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TANDEM RADICAL CYCLIZATION REACTIONS, INITIATED AT NITROGEN, AS AN APPROACH TO THE CDE-TRICYLIC CORES OF CERTAIN POST-SECODINE ALKALOIDS

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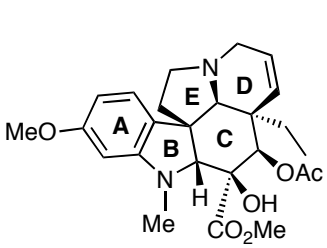
Abstract – The nitrogen-radical precursors (**10–15**) have been prepared and subjected to reaction conditions expected to promote tandem radical cyclization sequences leading to the CDE-tricyclic frameworks associated with alkaloids such as vindoline (**1**) and ibophyllidine (**2**). In the event, each of precursors (**10**, **11**, **12** and **13**) participated in the desired processes and thus providing products, (**28**, **29**, **30** and **31)** respectively, embodying ring systems related to ibophyllidine (**2**). In contrast, the higher homologue (**14**) of PTOC-carbamate (**12**) decomposed upon exposure to radical chain initiation conditions while the *N*-chloro-analogue (**15**) simply underwent reductive dechlorination to give compound (**27**). As such the title processes appear unlikely to offer a useful approach to the CDE-tricyclic ring system associated with vindoline-type alkaloids.

INTRODUCTION

The monoterpenoid indole alkaloids (+)-vindoline (**1**) and (+)-ibophyllidine (**2**) are members of the so-called "post-secodine" class.[1] The former natural product has been isolated, as a major constituent, from various plants including *Catharanthus* (*Vinca*) *rosea*, *Catharanthus ovalis* and *Melodinus fusiformis*.[1b,2] Significantly, compound (**1**) embodies one half of and is a biosynthetic precursor to the clinically important indole-indoline alkaloids vinblastine and vincristine.[3] Unlike the latter alkaloids, however, vindoline does not display significant anti-mitotic activity nor is it a particularly cytotoxic entity.[4] Ibophyllidine (**2**) has been obtained from, *inter alia*, the plants *Tabernaemontana albiflora* and *Tabernanthe iboga*.[5] Extracts of the roots of the latter plant are used in West Africa as a ceremonial hallucinogen or, in smaller doses, as a stimulant. Biogenetically speaking, compound (**2**) is probably

derived from the hydroxylated D-ring homologue pandoline.[6] While they differ in the nature and size of the D-ring, alkaloids (**1**) and (**2**) have many structural features in common – most conspicuously the overlap of their ABCE-substructures. These similarities are, clearly, a consequence of their closely related biogenetic origins.

Vindoline has been the subject of numerous preparative studies, including more than ten successful total or formal total syntheses[7] and much of the more recent work in the area has been reviewed.[1a] The most recently reported (and formal) synthesis was described by Murphy and co-workers[7a] who exploited a tandem radical cyclization process involving, as the second step, addition of a *C*-centered radical onto a tethered azide. Subsequent loss of dinitrogen then hydrogen atom abstraction by the resulting *N*-centered radical completed the assembly of a tetracyclic ring system corresponding to the ABCE-core associated with vindoline (**1**). This sequence allowed for access to an advanced intermediate associated with Büchi's original synthesis of the racemic modification of the alkaloid.[7k] Much less work has been focused on the development of syntheses of ibophyllidine with Kuehne and co-workers representing the only group to have, thus far, achieved total syntheses of the (±)- and then the (+)-form of this alkaloid.[6a,8] The work described herein was undertaken as part of a more general program[9] to develop syntheses of a range of monoterpenoid indole alkaloids including aspidospermidine (**3**) and, ultimately, vinblastine. A particular focus of the efforts detailed below was to establish protocols wherein an intact C-ring precursor to compound (**1** and/or **2**) could be used as the starting point in the synthesis of these natural products. This focus was prompted by having access to large quantities of an enantiomerically pure metabolite embodying functionalities closely related to those observed within the C-ring of vindoline.[10]



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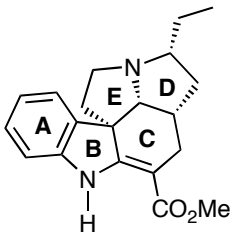

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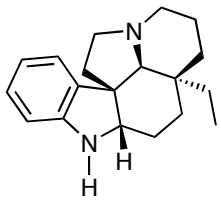

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The tandem *N*-radical initiated cyclization studies of Zard, as deployed in his recently reported synthesis of (±)-13-deoxyserratine,[11] provided the inspiration for the work detailed herein. In particular, it seemed reasonable to expect that an *N*-centered radical of the general type (**4**) would engage in a 5-*exo*-trig cyclization reaction to give the perhydroindole-based radical (**5**) (see Figure 1). The latter species could then engage in a second cyclization reaction leading to a six-membered ring (*via* either a 6-*endo*-trig or 6-*endo*-dig cyclization reaction depending on the nature of the tethered C–C multiple bond) or a five-membered ring (*via* a 5-*exo*-trig or 5-*exo*-dig cyclization process). The first mode of cyclization

(Path a) would be expected to lead, *via* intermediate radical (**6**), to the tricyclic species (**7**) embodying the CDE-ring substructure of vindoline and related alkaloids of this class. Alternately, if Path b were followed then radical (**8**) so formed would be expected to deliver the tricyclic compound (**9**) incorporating the CDE-ring system associated with ibophyllidine (**2**). The stereochemical outcomes of the initial steps of both sequences were expected to be analogous to those observed by Cossy *et al.*[12] during the course of their development of an *N*-centered radical cyclization route to the *cis*-ring fused perhydroindole substructure associated with the alkaloidal framework γ-lycorane and corresponding to the CE-ring substructure within compounds (**7** and **9**). With such ring-fusion established in the first steps of the reaction sequences the illustrated stereochemical relationship between the C- and D-rings, as established in the second cyclization event, necessarily follows. Of course, if the alkyne-containing cyclization precursor (**4**) were successfully employed in such processes then the unsaturation introduced into/onto the D-rings of each of compounds (**7** and **9**) would lead to functionality at these sites relevant to the synthesis of targets (**1** and **2**). The radical cyclization sequences proposed here are essentially the inverse of those employed by Murphy and his co-workers in developing their recent formal total synthesis of vindoline.[7a]

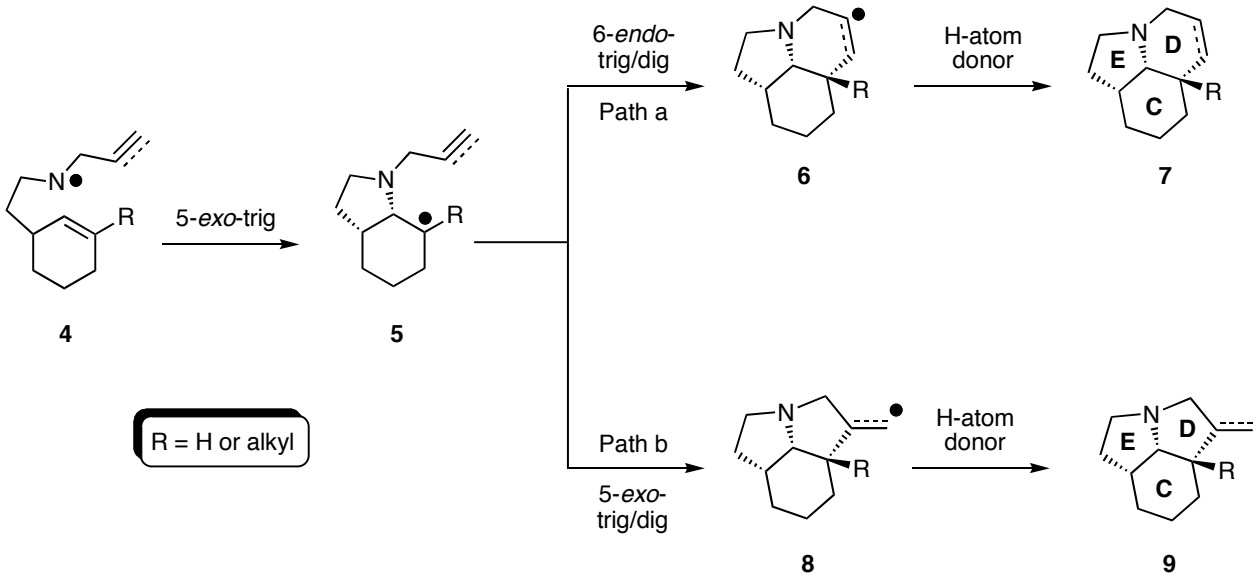
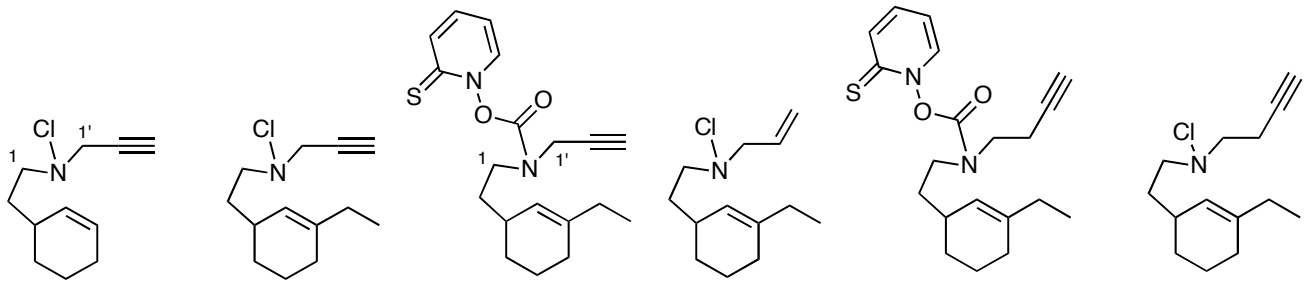


Figure 1.

