2780, 1730, 1620 cm^{-1}; ^1H N.M.R. δ 5.8-6.05 (m, 2H), 3.64 (s, 3H), 2.8-3.4 (m, 3H), 1.3-2.5 (m, 7H); ^{13}C N.M.R. δ 173.1 (s), 131.6 (d), 126.8 (d), 69.0 (d), 58.5 (d), 51.3 (q), 50.6 (t), 41.9 (t), 25.1 (t), 21.4 (t); *m/e* 181, 179, 150, 120 (100). HRMS calcd. for $C_{10}H_{15}NO_2$: 181.1103. Found: 181.1103.

(b) Using cyclization method B. A solution of **14a** (55 mg, 0.21 mmol) in benzene (2 mL) was deoxygenated and was heated under reflux. A separate deoxygenated solution of Bu_3SnH (63 μL, 0.23 mmol) and AIBN (2 mg, 0.01 mmol) in benzene (5 mL) was added by syringe pump over 4h. G.L.C. analysis of the reaction mixture showed that the ratio of **23**:**24**:**14e** was now 62:22:16.

Cyclization of 1-(2-Bromobenzyl)-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine (14c). *(a) Using cyclization method A.* Aryl bromide **14c** (230 mg, 0.74 mmol) was treated with Bu_3SnH (210 μL, 0.78 mmol) and AIBN (5 mg, 0.03 mmol). G.L.C. analysis (column temp. = 250 °C) of the residue isolated after workup showed that, in addition to some unreacted starting material, three products were formed. Two had similar retention times (5.9 and 6.7 min.) and the third had a longer retention time (9.5 min.). The relative product ratios (in order of increasing retention time) were 59:19:22. The residue was purified by m.p.l.c. (2% $MeOH/CH_2Cl_2$). Initial elution afforded 28 mg (16%) of **1-benzyl-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine (30)** as a clear oil: IR ($CHCl_3$) 3060, 1730, 1670, 1620 cm^{-1}; ^1H N.M.R. δ 7.3 (br s, 5H), 7.2 (br s, 1H), 4.20 (br s, 2H), 3.65 (s, 3H), 3.08 (m, 2H), 2.2-2.5 (m, 2H), 1.6-1.9 (m, 2H); *m/e* 229 (M^+), 228, 214, 198, 91 (100). Further elution afforded 68 mg (40%) of ***rel*-(8*S*, 8a*S*)-8-methoxycarbonyl-perhydrobenz[a]indolizine (32)** as a yellow oil which darkened on storage: IR ($CHCl_3$) 3000, 2760, 1730, 1600 cm^{-1}; ^1H N.M.R. δ 7.1 (br s, 4H), 4.07 (d, 1H, J = 7 Hz), 3.62 (d, 1H, J = 16 Hz), 3.48 (d, 1H, J = 16 Hz), 3.43 (s, 3H), 3.0-3.2 (m, 2H), 1.4-2.6 (m, 5H); ^{13}C N.M.R. δ 172.9 (s), 139.4 (s), 126.5 (d), 126.1 (d), 125.9 (s), 122.2 (d), 121.9 (d), 68.9 (d), 58.3 (t), 52.1 (t), 51.3 (q), 41.1 (d), 26.2 (t), 22.7 (t); *m/e* 231 (M^+), 200, 172, 170, 131 (100). HRMS calcd. for $C_{14}H_{17}NO_2$: 231.1259. Found: 231.1260. Further elution afforded 21 mg (12%) of ***rel*-(8*R*,8a*S*)-8-methoxycarbonyl-perhydrobenz[a]indolizine (31)** as a yellow oil which also darkened on storage: IR ($CHCl_3$) 3000, 2760, 1730, 1600 cm^{-1}; ^1H N.M.R. δ 7.1 (m, 4H), 4.02 (d, 1H, J = 11 Hz), 3.72 (s, 3H), 3.65 (m, 2H), 3.0-3.2 (m, 1H), 1.5-2.6 (m, 5H); ^{13}C N.M.R. δ 175.0 (s), 139.9 (s), 127.0 (s), 126.9 (d), 126.6 (d), 122.4 (d), 121.5 (d), 67.0 (d), 56.7 (t), 51.7 (q), 49.9 (t), 46.1 (d), 28.9 (t), 23.8 (t); *m/e* 231(M^+), 200, 172, 170, 131 (100). HRMS calcd. for $C_{14}H_{17}NO_2$: 231.1259. Found: 231.1260.