While both aminyl and amidyl radicals can be used in *N*-centered radical cyclization reactions it was decided to focus attention on the former species as they have been examined more extensively and would, hopefully, provide direct access to the target tricyclic amines (as opposed to the corresponding lactams).[13] Many routes to aminyl radicals have been established since the pioneering work of Stella and Surzur[13p,r] but the use of *N*-chloroamines and *N*-hydroxypyridine-2-thione carbamates (PTOC carbamates), as developed by Tokuda[13a,e,h] and Newcomb[13f,k,l,m] respectively, seemed especially attractive protocols. So, for example, it has been demonstrated, by Tokuda, that when *N*-chloroamines are exposed, in refluxing

benzene, to tri-*n*-butyltin hydride and the radical initiator AIBN then a neutral *N*-radical is formed and this might be expected to cyclize onto the pendant cyclohexenyl double bond. PTOC-carbamates behave in a similar manner to Barton esters and can be photolyzed, in the presence of either a Lewis or Brønsted acid, to generate cationic *N*-radicals that can also participate in cyclization reactions of the desired type. Interestingly, when the acidic additive (e.g. malonic acid) is omitted from these types of reactions then the cyclization reaction does not proceed and the major product is the amine arising from reductive cleavage of the PTOC moiety.[13f,k,l,m]

On the basis of the foregoing discussion, the *N*-radical precursors sought for the purposes of undertaking the present study were the 2-(cyclohex-2-enyl)ethylamine systems (**10**–**15**). This series of compound varies in, (i), the nature of the second carbon-based (and unsaturated) substituent at nitrogen (propargyl, allyl or homopropargyl), (ii) the precursor to the *N*-centered radical (*N*-chloroamine or PTOC carbamate) and, (iii) the presence or absence of an ethyl group on the cyclohexenyl double bond. This last feature allows for an investigation of the capacity of the proposed tandem radical cyclization sequence to construct tertiary and quaternary carbon centers at the junction between the C- and D-rings of target (**1**). The following section details the protocols established for the synthesis of the target substrates (**10**–**15**) while the one thereafter describes studies associated with efforts to engage these materials in the proposed cyclization sequences.



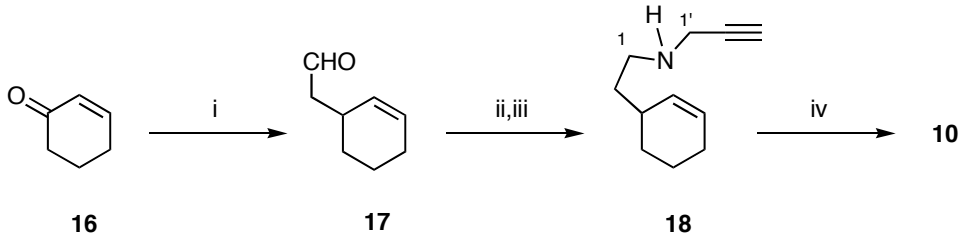
10 **11** **12** **13** **14** **15**

RESULTS AND DISCUSSION

Synthesis of Substrates for Cyclization Studies

The synthesis of the first of the target substrates (**10**) was accomplished using the reaction sequence defined in Scheme 1. Thus, following the five-step protocol reported by Cossy *et al.*[12] and involving a Pd[0]-catalyzed allylic substitution reaction as the key process, the commercially available 2-cyclohexenone (**16**) was converted into the previously reported aldehyde (**17**) (60% from **16**).[12,14] The latter compound was then condensed with propargylamine in the presence of 4 Å molecular sieves and

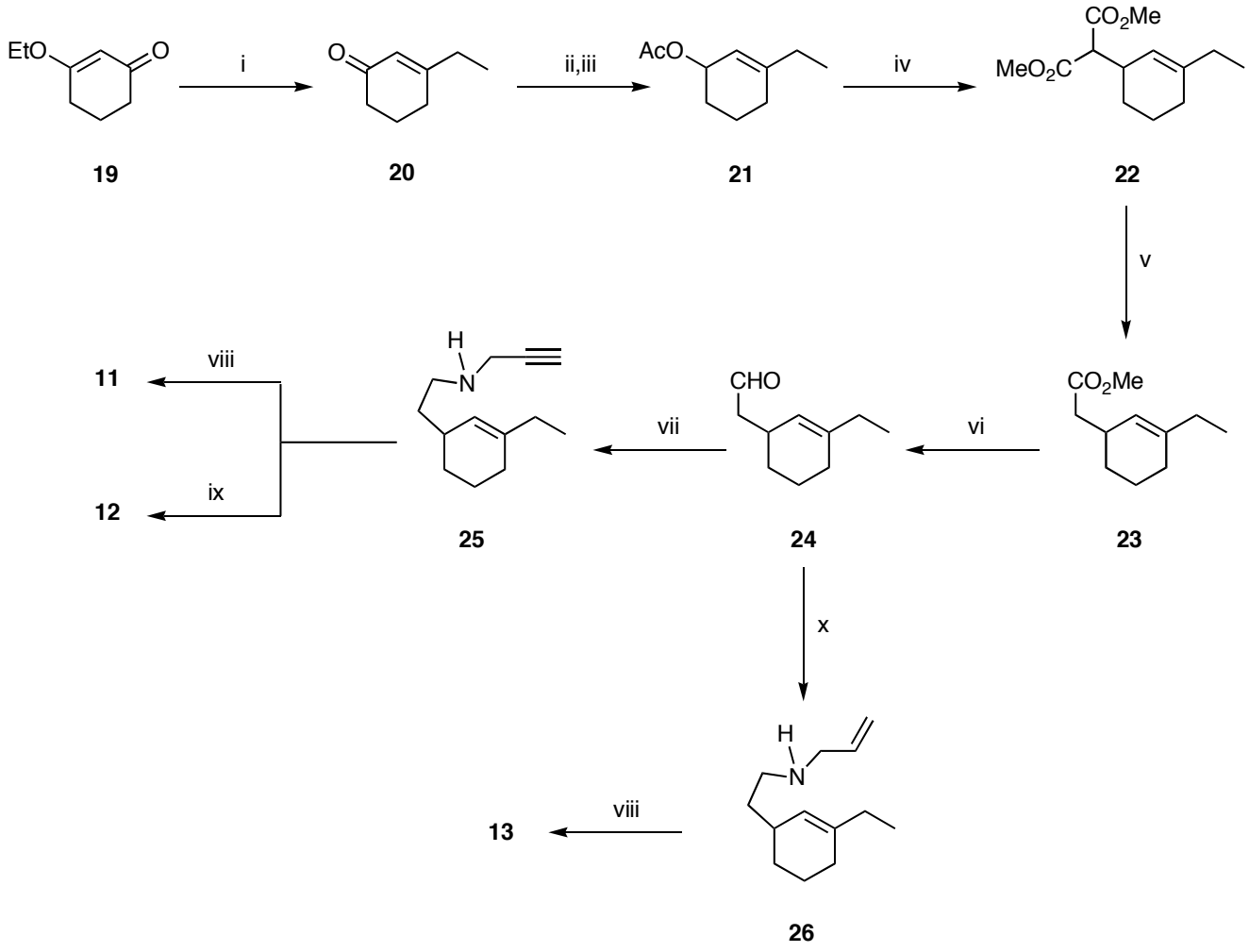
the resulting imine immediately reduced, using $NaBH_4$ in methanol, to the corresponding secondary amine **18** which was obtained in 94% yield over the two steps involved. Reaction of compound (**18**) with *N*-chlorosuccinimide in CH_2Cl_2 then afforded the target cyclization substrate (**10**) in quantitative yield. Satisfactory ^1H and ^{13}C NMR spectral data could be obtained on this chromatographically stable material and an accurate MS measurement consistent with the expected molecular formula was recorded on the $[M–H\cdot]^+$ ion observed in the electron impact MS spectrum. The significant downfield shift ($\Delta\delta$ *ca.* 0.4) of the resonances due to the C–1 and C–1' protons observed on converting amine (**18**) into its *N*-chloro-derivative was taken as a clear indication that the desired compound (**10**) had indeed been formed.



Scheme 1. *Reagents and conditions*: (i) see reference 12; (ii) $HC{\equiv}CCH_2NH_2$ (5 mol equiv.), 4 Å molecular sieves, THF, 18°C, 16 h; (iii) $NaBH_4$, (1 mol equiv.), methanol, 0°C, 0.5 h; (iv) *N*-chlorosuccinimide (1.2 mol equiv.), CH_2Cl_2, 0°C, 1 h.

The ethylated equivalent of substrate (**10**), namely compound (**11**), was obtained from commercially available 3-ethoxycyclohexenone (**19**) by the route indicated in Scheme 2 and which represents, in its opening stages, a straightforward adaptation of the reaction sequence used by Cossy *et al.*[12] in their synthesis of aldehyde (**17**). Thus, reaction of compound (**19**) with ethylmagnesium bromide and subjection of the resulting tertiary alcohol to acidic workup then gave the previously reported[15] 3-ethylcyclohexenone (**20**) in 89% yield. Sodium borohydride-mediated reduction of the latter compound afforded the corresponding allylic alcohol which was immediately acetylated, under standard conditions, to give the previously reported[16] allylic acetate (**21**) in quantitative yield over the two steps just described. Treatment of compound (**21**) with Pd_2dba_3/1,2-dppe and the sodium salt of dimethyl malonate in refluxing THF then afforded the allylic substitution product (**22**) in a completely regioselective manner and 90% yield (at 74% conversion). Following a procedure reported by Wenkert,[17] this diester was treated with lithium iodide in DMSO at 180°C and by such means one of the carbomethoxy groups was removed and thus affording the monoester (**23**) in 80% yield. Reduction of this last compound with DIBAL-H in CH_2Cl_2 at –78°C afforded the corresponding aldehyde (**24**) (75%) and this was then subjected to a reductive amination sequence using propargylamine. The secondary amine (**25**) (75%) so-formed, and for which satisfactory ^1H and ^{13}C NMR spectral data were obtained, was then reacted with

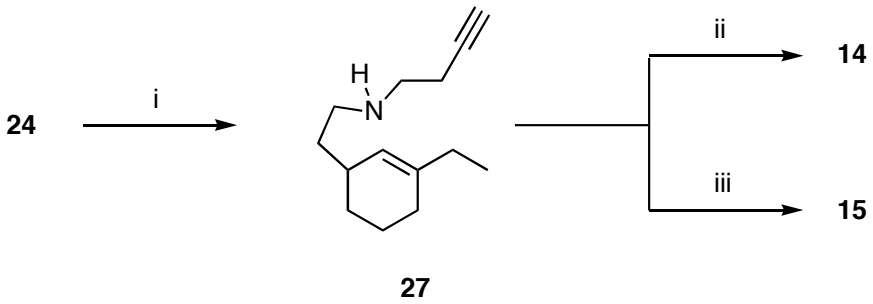
N-chlorosuccinimde, in same manner as detailed above, to give the *N*-chloroamine (**11**) (quant.) which could only be partially characterized because of its rather unstable nature. The equivalent PTOC-derivative (**12**) was prepared (Scheme 2) by reacting the same amine with 1-oxa-2-oxo-3-thiaindolizinium chloride[18] according to method of Newcomb *et al.*[13f] In the 300 MHz ^{1}H NMR spectrum of this material the C–1' protons resonated as two distinct singlets (at δ 4.43 and 4.21) while the C–1 protons appeared as two distinct triplets (at δ 3.72 and 3.53). Such "splittings" suggest this compound exists in two distinct forms arising from restricted rotation about the N to C=O bond associated with the newly installed carbamate residue.



Scheme 2. *Reagents and conditions*: (i) EtMgBr (1.66 mol equiv.), THF, 0°C, 3 h; (ii) $NaBH_4$ (1.2 mol equiv.), methanol, 0 to 18°C, 16 h; (iii) Ac_2O, pyridine, DMAP (cat.), 0 to 18°C, 10.5 h; (iv) $(MeO_2C)_2CHNa$ (1.7 mol equiv.), Pd[0] (cat.), THF, 68°C, 24 h; (v) $LiI•3H_2O$ (1 mol equiv.), DMSO, 180°C, 1.5 h; (vi) DIBAL-H (1.1 mol equiv.), CH_2Cl_2,/hexane, –78°C, 1.5 h; (vii) $HC{\equiv}CCH_2NH_2$ (5 mol equiv.), 4 Å molecular sieves, THF, 18°C, 16 h, then $NaBH_4$, MeOH, 0°C; (viii) *N*-chlorosuccinimide (1.2 mol equiv.), CH_2Cl_2, –30 to 18°C, 1 h; (ix) 1-oxa-2-oxo-3-thiaindolizinium chloride (1.2 mol equiv.), Et_3N (1.1 mol equiv.), C_6H_6, 18°C, 2 h; (x) $H_2C{=}CCH_2NH_2$ (5 mol equiv.), 4 Å molecular sieves, THF, 18°C, 4 h, then $NaBH_4$, MeOH, 0°C.

The preparation of the cyclization substrate (**13**) was achieved (Scheme 2) by subjecting the above-mentioned aldehyde (**24**) to reaction with allylamine in the presence of 4Å molecular sieves and the resulting imine immediately reduced with $NaBH_4$. In this manner compound (**26**) was obtained in 75% yield. Reaction of the last species with *N*-chlorosuccinimide in the same manner as described above then afforded the targeted *N*-chloroamine (**13**) in 97% yield. The unstable nature of compound (**13**) precluded the acquisition of MS spectral data but the derived NMR spectral data (see EXPERIMENTAL) were in full accord with the assigned structure and similar to those obtained on congener (**11**).

The final substrates (**14** and **15**), sought in connection with the present study were prepared by the route defined in Scheme 3. The approach involved was slightly different from that employed in obtaining congeners (**11** and **12**) because, despite many attempts, we were unable to engage homopropargylamine in a Schiff-base condensation with aldehyde (**24**). However, the ylide derived from homopropargyl azide and triphenyphosphine was readily obtained and this reacted with aldehyde (**24**) to form the necessary imine.[19] The so-obtained and crude samples of this material were treated with sodium cyanoborohydride and upon work up then chromatography the, by now long sought after, amine (**27**) was finally obtained, albeit in only 33% yield. This material was then converted, in high yields, into the corresponding PTOC- and *N*-chloro-derivatives (**14** and **15**) respectively, using the protocols defined above for the generation of their lower homologues. While the former product was so unstable that no useful spectroscopic analysis could be carried out, the 300 MHz ^{1}H NMR spectrum of compound (**15**) was acquired and proved fully consistent with the assigned structure.



Scheme 3. *Reagents and conditions*: (i) $H_2C{\equiv}CCH_2CH_2N_3$ (1 mol equiv.), PPh_3 (1 mol equiv.), THF, 68°C, 16 h then $NaCNBH_3$ (1.5 mol equiv.); (ii) 1-oxa-2-oxo-3-thiaindolizinium chloride (1.2 mol equiv.), Et_3N (1 mol equiv.), C_6H_6, 18°C, 2 h; (iii) *N*-chlorosuccinimide (1.1 mol equiv.), CH_2Cl_2, –30 to 18°C, 1 h.

Cyclization Studies

The results of subjecting substrates (**10**–**15**) to the foreshadowed cyclization conditions are shown in Table 1 as well as Schemes 4–6. Thus, treatment of the first of these compounds, *N*-chloroamine (**10**), at 40 mmolar concentration to reaction with *n*-Bu_3SnH in refluxing toluene and in the presence of AIBN (Entry 1) afforded the dechlorinated compound (**18**) (41%) as the major product of reaction but the

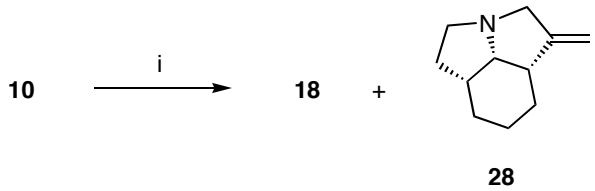
anticipated and chromatographically separable tandem radical cyclization product (**28**) (Scheme 4) was also obtained in 34% yield. Despite the less than complete mass balance encountered in this reaction, no evidence for the formation of other cyclization products was obtained. The samples of compound (**18**) generated in this manner were identical, as judged by ^{1}H and ^{13}C NMR spectral analyses, to those obtained earlier. Spectral data derived from the latter product (**28**) were in full accord with the assigned structure. In particular, the electron-impact MS spectrum displayed a molecular ion at *m/z* 163 and an accurate MS measurement on this species confirmed that it was of the expected composition, *viz*. $C_{11}H_{17}N$. While the IR spectrum was rather non-descript, the 300 MHz ^{1}H NMR spectrum revealed, as the most significant feature, two slightly broadened one-proton singlets at δ 4.81 and 4.78 which are assigned to the hydrogens attached to the terminal and exocyclic olefin associated with tricyclic compound (**28**). The 75 MHz ^{13}C NMR spectrum was even more informative, displaying the expected eleven signals including two due to sp^2-hydridized carbons associated with an exocyclic alkene and three due to sp^3-hydridized carbons attached to nitrogen. Such data compare favorably with those reported for a structurally related compound prepared by Kuehne and co-workers.[20] These spectral features clearly demonstrate that a tandem radical cyclization process has taken place with the second of the steps involved occurring in a 5-*exo*-trig manner (i.e. following Path b as shown in Figure 1). While rigorous proof of stereochemistry for compound (**28**) has not been obtained, the illustrated structure is the only one that can reasonably

Table 1: Outcomes of the Subjection of Cyclization Substrates (**10**–**15**) to Conditions for Generating *N*-Centered Radicals[a]

Entry	Substrate (mmol conc.)	Reaction Conditions	Product(s) (yield %)
1	**10** (40)	*n*-Bu_3SnH, AIBN, toluene, reflux	**18** (41), **28** (34)
2	**10** (100)	*n*-Bu_3SnH, AIBN, benzene, reflux	**18** (63), **28** (19)
3	**10** (20)	*n*-Bu_3SnH, AIBN, benzene, reflux	**18** (50), **28** (27)
4	**10** (10)	*n*-Bu_3SnH, AIBN, benzene, reflux	**18** (0), **28** (74)
5	**11** (60)	*n*-Bu_3SnH, AIBN, toluene, reflux	**29** (68)
6	**12** (50)	BF_3•Et_2O, hν, acetonitrile	**30** (71)
7	**12** (50)	Malonic acid, hν, acetonitrile	**30** (65)
8	**13** (40)	*n*-Bu_3SnH, AIBN, toluene, reflux	**26** (35), **31** (44)
9	**13** (10)	*n*-Bu_3SnH, AIBN, benzene, reflux	**26** (1), **31** (62)
10	**14** (25)	BF_3•Et_2O, hν, acetonitrile	Decomposition
11	**14** (25)	Malonic acid, hν, acetonitrile	Decomposition
12	**15** (27.5)	*n*-Bu_3SnH, AIBN, toluene, reflux	**27** (~50)