(b) Using cyclization method B. Aryl bromide **14c** (310 mg, 1.0 mmol) was treated with a solution of Bu_3SnH (300 μL, 1.1 mmol) and AIBN (10 mg, 0.06 mmol). G.L.C. analysis of the crude reaction mixture showed that the ratio of **32**:**31**:**30** was 65:20:15. The crude residue isolated after workup was purified by column chromatography. Initial elution with 2% $MeOH/CH_2Cl_2$ afforded 30 mg (13%) of reduction product **35**. Further elution with 5% $MeOH/CH_2Cl_2$ afforded 110 mg (48%) of **32**. Further elution afforded 25 mg of a mixture of **32** and **31**, then 35 mg (15%) of **31**.

Cyclization of 1-(3-Bromopropyl)-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine (14b). *(a) Using cyclization method A.* Propyl bromide **14b** (100 mg, 0.38 mmol) was treated with Bu_3SnH (110 μL, 0.4 mmol) and AIBN (10 mg, 0.06 mmol). G.L.C. analysis (column temp. = 250 °C)of the residue isolated after workup showed the formation of two products in the ratio 74:26. The products were separated by flash chromatography (2% $MeOH/CH_2Cl_2$). Initial elution afforded 15 mg (21%) of **3-methoxycarbonyl-1-propyl-1, 4, 5, 6-tetrahydropyridine (25)** as a clear oil: ^1H N.M.R. δ 7.15 (br s, 1H), 3.55 (s, 3H), 3.09 (t, 2H, J = 7 Hz), 3.03 (m, 2H), 2.26 (br t, 2H), 1.2-2.4 (m, 6H), 0.91 (t, 3H, J = 7 Hz). Further elution afforded 44 mg (63%) of ***rel*-(8*R*, 8a*S*)-8-methoxycarbonylperhydroindolizine (26)** as a yellow oil: IR ($CHCl_3$) 2780, 1730 cm^{-1}; ^1H N.M.R. δ 3.65 (s, 3H), 3.1-3.3 (m, 5H), 1.2-2.4 (m, 9H); ^{13}C N.M.R. δ 172.3 (s), 65.3 (d), 54.1 (t), 52.3 (t), 51.7 (q), 47.8 (d), 29.2 (t), 28.2 (t), 24.7 (t), 20.5 (t); *m/e* 183 (M^+), 182, 168, 152, 96 (100). HRMS calcd. for $C_{10}H_{17}NO_2$: 183.1259. Found: 183.1259.

(b) Using cyclization method B. A heated solution of bromide **14b** (1.3 g, 5 mmol) in benzene (25 mL) was treated with a solution of Bu_3SnH (1.9 mL, 7 mmol) and AIBN (20 mg, 0.12 mmol) in benzene (25 mL). The addition was carried out over 8 h. G.L.C. analysis showed the ratio of **26**:**25** was now 89:11. The crude mixture was purified by column chromatography. Initial elution with 2% $MeOH/CH_2Cl_2$ afforded 73 mg (8%) of direct reduction product **25**. Further elution with 5% $MeOH/CH_2Cl_2$ afforded 805 mg (72%) of cyclization product **26**.

Chemical correlation of (23) and (26). A solution of unsaturated indolizidine **23** (10 mg, 0.05 mmol) in methanol (2 mL) was hydrogenated over 5% Pd/C catalyst. When one equivalent of hydrogen had been taken up, the mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to give 9 mg (90%) of a yellow oil whose G.L.C. retention time and ^{13}C and ^1H N.M.R. spectra were identical with those of cyclization product **26**.

***rel*-(8*R*, 8a*S*)-8-Hydroxymethylperhydroindolizine (38).** A solution of cyclization product **26** (25 mg, 0.14 mmol) in THF (1 mL) was added carefully to an ice-cooled suspension of $LiAlH_4$ (20 mg, 0.56 mmol) in THF (2 mL). The reaction mixture was stirred for 1h at room temperature. The solution was treated sequentially with water (25 μL), 20% aqueous NaOH (75 μL) and water (25 μL). The mixture was filtered to remove the precipitated aluminium salts and the filtrate was concentrated under reduced pressure to give 18 mg (86%) of **38** as a clear oil: IR 3450, 2800 cm^{-1}; ^1H N.M.R. δ 3.3-3.8 (m, 4H), 2.6-2.9 (m, 4H), 1.1-2.1 (m, 9H); ^{13}C N.M.R. δ 66.4, 65.4, 54.1, 52.6, 44.6, 29.0, 27.6, 25.6, 25.1, 20.7; *m/e* 155 (M^+), 154, 138, 128.