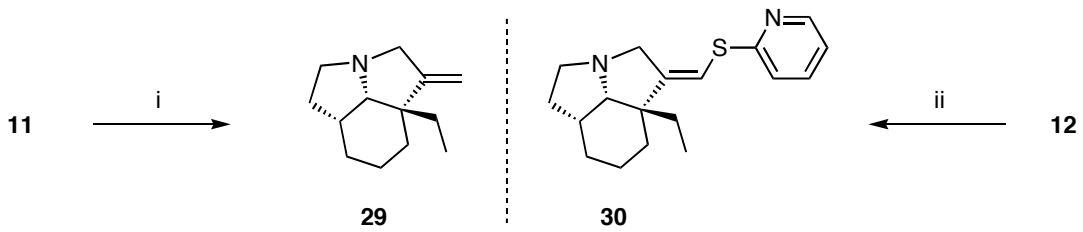
[a] Full details provided in the EXPERIMENTAL.

accommodate the fusion of two five-membered rings across contiguous positions of a six-membered ring system. Unsurprisingly, the concentration of substrate (**10**) used in effecting the reductive cyclization process has a significant impact on the ratio of products (**18** and **28**) observed. For example, when 100 mmolar concentrations of substrate were used (Entry 2, Table 1) along with benzene as the reaction solvent then the reductive dechlorination product (**18**) was obtained in 63% yield and the yield of target (**28**) dropped to 19%. While lowering the concentration of substrate to 20 mmol (Entry 3, Table 1) had little useful effect, when the reaction was run at the 10 mmolar level (Entry 4, Table 1) the tricyclic species (**28**) became the exclusive product of reaction and was obtained in 74% yield.



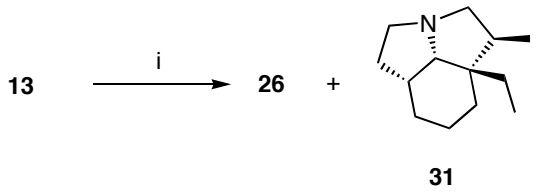
Scheme 4. *Reagents and conditions*: (i) *n*-Bu_3SnH (1 mol equiv.), AIBN (5 mol %), C_6H_6, 80°C, 1.5 h.

Cyclization of the ethyl-substituted counterpart to compound (**10**), *viz.* the *N*-chloroamine (**11**), at 60 mmolar concentrations in refluxing toluene with *n*-Bu_3SnH and using AIBN as the radical initiator (Entry 5, Table 1) led to the tricyclic amine (**29**) (68%) as the only observed product of reaction (Scheme 5). This outcome, when compared to that observed for the equivalent process involving substrate (**10**) (Entry 1, Table 1), suggests that the presence of the ethyl group on the double-bond being attacked by the initially formed *N*-radical facilitates the first of the two cyclization steps involved in these types of tandem radical cyclization processes. As before, the spectral data obtained on compound (**29**) were in full accord with the assigned structure. Interestingly, when a 50 mmolar solution of the PTOC-carbamate analogue of *N*-chloroamine (**11**), namely compound (**12**), in acetonitrile was subjected to irradiation with a 250 W tungsten lamp in the presence of equimolar amounts of BF_3•Et_2O or malonic acid (Entries 6 and 7), as specified in work reported by Newcomb and co-workers, then the thioenol ether (**30**) (65–71%) was obtained (Scheme 5) as a single geometric isomer and as the only isolable reaction product. In the ^1H NMR spectrum of this product resonances due to the thiopyridine reside were observed between δ 8.42 and 6.99 while the olefinic proton gave rise to a one-proton triplet (*J* 2.1 Hz) at δ 6.25. The diastereotopic and mutually coupled (*J* 16.2 Hz) methylene protons immediately adjacent to the double bond resonated at δ 3.94 and 3.40. In the 70 eV electron-impact MS spectrum only a weak molecular ion was observed but an accurate MS measurement could still be recorded on this species. The base peak, at *m/z* 190, corresponds to that fragment arising from the loss of the thiopyridine radical from the molecular ion.



Scheme 5. *Reagents and conditions*: (i) *n*-Bu_3SnH (1 mol equiv.), AIBN (20 mol %), C_6H_6, 80°C, 5 h; (ii) malonic acid (3 mol equiv.) or BF_3•Et_2O (3 mol equiv.), acetonitrile, irradiation, 0.5 h, *ca.* 18°C.

Subjection of the *N*-chloroamine (**13**) to reaction with *n*-Bu_3SnH and AIBN in refluxing toluene at 40 mmolar concentrations (Entry 8, Table 1) led to a chromatographically separable mixture of the dechlorinated amine (**26**) (35%) and the reductive cyclization product (**31**) (44%) (Scheme 6). A related experiment conducted in benzene at 10 mmolar concentrations (Entry 9, Table 1) afforded the latter compound as the essentially exclusive product of reaction and in 68% yield. In each instance compound (**31**) was obtained as a single diastereoisomer and the illustrated structure in which both the ethyl and methyl substituents reside on the *exo*-face of the tricyclic framework follows from mechanistic considerations. In particular, at the transition state associated with the second of the two cyclization steps involved, and the one in which the stereochemistry of the ring substituents is determined, we assume that as the favored all-*cis*-fused tricyclic ring system is developing the ethyl and incipient methyl substituents are both in the thermodynamically favored *exo*-orientations. However, rigorous independent proof of the illustrated stereochemistry within product (**31**) has not been obtained.



Scheme 6. *Reagents and conditions*: (i) *n*-Bu_3SnH (1.2 mol equiv.), AIBN (20 mol %), C_6H_6, 80°C, 6 h.

In an effort to establish routes to the CDE-tricyclic core associated with vindoline (**1**), the homopropargyl-containing PTOC-carbamate (**14**) was subject to Newcomb's radical cyclization conditions as successfully deployed in the conversion **12** → **30**. In the event, however, when the relevant reactions were carried out (Entries 10 and 11, Table 1) only decomposition of the substrate was observed. When the *N*-chloro-analogue of substrate (**14**), namely compound (**15**), was subjected to reaction with *n*-Bu_3SnH and AIBN in refluxing toluene at *ca.* 30 mmolar concentrations then only the dechlorinated amine (**27**) was observed (50% yield). This disappointing outcome contrasts dramatically with the behavior of the lower homologue of compound (**15**), *viz.* *N*-chloroamine (**11**), which cyclized in an

efficient manner to give product (**29**) embodying the CDE-tricyclic core associated with alkaloids such as ibophyllidine (**2**). The divergent behaviors of compounds (**11** and **15**) probably arises because the cyclization processes each engages in are reversible with the second one being rather slow (in the forward direction) in the case of the higher homologue.[13m,21] As a consequence, the equilibrium concentration of nitrogen radical derived from compound (**15**) will be much higher than those of the corresponding carbon-centered isomers with the result that only the direct reduction product (**27**) is observed. The situation is essentially reversed in the case of those radical cyclization processes involving compounds (**10**, **11** and **12**). As a result the tricyclic products (**28**, **29** and **30**) become the major products of the reactions of these substrates.

CONCLUSIONS

The successful radical cyclization reactions of compounds (**10**–**13**) clearly indicate that the title processes offer a useful means of obtaining compounds (**28**, **29**, **30** and **31**), respectively, embodying the CDE-tricyclic core associated with alkaloids such as ibophyllidine (**2**). Indeed, the efficiency of such conversions suggests that the tandem radical cyclization reactions involved could provide an effective basis for establishing concise routes to this and related alkaloids, the biological profiles of which remain ill defined. Work directed towards such ends are now underway in these laboratories and will be reported upon in due course.

In contrast to the success associated with studies involving the cyclization of substrates (**10**–**13**), the lack of useful outcomes encountered during analogous studies on their higher homologues (**14** and **15**) highlights the likely inability of tandem radical cyclization reactions of the type defined in Figure 1 to deliver the CDE-tricyclic core associated with alkaloids such as vindoline. The ineffectiveness of this approach is probably the consequence of the reversible nature of the cyclization processes involved and the unfavorable kinetics associated with the relevant radical cyclization and/or chain termination events.

EXPERIMENTAL

General Experimental Procedures. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Gemini 300 NMR spectrometer, operating at 300 MHz (for proton) and 75 MHz (for carbon). Unless otherwise specified, spectra were acquired at 20°C in deuterochloroform ($CDCl_3$) that had been filtered through basic alumina immediately prior to use. Chemical shifts are recorded as δ values in parts per million (ppm). IR spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer and samples were analyzed as thin films on KBr plates. Low resolution MS spectra were recorded on a Micromass–Waters LC-ZMD single quadrupole liquid chromatograph-MS or VG Quattro II triple quadrupole MS instrument using electron impact techniques. High resolution MS spectra were recorded

on an AUTOSPEC spectrometer. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride and THF was distilled, under nitrogen, from sodium benzophenone ketyl. Where necessary, reactions were performed under a nitrogen atmosphere.

Section A: Synthesis of Substrates for Radical Cyclization Studies

(2-Cyclohex-2-enylethyl)prop-2-ynylamine (18).