Cyclization of 1-(4-Bromobutyl)-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine (14d). *Using cyclization method A.* Butyl bromide **14d** (130 mg, 0.47 mmol) was treated with Bu_3SnH (150 μL, 0.55 mmol) and AIBN (5 mg, 0.03 mmol). G.L.C. analysis (column temp. = 250 °C) of the residue isolated after workup showed the formation of two products in the ratio 64:36. The products were separated by column chromatography (5% $MeOH/CH_2Cl_2$). Initial elution afforded 19 mg (21%) of **1-butyl-3-methoxycarbonyl-**

1,4,5,6-tetrahydro pyridine (33) as a clear oil: ^{1}H N.M.R. δ 7.15 (br s, 1H), 3.58 (s, 3H), 3.09 (t, 2H, *J* = 7 Hz), 3.00 (m, 2H), 2.26 (br t, 2H), 1.2-2.4 (m, 8H), 0.92 (t, 3H, *J* = 7 Hz). Further elution afforded 44 mg (47%) of ***rel*-(1*R*, 9a*R*)-1-methoxycarbonylperhydroquinolizine (34)** as a yellow oil: IR 2760, 1730 cm^{-1}; ^{1}H N.M.R. δ 3.64 (s, 3H), 2.8-3.0 (m, 5H), 1.2-2.4 (m, 11H); ^{13}C N.M.R. δ 175.3 (s), 63.6 (d), 56.7 (t), 56.1 (t), 51.6 (q), 49.5 (d), 31.1 (t), 28.8 (t), 25.8 (t), 24.7 (t), 24.4 (t); *m/e* 197 (M+), 196, 182, 166, 110 (100).

(±) Epilupinine (39). A solution of cyclization product **34** (52 mg, 0.26 mmol) in THF (1 mL) was carefully added to an ice-cooled suspension of $LiAlH_4$ (50 mg, 1.3 mmol) in THF (2 mL). Workup as described for the reduction of **26** afforded 41 mg (95%) of (±)-epilupinine, **39**, as a clear oil which slowly crystallised on standing: IR ($CHCl_3$) 3460, 2800 cm^{-1}; ^{1}H N.M.R. δ 3.4-3.8 (m, 3H), 2.7-2.9 (m, 4H), 2.4 (br s, 1H, ex. D_2O), 1.1-2.1 (m, 11H); ^{13}C N.M.R. δ 64.4, 64.3, 56.8, 56.5, 43.8, 29.6, 28.2, 25.5, 24.9, 24.5; *m/e* 169 (M+), 167, 152, 142.

Cyclization of 3-Methoxycarbonyl-1-(1-oxo-3-bromopropyl)-1,4,5,6-tetrahydropyridine (17). *Using cyclization method B.* A solution of Bu_3SnH (2.5 mL, 7.5 mmol) and AIBN (40 mg, 0.24 mmol) in benzene (25 mL) was added over 8h. to a heated solution of bromoamide **17** (1.9 g, 6.9 mmol) in benzene (25 mL). The crude residue isolated after workup was purified by flash chromatography (20% ethyl acetate/hexane). Initial elution afforded 510 mg (38%) of **3-methoxycarbonyl-1-(1-oxopropyl)-1,4,5,6-tetrahydropyridine (27)**: IR ($CHCl_3$) 1750, 1730, 1670 cm^{-1}; ^{1}H N.M.R. δ 7.3 (br s, 1H), 3.65 (s, 3H), 3.3-3.6 (m, 2H), 2.2-2.5 (m, 2H), 2.21 (q, 2H, *J* = 7 Hz), 1.5-1.9 (m, 2H), 0.95 (t, 3H, *J* = 7 Hz); *m/e* 197(M+), 166, 141 (100), 126. Further elution afforded 670 mg (50%) of a 9:1 mixture (by ^{1}H N.M.R.) of both diastereoisomers of **8-methoxycarbonyl-3-oxoperhydroindolizine, (28)** and **(29)**, as a waxy solid: IR 2780, 1730, 1675 cm^{-1}; ^{1}H N.M.R. (major isomer, **28**) δ 4.1-4.3 (m, 2H), 3.64 (s, 3H), 3.4-3.5 (m, 1H), 2.3-2.5 (m, 2H), 1.5-2.1 (m, 7H); *m/e* 197 (M+), 182, 169, 166, 83 (100). HRMS calcd. for $C_{10}H_{15}NO_3$: 197.1048. Found: 197.1050.

Chemical correlation of (28) with (26). A solution of amide **28** (200 mg, 1.0 mmol) in THF (2 mL) was reduced with $LiAlH_4$ (150 mg, 4 mmol) in THF (3 mL). Workup as described for the reduction of **26** afforded 150 mg (96%) of a clear oil whose G.L.C. retention time and ^{13}C N.M.R. spectra were identical with those of the amino alcohol **38** prepared previously by reduction of **26**.

Cyclization of 1-(2-Bromobenzyl)-1,4-dihydro-3-methoxycarbonylpyridine (20a). *Using cyclization method A.* Bromide **20a** (130 mg, 0.42 mmol) was treated with Bu_3SnH (140 μL, 0.52 mmol) and AIBN (10 mg, 0.06 mmol). The crude residue isolated after workup was purified by flash chromatography. Elution with 20% ethyl acetate/hexane afforded 21 mg (22%) of **1-benzyl-3-methoxycarbonyl-1,4-dihydropyridine (35a)** as a yellow solid. Further elution afforded 33 mg (34%) of ***rel*-(8a*S*)-6-methoxycarbonyl-1,2,3,7,8,8a-hexahydrobenz-[a]-indolizine (37)** as a yellow oil which darkened on exposure to air: IR 3060, 1730, 1670, 1615, 1590 cm^{-1}; ^{1}H N.M.R. δ 7.65 (br s, 1H), 7.2-7.4 (m, 4H), 4.86 (d, 1H, *J* = 15 Hz), 4.50 (d, 1H, *J* = 15 Hz), 4.4 (m, 1H), 3.65 (s, 3H), 2.3-2.8 (m, 2H), 1.4-1.6 (m, 2H); *m/e* 229 (M+, 100), 228, 214, 199, 198, 170. HRMS calcd. for $C_{14}H_{15}NO_2$: 229.1103. Found: 229.1104.

Cyclization of 1-(2-Bromobenzyl)-1,4-dihydro-3-methoxycarbonylpyridine (20a) with excess Bu_3SnH. A solution of dihydropyridine **20a** (450 mg, 1.46 mmol), Bu_3SnH (1.3 mL, 5 mmol) and AIBN (10 mg, 0.06 mmol) in benzene (15 mL) was heated under reflux for 3h. The crude residue isolated after the standard workup was purified by flash chromatography. Initial elution with 1% MeOH/CH_2Cl_2 afforded 73 mg (22%) of the direct reduction product **35a**. Further elution with 3% MeOH/CH_2Cl_2 afforded 110 mg (33%) of **37**. Further elution with 5% MeOH/CH_2Cl_2 afforded 40 mg (12%) of a product whose ^{1}H and ^{13}C N.M.R. spectra were identical with those of perhydroindolizine **32**.

Cyclization of 1-(2-Bromobenzyl)-1,4-dihydro-3,5-dimethoxycarbonylpyridine (20b). *Using cyclization method B.* Bromide **20b** (360 mg, 1.0 mmol) was treated with Bu_3SnH (300 μL, 1.1 mmol) and AIBN (15 mg, 0.09 mmol). The crude residue isolated after workup was purified by flash chromatography. Initial elution with 10% ethyl acetate/hexane afforded 36 mg (13%) of **1-benzyl-1,4-dihydro-3,5-dimethoxycarbonylpyridine (35b)** as a yellow solid: IR ($CHCl_3$) 3000, 1710, 1595 cm^{-1}; ^{1}H N.M.R. δ 7.5 (br s, 5H), 7.03 (s, 2H), 4.48 (s, 2H), 3.70 (s, 6H), 3.25 (s, 2H); *m/e* 287(M+), 262, 230. Further elution with 20% ethyl acetate/hexane gave 145 mg (52%) of a mixture of ***rel*-(8*S*, 8a*S*)** and ***rel*-(8*R*, 8a*S*)-6,8-bis(methoxycarbonyl)-1,2,3,7,8,8a-hexahydrobenz-[a]-indolizine (36b)** as a yellow oil which rapidly darkened on exposure to air: IR ($CHCl_3$) 1730, 1710, 1680, 1620, 1590 cm^{-1}; ^{1}H N.M.R. (major isomer) δ 7.0-7.6 (m, 4H), 7.1 (br s, 1H), 4.85 (d, 1H, *J* = 4 Hz), 4.80 (d, 1H, *J* = 15 Hz), 4.62 (d, 1H, *J* = 15 Hz), 3.72 (s, 3H), 3.58 (s, 3H), 2.2-2.9 (m, 3H); ^{13}C N.M.R. δ 174.9 (s), 168.2 (s), 142.7 (d), 138.4 (d), 136.4 (s), 128.2 (d), 127.8 (d), 122.9 (s), 122.5 (d), 95.4 (s), 62.6 (q), 55.8 (t), 51.9 (d), 42.7 (t), 29.5 (d); *m/e* 287, 272, 256, 228 (100).

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