A magnetically stirred solution of aldehyde (**17**)[12,14] (905 mg, 7.3 mmol) in THF (25 mL) was treated with propargylamine (2.00 g, 36.5 mmol) then activated 4 Å molecular sieves (650 mg). The ensuing mixture was stirred at 18°C for 16 h then filtered through a pad of Celite™ contained in a sintered-glass funnel. The filtrate was concentrated under reduced pressure and the pale-yellow oil so obtained was dissolved in methanol (15 mL) and the resulting and magnetically stirred solution cooled to 0°C then treated, in one portion, with $NaBH_4$ (280 mg, 7.3 mmol). After 0.5 h the reaction mixture was poured into NaOH (100 mL of a 2 M aqueous solution) then extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were then washed with brine (1 × 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the *title amine (**18**)* (1.10 g, 94%) as a clear, colorless oil [Found: $[(M–H\cdot)^+$, 162.1283. $C_{11}H_{17}N$ requires $[(M–H\cdot)^+$, 162.1283]. ^{1}H NMR (300 MHz) δ 5.66–5.55 (complex m, 1H), 5.48 (dm, *J* 9.9 Hz, 1H), 3.34 (d, *J* 2.4 Hz, 2H), 2.66 (t, *J* 7.2 Hz, 2H), 2.15 (t, *J* 2.4 Hz, 1H), 2.07 (m, 1H), 1.88 (m, 2H), 1.78–1.10 (complex m, 7H); ^{13}C NMR (75 MHz) δ 131.4, 126.9, 82.1, 71.1, 46.0, 37.9, 36.1, 32.9, 28.8, 25.1, 21.2; IR (neat) ν_{max} 3297, 3021, 2927, 2847, 1447, 1432, 1327, 1114 cm^{-1}; MS (EI) *m/z* 162 [$(M–H\cdot)^+$, 20%], 161 (10), 108 (50), 93 (40), 82 (100), 68 (95).

N-Chloro-(2-cyclohex-2-enylethyl)prop-2-ynylamine (10).

A magnetically stirred solution of propargylamine (**18**) (1.10 g, 6.75 mmol) in CH_2Cl_2 (40 mL) maintained at 0°C was treated, in one portion, with *N*-chlorosuccinimide (1.07 g, 8.1 mmol). After 1 h the entire reaction mixture was added to the top of a pad of flash chromatographic-grade silica gel contained in a sintered-glass funnel and the pad was then eluted with 3:7 v/v ethyl acetate/hexane. Concentration of the appropriate fractions (R_f 0.35 in 1:9 v/v ethyl acetate/hexane) under reduced pressure then afforded the *title* N*-chloroamine (**10**)* (1.32 g, 100%) as a clear, colorless oil [Found: $(M–H\cdot)^+$, 196.0891. $C_{11}H_{16}{}^{35}ClN$ requires $(M–H\cdot)^+$, 196.0893]. ^{1}H NMR (300 MHz) δ 5.65 (m, 1H), 5.51 (dm, *J* 9.9 Hz, 1H), 3.79 (d, *J* 2.4 Hz, 2H), 3.02 (t, *J* 7.2 Hz, 2H), 2.39 (t, *J* 2.4 Hz, 1H), 2.15 (m, 1H), 1.92 (m, 2H), 1.79–1.38 (complex m, 5H), 1.20 (m, 1H); ^{13}C NMR (75 MHz) δ 131.0, 127.3, 77.4, 74.7, 59.6, 52.3, 34.1, 32.6, 28.8, 25.1, 21.1; IR (neat) ν_{max} 3297, 3014, 2913, 2847, 1645, 1436, 1320, 1255, 1165, 1082 cm^{-1}; MS (EI) *m/z* 198 and 196 [$(M–H\cdot)^+$, both 10%], 162 (27), 160 (17), 120 (70), 68 (100).

3-Ethylcyclohex-2-en-1-one (20).

Ethylmagnesium bromide (100 mL of a 3 M solution in ether, 0.30 mol, ex. Aldrich Chemical Company)

was added dropwise to a magnetically stirred solution of 3-ethoxycyclohex-2-en-1-one (25.0 g, 0.18 mol, ex. Aldrich Chemical Company) in THF (300 mL) maintained at 0°C. After 3 h the by now burnt-orange colored solution was poured into ice-cold HCl (500 mL of a 10% w/v aqueous solution) and the resulting yellow suspension stirred for 16 h at 18°C. The ensuing mixture was then extracted with ether (3 × 900 mL), washed with water (1 × 200 mL), NaOH (2 × 200 mL of a 5 % w/v aqueous solution), water (1 × 200 mL) and brine (1 × 200 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give compound (**20**)[15] (19.7 g, 89%) as a clear, colorless oil, R_f 0.5 (3:7 v/v ethyl acetate/hexane) (Found: $M^{+\bullet}$, 124.0893. Calcd for $C_8H_{12}O$ $M^{+\bullet}$, 124.0888). ^{1}H NMR (300 MHz) δ 5.75 (s, 1H), 2.28–2.09 (complex m, 6H), 1.88 (m, 2H), 0.99 (t, *J* 7.5 Hz, 3H); ^{13}C NMR (75 MHz) δ 199.6 (C), 167.6 (C), 124.2 (CH), 37.1 (CH_2), 30.6 (CH_2), 29.4 (CH_2) 22.4 (CH_2), 10.9 (CH_3); IR (neat) ν_{max} 2969, 2938, 2879, 1670, 1625, 1458, 1429, 1374, 1348, 1283, 1255, 1192, 1137, 887 cm^{-1}; MS (EI) *m/z* 124 ($M^{+\bullet}$, 60%), 105 (15), 96 (100), 91 (50), 81 (47), 79 (44), 77 (42), 65 (31).

3-Ethylcyclohex-2-enyl Acetate (21).

A magnetically stirred solution of enone (**20**) (19.0 g, 153 mmol) in methanol (250 mL) maintained at 0°C was treated, in one portion, with sodium borohydride (6.98 g, 184 mmol). After the initially rapid reaction had subsided, the reaction mixture was allowed to warm to 18°C and after a further 16 h it was treated with water (250 mL) then ether (500 mL). The separated aqueous phase was extracted with ether (3 × 500 mL) and the combined organic phases were then washed with brine (1 × 200 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the expected allylic alcohol (18.0 g, 96%). This was immediately converted into the corresponding acetate. Thus, a magnetically stirred solution of the allylic alcohol (18.0 g, 147 mmol) and pyridine (20 mL) in acetic anhydride (30 mL) maintained at 0°C was treated with DMAP (300 mg). When the initially rapid reaction had subsided, the reaction mixture was allowed to warm to 18°C. After a further 10 h excess acetic anhydride was destroyed by adding methanol (100 mL) to the ice-cooled reaction mixture. After a further 4 h the reaction mixture was partitioned between ether (700 mL) and water (300 mL) and the separated aqueous phase extracted with ether (3 × 400 mL). The combined organic phases where then washed with HCl (2 × 100 mL of a 1 M aqueous solution) and brine (2 × 200 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford acetate (**21**)[16] (20.0 g, 100%) as a clear colorless oil, R_f 0.5 (7:93 v/v ethyl acetate/hexane) (Found: $M^{+\bullet}$, 168.1153. Calcd for $C_{10}H_{16}O_2$ $M^{+\bullet}$, 168.1150). ^{1}H NMR (300 MHz) δ 5.41 (m, 1H), 5.30 (m, 1H), 2.01 (s, 3H), 2.02–1.88 (complex m, 3H), 1.80–1.56 (complex m, 5H), 0.98 (t, *J* 7.5 Hz, 3H); ^{13}C NMR (75 MHz) δ 170.8 (C), 146.2 (C), 118.1 (CH), 68.8 (CH), 30.2 (CH_2), 28.3 (CH_3), 28.2 (CH_2), 21.4 (CH_2), 19.1 (CH_2), 11.8 (CH_3); IR (neat) ν_{max} 2937, 2876, 1732, 1667, 1456, 1370, 1312, 1242, 1163, 1022, 956, 910 cm^{-1}; MS (EI) *m/z* 168 [($M^{+\bullet}$, 2%], 126 (3), 109 (50), 108 (55), 97 (100), 93 (85), 79 (98), 67 (57).

2-(3-Ethylcyclohex-2-enyl)malonic Acid Dimethyl Ester (22).

1,2-Bis(diphenylphosphino)ethane (131 mg, 0.34 mmol) and Pd_2dba_3 (181 mg, 0.17 mmol) were added to a magnetically stirred solution of acetate (**21**) (5.70 g, 29 mmol) in THF (50 mL). After 10 min a solution of sodium dimethyl malonate in THF [prepared by the slow addition of malonic acid dimethyl ester (3.17 g, 49 mmol) to a magnetically stirred suspension of sodium hydride (1.18 g, 49 mmol) in THF (100 mL)] was added dropwise. The resulting solution was heated at reflux for 24 h then cooled to 18°C, diluted with ether (500 mL) and washed with water (1 × 200 mL). The separated aqueous phase was extracted with ether (1 × 200 mL) and the combined ethereal fractions were then washed with brine (1 × 150 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subjection of the ensuing residue to flash chromatography (7:93 v/v ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A (R_f 0.5) afforded the starting acetate (**21**) (1.50 g, 26% recovery) as a clear, colorless oil and identical, in all respects, with an authentic sample.[16]

Concentration of fraction B (R_f 0.2) provided *malonate (**22**)* (5.42 g, 90% at 74% conversion) as a clear colorless oil [Found: $(M+H)^+$, 241.1437. $C_{13}H_{20}O_4$ requires $(M+H)^+$, 241.1440]. ^{1}H NMR (300 MHz) δ 5.16 (s, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 3.21 (d, *J* 9.6 Hz, 1H), 2.83 (br s, 1H), 1.96–1.82 (complex m, 3H), 1.74–1.43 (complex m, 3H), 1.30–1.18 (complex m, 2H), 0.92 (t, *J* 7.5 Hz, 3H); ^{13}C NMR (75 MHz) δ 168.7 (C), 168.6 (C), 142.1 (C), 119.6 (CH), 57.1 (CH), 52.2 (CH_3), 35.5 (CH), 30.6 (CH_2), 28.1 (CH_2), 26.6 (CH_2), 21.2 (CH_2), 12.3 (CH_3) (one signal obscured or overlapping); IR (neat) ν_{max} 2933, 1738, 1435, 1333, 1296, 1245, 1193, 1152, 1022 cm^{-1}; MS (EI) *m/z* 240 [$(M)^{+\bullet}$, 12%], 180 (100), 165 (15), 151 (50), 133 (42), 109 (75), 108 (69), 81 (65), 67 (48).

(3-Ethylcyclohex-2-enyl)acetic Acid Methyl Ester (23).

A magnetically stirred solution of malonate (**22**) (9.60 g, 41.2 mmol) in degassed DMSO (125 mL) was treated, in one portion, with LiI•3H_2O (7.75 g, 41.2 mmol). The ensuing mixture was heated at 180°C for 1.5 h then cooled to 18°C, diluted with water (75 mL) and extracted with ether (3 × 125 mL). The combined organic fractions were then washed with brine (1 × 120 mL before being dried ($MgSO_4$) filtered and concentrated under reduced pressure. Subjection of the resulting dark-brown oil to flash chromatography (5:95 → 7:93 v/v ethyl acetate/hexane gradient elution) afforded, after concentration of the appropriate fractions (R_f 0.5 in 7:93 v/v ethyl acetate/hexane), the *title methyl ester (**23**)* (5.96 g, 80%) as a clear, colorless oil (Found: $M^{+\bullet}$, 182.1304. $C_{11}H_{18}O_2$ requires $M^{+\bullet}$, 182.1307). ^{1}H NMR (300 MHz) δ 5.18 (s, 1H), 3.62 (s, 3H), 2.50 (br s, 1H), 2.20 (m, 2H), 2.00–1.08 (complex m, 8H), 0.93 (t, *J* 7.5 Hz, 3H); ^{13}C NMR (75 MHz) δ 173.0 (C), 140.4 (C), 122.3 (CH), 51.2 (CH_3), 40.9 (CH_2), 32.3 (CH), 30.4 (CH_2), 28.8 (CH_2), 28.2 (CH_2), 21.4 (CH_2), 12.3 (CH_3); IR (neat) ν_{max} 2930, 2876, 1740, 1435, 1361, 1279, 1245, 1163, 1015, 884, 838 cm^{-1}; MS (EI) *m/z* 182 ($M^{+\bullet}$, 40%), 167 (55), 153 (22), 122 (42), 109 (100), 108 (90), 93 (60), 79 (72), 67 (52).

(3-Ethylcyclohex-2-enyl)acetaldehyde (24).

A magnetically stirred solution of ester (**23**) (1.7 g, 9.39 mmol) in CH_2Cl_2 (42 mL) was cooled to –78°C then DIBAL-H (10.33 mL of a 1 M solution in hexanes, 10.33 mmol) was added dropwise over 25 min. After a further 1 h the reaction mixture was quenched by the addition of methanol (3 mL) then potassium sodium tartrate (50 mL of a saturated aqueous solution). The ensuing mixture was extracted with ether (3 × 100 mL) and the combined organic fractions then washed with brine (1 × 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide an opaque and light-yellow oil. Subjection of this material to flash chromatography (7:93 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions (R_f 0.5), the *aldehyde (**24**)* (1.09 g, 75%) as an opaque and light-yellow oil (Found: $M^{+\bullet}$, 152.1202. $C_{10}H_{16}O$ requires $M^{+\bullet}$, 152.1201). ^{1}H NMR (300 MHz) δ 9.76 (s, 1H), 5.21 (s, 1H), 2.66 (br s, 1H), 2.38 (m, 2H), 1.98–1.45 (complex m, 6H), 1.28–1.12 (complex m, 2H), 0.96 (t, *J* 7.2 Hz, 3H); ^{13}C NMR (75 MHz) δ 202.6 (CH), 140.9 (C), 122.0 (CH), 50.4 (CH_2), 30.5 (CH_2), 30.3 (CH), 29.1 (CH_2), 28.1 (CH_2), 21.5 (CH_2), 12.3 (CH_3); IR (neat) ν_{max} 2962, 2928, 2714, 1725, 1456, 1263, 1117, 1056, 1025, 920, 840 cm^{-1}; MS (EI) *m/z* 152 ($M^{+\bullet}$, 25%), 123 (75), 109 (45), 108 (55), 107 (45), 95 (37), 88 (60), 79 (58), 70 (82), 61 (100).

[2-(3-Ethylcyclohex-2-enyl)ethyl]prop-2-ynylamine (25).

A solution of aldehyde (**24**) (1.09 g, 7.21 mmol) in THF (30 mL) containing propargylamine (1.98 g, 36.1 mmol) and 4 Å molecular sieves (1.5 g) was stirred at 18°C for 16 h then filtered through a pad of dry Celite™ and the filtrate concentrated under reduced pressure to a light-yellow oil presumed to contain the expected imine. A solution of this material in methanol (20 mL) was cooled to 0°C then treated with $NaBH_4$ (301 mg, 7.93 mmol). After 0.33 h the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 60 mL). The combined organic fractions were washed with brine (1 × 50 mL) before being dried ($MgSO_4$) filtered and concentrated under reduced pressure to give the *title amine (**25**)* (1.03 g, 75%) as an opaque and light-yellow oil (Found: $M^{+\bullet}$, 191.1676. $C_{13}H_{21}N$ requires $M^{+\bullet}$, 191.1674). ^{1}H NMR (300 MHz) δ 5.24 (s, 1H), 3.42 (d, *J* 2.4 Hz, 2H), 2.73 (t, *J* 7.5 Hz, 2H), 2.20 (t, *J* 2.4 Hz, 1H), 2.10 (br s, 1H), 1.98–1.82 (complex m, 4H), 1.72 (m, 2H), 1.60–1.38 (complex m, 3H), 1.15 (m, 1H), 0.96 (t, *J* 7.5 Hz, 3H); ^{13}C NMR (75 MHz) δ 138.8 (C), 123.4 (CH), 81.9 (C), 70.8 (CH), 45.9 (CH_2), 37.7 (CH_2), 36.2 (CH_2), 32.8 (CH), 30.2 (CH_2), 28.8 (CH_2), 28.1 (CH_2), 21.5 (CH_2), 12.0 (CH_3); IR (neat) ν_{max} 3308, 2925, 2854, 1678, 1612, 1455, 1371, 1327, 1118, 906, 840, 646 cm^{-1}; MS (EI) *m/z* 191 ($M^{+\bullet}$, 10%), 190 (6), 176 (10), 163 (40), 162 (23), 136 (100), 121 (32), 107 (75), 93 (20), 79 (33), 68 (81). This material was sufficiently pure for use in subsequent transformations.

***N*-Chloro-[2-(3-ethylcyclohex-2-enyl)ethyl]prop-2-ynylamine (11).**

A magnetically stirred solution of amine (**25**) (100 mg, 0.52 mmol) in CH_2Cl_2 (4 mL) maintained at –30°C was treated, in one portion, with *N*-chlorosuccinimide (77 mg, 0.58 mmol). The ensuing mixture

was warmed to 18°C over 1 h then the entire reaction mixture was added to the top of a pad of flash chromatographic-grade silica containing in a sintered-glass funnel and the pad eluted with 3:7 v/v ethyl acetate/hexane. Concentration of the relevant fractions of the eluent afforded the rather unstable N-*chloroamine (**11**)* (118 mg, 100 %) as a pale-yellow oil, R_f 0.35 (1:9 v/v ethyl acetate/hexane). ^{1}H NMR (300 MHz) δ 5.23 (s, 1H), 3.82 (d, *J* 1.8 Hz, 2H), 3.05 (t, *J* 7.2 Hz, 2H), 2.41 (t, *J* 1.8 Hz, 1H), 2.15 (br s, 1H), 2.00–1.40 (complex m, 9H), 1.15 (m, 1H), 0.97 (t, *J* 7.5 Hz, 3H); ^{13}C NMR (75 MHz) δ 140.2, 123.7, 77.3, 75.0, 60.3, 52.8, 35.0, 33.3, 30.9, 29.4, 28.8, 22.2, 12.8.

PTOC-Derivative (12) of [2-(3-Ethylcyclohex-2-enyl)ethyl]prop-2-ynylamine.

A solution of amine (**25**) (100 mg, 0.52 mmol) and triethylamine (58 mg, 0.57 mmol) in benzene (2 mL) was added dropwise to a magnetically stirred suspension of 1-oxa-2-oxo-3-thiaindolizinium chloride[18] (120 mg, 0.63 mmol) in benzene (2 mL). The ensuing mixture was stirred at 18°C for 2 h then filtered through a pad of flash chromatographic-grade silica gel contained in a sintered-glass funnel. The pad was then eluted with benzene and the yellow-colored fractions concentrated under reduced pressure to yield the *title compound (**12**)* (100 mg, 60%) as a clear, yellow oil. This highly unstable material was used, without further purification, in the relevant radical cyclization reaction detailed in Section B.

***N*-Allyl-[2-(3-ethylcyclohex-2-enyl)ethyl]amine (26).**

A magnetically stirred solution of aldehyde (**24**) (190 mg, 1.25 mmol) in THF (5 mL) was treated with allylamine (350 mg, 6.25 mmol) followed by activated 4 Å molecular sieves (250 mg). The resulting mixture was stirred at 18°C for 4 h then filtered through a pad of dry Celite™ contained in a sintered-glass funnel. The retained solids were washed with THF (10 mL) and the combined filtrates then concentrated under reduced pressure to give a light-yellow oil. A magnetically stirred solution of this material in methanol (3 mL) was cooled to 0°C and treated, in one portion, with $NaBH_4$ (47.5 mg, 1.25 mmol). After 0.3 h the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organic fractions were washed with brine (1 × 30 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the *title compound (**26**)* (181 mg, 75%) as an opaque oil (Found: $M^{+\bullet}$, 193.1830. $C_{13}H_{23}N$ requires $M^{+\bullet}$, 193.1831). ^{1}H NMR (300 MHz) δ 5.86 (m, 1H), 5.21 (s, 1H), 5.12 (dm, *J* 17.1 Hz, 1H), 5.03 (dm, *J* 10.2 Hz, 1H), 3.21 (d, *J* 6.0 Hz, 2H), 2.62 (t, *J* 7.8 Hz, 2H), 2.08 (br s, 1H), 1.94–1.82 (complex m, 4H), 1.68 (m, 2H), 1.51–1.34 (complex m, 4H), 1.10 (m, 1H), 0.93 (t, *J* 7.2 Hz, 3H); ^{13}C NMR (75 MHz) δ 139.3 (C), 136.7 (CH), 123.8 (CH), 115.5 (CH_2), 52.5 (CH_2), 47.1 (CH_2), 36.9 (CH_2), 33.3 (CH), 30.5 (CH_2), 29.1 (CH_2), 28.4 (CH_2), 21.8 (CH_2), 12.4 (CH_3); IR (neat) ν_{max} 2962, 2926, 2856, 1643, 1455, 1371, 1262, 1117, 993, 916, 839, 743 cm^{-1}; MS (EI) *m*/*z* 193 ($M^{+\bullet}$, 21%), 178 (5), 164 (16), 150 (10), 136 (77), 121 (25), 107 (65), 79 (31), 70 (100).

***N*-Allyl-*N*-chloro-[2-(3-ethylcyclohex-2-enyl)ethyl]amine (13).**

A magnetically stirred solution of amine (**26**) (100 mg, 0.52 mmol) in CH_2Cl_2 (4 mL) was cooled to

–30°C then treated with *N*-chlorosuccinimide (83 mg, 0.62 mmol) and the resulting mixture allowed to warm to 18°C over 2 h then loaded onto the top of a pad of flash chromatographic-grade silica gel contained in a sintered-glass funnel. The pad was eluted with 1:1 v/v ethyl acetate/hexane and concentration of the appropriate fractions (R_f 0.8 in 1:4 v/v ethyl acetate/hexane) under reduced pressure then afforded the *title compound (**13**)* (114 mg, 97%) as an unstable and pale-yellow oil. ^{1}H NMR (300 MHz) δ 5.96 (m, 1H), 5.32–5.22 (complex m, 3H), 3.61 (dt, *J* 6.6 and 1.5 Hz, 2H), 2.99 (t, *J* 7.5 Hz, 2H), 2.15 (br s, 1H), 2.00–1.86 (complex m, 3H), 1.79–1.44 (complex m, 6H), 1.15 (m, 1H), 0.99 (t, *J* 7.5 Hz, 3H); ^{13}C NMR (75 MHz) δ 139.7 (C), 133.5 (CH), 123.5 (CH), 119.0 (CH_2), 66.7 (CH_2), 60.9 (CH_2), 34.5 (CH_2), 33.0 (CH), 30.6 (CH_2), 29.1 (CH_2), 28.4 (CH_2), 21.8 (CH_2), 12.4 (CH_3); IR (neat) ν_{max} 2927, 1374, 1295, 1184, 922, 817, 647 cm^{-1}. Satisfactory MS spectral data could not be obtained on this material.

But-3-ynyl-[2-(3-ethylcyclohex-2-enyl)ethyl]amine (27).

A solution of triphenylphosphine (176 mg, 0.6 mmol) in THF (4 mL) was added to a magnetically stirred solution of homopropargyl azide[22] (57 mg, 0.6 mmol) in THF (4 mL). After 2 h aldehyde (**24**) (91 mg, 0.6 mmol) was added to the reaction mixture and the ensuing solution heated at reflux for 16 h. The reaction mixture was then cooled to 0°C and $NaCNBH_3$ (57 mg, 0.9 mmol) added. After 0.5 h the reaction mixture was poured into NaOH (50 mL of a 2 M aqueous solution) and extracted with ether (3 × 75 mL). The organic phases were combined, washed with brine (1 × 100 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. This material was subject to flash chromatography (74:25:1 v/v/v ethyl acetate/hexane/triethylamine elution) and thereby yielding, after evaporation of appropriate fractions (R_f 0.1 in 3:1 v/v ethyl acetate/hexane), *homopropargylamine (**27**)* (40 mg, 33%) as a clear, colorless oil (Found: $M^{+\bullet}$, 205.1830. $C_{14}H_{23}N$ requires $M^{+\bullet}$, 205.1831). ^{1}H NMR (300 MHz) δ 5.25 (s, 1H), 2.79 (t, *J* 6.6 Hz, 2H*)*, 2.68 (t, *J* 7.5 Hz, 2H), 2.40 (m, 2H), 2.11 (m, 1H), 2.01–1.84 (complex m, 4H), 1.73 (m, 2H), 1.58–1.40 (complex m, 4H), 1.25–1.09 (complex m, 2H), 0.97 (t, *J* 7.5 Hz, 3H); ^{13}C NMR (75 MHz) δ 139.5 (C), 123.8 (CH), 82.4 (C), 69.5 (CH), 48.0 (CH_2), 47.1 (CH_2), 36.8 (CH_2), 33.4 (CH), 30.6 (CH_2), 29.2 (CH_2), 28.5 (CH_2), 21.9 (CH_2), 19.5 (CH_2), 12.5 (CH_3); IR (neat) ν_{max} 2956, 2920, 2847, 1454, 1371, 1122, 1078, 1053, 1035 630 cm^{-1}; MS (EI) *m/z* 205 ($M^{+\bullet}$, 10%), 166 (22), 136 (100), 121 (12), 107 (63), 82 (25), 79 (28), 67 (18).

PTOC-Derivative (14) of But-3-ynyl-[2-(3-ethylcyclohex-2-enyl)ethyl]amine.

A solution of amine (**27**) (10 mg, 0.05 mmol) and triethylamine (5.0 mg, 0.05 mmol) in benzene (0.5 mL) was added dropwise to a magnetically stirred suspension of 1-oxa-2-oxo-3-thiaindolizinium chloride[18] (11 mg, 0.06 mmol) in benzene (0.5 mL). The ensuing mixture was stirred at 18°C for 2 h then filtered through a pad of flash chromatographic-grade silica gel contained in a sintered-glass funnel. The pad was then eluted with benzene. Concentration of the ensuing yellow-colored fractions under reduced pressure afforded the *title compound (**14**)* (17 mg, quant.) as a clear, yellow oil. This instability of this material

precluded the acquisition of spectroscopic data and it was used, without purification, in the radical cyclization reaction detailed in Section B.

***N*-Chloro-*N*-[2-(3-ethylcyclohex-2-enyl)ethyl]but-3-ynylamine (15).**

A magnetically stirred solution of amine (**27**) (40 mg, 0.20 mmol) in CH_2Cl_2 (4 mL) was cooled to –30°C then treated with *N*-chlorosuccinimide (29 mg, 0.22 mmol). The resulting mixture was allowed to warm to 18°C over 1 h then adsorbed onto a pad of flash chromatographic-grade silica contained in a sintered-glass funnel. The pad was then eluted with 3:7 v/v ethyl acetate/hexane. Concentration of the relevant fractions (R_f 0.5) then afforded the unstable N-*chloroamine (**15**)* (42 mg, 92%) as a pale-yellow oil. ^{1}H NMR (300 MHz) δ 5.24 (s, 1H), 3.11 (t, *J* 7.5 Hz, 2H), 3.03 (t, *J* 7.5 Hz, 2H), 2.59 (m, 2H), 2.11 (br s, 1H), 2.01–1.85 (complex m, 4H), 1.80–1.43 (complex m, 6H), 1.15 (complex m, 1H), 0.97 (t, *J* 7.5 Hz, 3H).

Section B: Radical Cyclization Studies

1-Methylenedecahydropyrolo[3,2,1-*hi*]indole (28).

A magnetically stirred solution of *N*-chloroamine (**10**) (31 mg, 0.15 mmol) and *n*-Bu_3SnH (54 mg, 0.15 mmol) in benzene (15.7 mL) was treated with AIBN (3 mg, 5 mol%) and the ensuing mixture heated at reflux for 1.5 h then cooled to 18°C and extracted with HCl (1 × 50 mL of a 3 M aqueous solution). The combined aqueous phases were basified with NaOH (*ca.* 100 mL of a 2 M solution) then extracted with ethyl acetate (3 × 50 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (50:2:2:1 v/v/v/v ethyl acetate/methanol/triethylamine/water) and concentration of the appropriate fractions (R_f 0.2) afforded the *title amine (**28**)* (19 mg, 74%) as a pale-yellow oil (Found: $M^{+\bullet}$, 163.1354. $C_{11}H_{17}N$ requires $M^{+\bullet}$, 163.1361). ^{1}H NMR (300 MHz) δ 4.81 (s, 1H), 4.78 (s, 1H), 3.56 (m, 1H), 3.21 (dq, *J* 13.3 and 1.5 Hz, 1H), 3.02 (m, 1H), 2.57 (m, 1H), 2.15–1.50 (complex m, 10H); ^{13}C NMR (75 MHz) δ 155.6 (C), 103.5 (CH_2), 65.5 (CH), 58.7 (CH_2), 54.3 (CH_2), 41.2 (CH), 35.7 (CH), 34.4 (CH_2), 28.5 (CH_2), 28.4 (CH_2), 20.3 (CH_2); IR (neat) ν_{max} 2929, 2855, 1665, 1614, 1447, 1288, 1144, 1111, 883 cm^{-1}; MS (EI) *m/z* 163 ($M^{+\bullet}$, 45%), 162 (100), 120 (70), 82 (30), 68 (100).

8a-Ethyl-1-methylenedecahydropyrolo[3,2,1-*hi*]indole (29).

A magnetically stirred solution of amine (**11**) (70 mg, 0.31 mmol) and *n*-Bu_3SnH (90 mg, 0.31 mmol) in toluene (5 mL) was treated with AIBN (10 mg, 20 mol %) then heated at reflux for 5 h. The cooled mixture was extracted with HCl (1 × 100 mL of a 2 M aqueous solution) and the separated aqueous phase basified using NaOH (*ca.* 110 mL of a 2 M aqueous solution) then extracted with ether (3 × 100 mL). The combined organic extracts were washed with brine (1 × 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Subjection of this material to flash chromatography (basic alumina, benzene → 1:3:6 v/v/v methanol/ethyl acetate/benzene gradient elution)

afforded, after concentration of the relevant fractions (R_f = 0.1 in 1:4 v/v methanol/ethyl acetate, silica), *compound (**29**)* (40 mg, 68%) as a pale-yellow and opaque oil [Found: $(M+H)^+$, 192.1748. $C_{13}H_{21}N$ requires $(M+H)^+$, 192.1752]. ^{1}H NMR (300 MHz) δ 4.85 (t, *J* 1.8 Hz, 1H), 4.63 (t, *J* 1.8 Hz, 1H), 3.82 (dt, *J* 14.4 and 1.8 Hz, 1H), 3.27 (d, *J* 7.2 Hz, 1H), 3.24 (dt, *J* 14.4 and 1.8 Hz, 1H), 3.01 (dt, *J* 10.5 and 6.3 Hz, 1H), 2.66 (dt, *J* 10.5, and 6.0 Hz, 1H), 2.07 (m, 1H), 1.82 (m, 1H), 1.66–1.30 (complex m, 9H), 0.85 (t, *J* 7.2 Hz, 3H); ^{13}C NMR (75 MHz) δ 155.7 (C), 102.5 (CH_2), 72.0 (CH), 61.5 (CH_2), 55.2 (CH_2), 46.2 (C), 36.8 (CH), 33.9 (CH_2), 33.0 (CH_2), 32.0 (CH_2), 26.6 (CH_2), 18.5 (CH_2), 8.8 (CH_3); MS (EI) *m*/*z* 192 [$(M+H)^+$, 5%], 191 ($M^{+\bullet}$, 22), 190 (100), 162 (28), 120 (45), 68 (60).

8a-Ethyl-1-(pyridin-2-ylsulfanylmethylene)decahydropyrrolo[3,2,1-*hi*]indole (30).

A magnetically stirred solution of compound (**12**) (100 mg, 0.30 mmol) in acetonitrile (6 mL) containing malonic acid (93 mg, 0.90 mmol) or BF_3•Et_2O (126 mg, 0.90 mmol) was irradiated with a 250 W tungsten lamp for 0.5 h then cooled and partitioned between ether (100 mL) and HCl (150 mL of a 3 M aqueous solution). The aqueous phase was then basified with NaOH (*ca*. 200 mL of a 2 M aqueous solution), extracted with ethyl acetate (3 × 100 mL) and the combined organic phases then washed with brine (1 × 10 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the *title compound (**30**)* [118 mg, 65% (when malonic acid was used) or 128 mg, 71% (when BF_3•Et_2O was used)] as a pale-orange oil (Found: $M^{+\bullet}$, 300.1660. $C_{18}H_{24}N_2S$ requires $M^{+\bullet}$, 300.1660). ^{1}H NMR (300 MHz) δ 8.42 (dm, *J* 4.8 Hz, 1H), 7.50 (td, *J* 7.5 and 2.1 Hz, 1H), 7.13 (dm, *J* 7.5 Hz, 1H), 6.99 (m, 1H), 6.25 (t, *J* 2.1 Hz, 1H), 3.94 (dd, *J* 16.2 and 2.1 Hz, 1H), 3.40 (dd, *J* 16.2 and 2.1 Hz, 1H), 3.31 (d, *J* 7.5 Hz, 1H), 3.02 (dt, *J* 10.8 and 6.6 Hz, 1H), 2.72 (dt, *J* 10.8 and 6.3 Hz, 1H), 2.08 (m, 1H), 1.78 (m, 1H), 1.66–1.38 (complex m, 9H), 0.90 (t, *J* 7.5 Hz, 3H); ^{13}C NMR (75 MHz) δ 158.6 (C), 151.8 (C), 149.5 (CH), 136.2 (CH), 121.2 (CH), 119.7 (CH), 106.4 (CH), 72.7 (CH_2), 60.6 (CH_2), 55.6 (CH), 48.4 (C), 36.8 (CH), 35.3 (CH_2), 32.4 (CH_2), 31.0 (CH_2), 26.0 (CH_2), 18.3 (CH_2), 8.9 (CH_3); MS (EI) *m*/*z* 300 ($M^{+\bullet}$, 2%), 299 (1), 267 (1), 220 (7), 191 (32), 190 (100), 160 (12).

8a-Ethyl-1-methyldecahydropyrrolo[3,2,1-*hi*]indole (31).

A magnetically stirred solution of amine (**13**) (210 mg, 0.93 mmol) and *n*-Bu_3SnH (323 mg, 1.12 mmol) in benzene (100 mL) was treated with AIBN (30 mg, 20 mol%) and the ensuing mixture heated at reflux for 6 h then cooled and extracted with HCl (200 mL of a 3 M solution). The combined aqueous phases were basified with NaOH (*ca*. 300 mL of a 2 M aqueous solution) then extracted with ethyl acetate (3 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (basic alumina, benzene → 3:7 v/v ethyl acetate/benzene → 5:30:65 v/v/v methanol/ethyl acetate/benzene gradient elution) afforded, after concentration of the appropriate fractions (R_f = 0.1 in 1:4 v/v methanol/ethyl acetate, silica), the *title amine (**31**)* (130 mg, 62%) as a clear, colorless oil (Found: $M^{+\bullet}$, 193.1835.

$C_{13}H_{23}N$ requires $M^{+\bullet}$, 193.1831). ^{1}H NMR (300 MHz) δ 3.29 (d, *J* 6.6 Hz, 1H), 3.12 (m, 1H), 2.90 (dd, *J* 9.6 and 2.4 Hz, 1H), 2.81 (dd, *J* 9.6 and 5.4 Hz, 1H), 2.56 (m, 1H), 2.16–1.95 (complex m, 3H), 1.76–1.62 (complex m, 3H), 1.52–1.11 (complex m, 6H), 1.03 (d, *J* 7.2 Hz, 3H), 0.84 (t, *J* 7.5 Hz, 3H); ^{13}C NMR (75 MHz) δ 70.7, 61.1, 53.0, 44.8, 43.7, 35.5, 34.6, 30.5, 28.9, 25.2, 19.2, 14.9, 9.0; IR (neat) ν_{max} 2928, 1452, 1379, 1261, 1151, 799 cm^{-1}; MS (EI) *m/z* 193 ($M^{+\bullet}$, 32%), 192 (100), 164 (12), 136 (10), 124 (12), 122 (15), 96 (12), 82 (31), 70 (25), 55 (15), 41 (24).

Attempted Cyclization of Compound 14.

A magnetically stirred solution of compound (**14**) (17 mg, 0.05 mmol) in acetonitrile (2 mL) containing malonic acid (15 mg, 0.14 mmol) or BF_3•Et_2O (21 mg, 0.14 mmol) was irradiated with a 250 W tungsten lamp for 0.5 h then cooled and partitioned between ether (20 mL) and HCl (20 mL of a 3 M aqueous solution). The separated aqueous phase was extracted with ethyl acetate (2 × 20 mL) and the combined organic phases then washed with brine (1 × 5 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil (10 mg). ^{1}H NMR spectroscopic analysis of this material suggested that extensive decomposition of the starting material had occurred.

Attempted Cyclization of Compound 15.

A magnetically stirred solution of *N*-chloroamine (**15**) (27 mg, 0.11 mmol) and *n*-Bu_3SnH (33 mg, 0.11 mmol) in toluene (4 mL) was treated with AIBN (3 mg, 20 mol%) and the ensuing mixture heated at reflux for 1 h then cooled to 18°C and extracted with HCl (20 mL of a 3 M aqueous solution). The combined aqueous phases were basified with NaOH (*ca*. 30 mL of a 2 M aqueous solution) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. Analysis of this oil by ^{1}H NMR spectroscopy indicated that only reductive dechlorination of compound (**15**) had occurred and thus producing *amine (**27**)* (*ca*. 10 mg, *ca*. 50%).

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