JOC Articles

Stereoselective Formation of Fused Tricyclic Amines from Acyclic Aldehydes by a Cascade Process Involving Condensation, Cyclization, and Dipolar Cycloaddition

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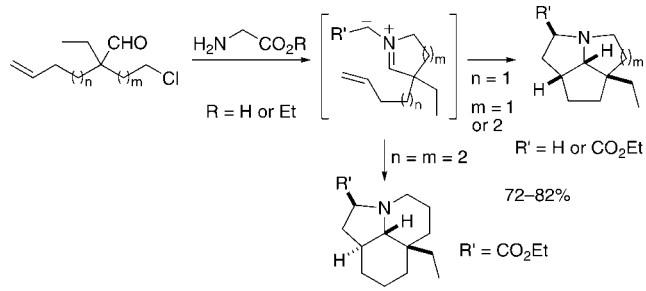

The preparation of tricyclic amines from acyclic precursors is described using a cascade of tandem reactions involving condensation of an aldehyde with a primary amine, cyclization (with displacement of a halide), and then in situ deprotonation or decarboxylation to give an azomethine ylide or nitrone followed by intramolecular dipolar cycloaddition. The methodology is straightforward, and the aldehyde precursors are prepared easily and quickly in high yield using nitrile alkylations followed by DIBAL-H reduction. The relative ease of reaction of various substrates with different tether lengths between the aldehyde and the halide or dipolarophile has been studied. Several primary amines including simple amino acids such as glycine, alanine, and phenylalanine and derivatives such as glycine ethyl ester and also hydroxylamine have been investigated. High yields are obtained in the formation of different tricyclic ring sizes; the dipolar cycloaddition necessarily creates a five-membered ring, and we have investigated the formation of five- and six-membered rings for the other two new ring sizes. In all cases, yields are high (except when using glycine when the tether to the terminal alkene dipolarophile leads to a six-membered ring), and most efficient is the formation of the tricyclic product in which all five-membered rings are formed. Examples with an alkyne as the dipolarophile were also successful. In all the reactions studied, the products are formed with complete regioselectivity and remarkably with complete stereoselectivity. The key step involves the formation of three new rings and potentially up to four new stereocenters in a single transformation. The power of the chemistry was demonstrated by the synthesis of the core ring systems of the alkaloids (±)-scandine and (±)-myrioneurinol and the total syntheses of the alkaloids (±)-aspidospermine, (±)-quebrachamine, and (±)-aspidospermidine.

Introduction

Intramolecular cycloaddition reactions provide a means to form at least two chemical bonds and new ring systems in a highly efficient manner. In this regard, we have been exploiting the dipolar cycloaddition of azomethine ylides in an intramo-

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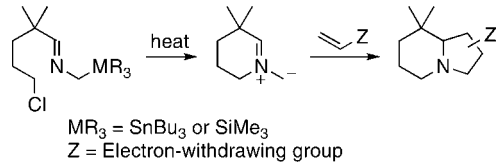
lecular reaction to give bicyclic amine products.[1,2] Such intramolecular cycloadditions typically occur with very high levels of regio- and stereocontrol and allow the formation of two new rings. The ability to form three rings in one transformation is less common but provides an even more efficient and rapid access to polycyclic compounds with significant structural and stereochemical complexity. The design of ever more efficient chemistry for molecular construction is an important current aim in synthesis; hence, the ability to form three rings in a controlled way through multicomponent or cascade processes is likely to find widespread interest and use.[3] Some excellent chemistry in this area involves the formation of cyclic carbonyl ylides and their in situ cycloaddition reactions,[4] the tandem [4 + 2]/[3 + 2] cycloaddition cascade of nitroalkenes or of oxadiazoles,[5] and the cyclization to give a nitrone that undergoes cycloaddition.[6] In this paper, we describe the formation of cyclic azomethine and nitrone ylides and their intramolecular cycloaddition to give tricyclic amines in one pot from acyclic precursors.[7] The preparation of an azomethine ylide by a cyclization process provides one of the three new rings. Cyclization processes to give azomethine ylides are rare; the vast majority of methods for the formation of cyclic azomethine ylides use a pre-existing cyclic amine or imine. However, one method has been described by Pearson and coworkers and employs a simple cyclization of an imine derived from an aldehyde bearing a tethered alkyl halide (Scheme 1).[8] This approach makes use of aminomethylstannanes or aminomethylsilanes to allow formation of the required azomethine ylide by destannylation or desilylation. Some drawbacks of this methodology are the need to prepare aminomethyl(tributyl)stannane [or aminomethyl(trimethyl)silane], their associated toxicity issues, and the requirement for a methylene group as part of the ylide.

SCHEME 1. Formation of Cyclic Azomethine Ylides[8]



In this paper, we describe a related cyclization that makes use of simple amino acids (or esters) for the formation of cyclic azomethine ylides (and the use of hydroxylamine for the formation of nitrones). Addition of secondary amino acids [R′NHCH(R)CO_2H] to aldehydes is known to allow azomethine ylide formation by a process involving condensation to the iminium ion, cyclization to give an oxazolidinone, and

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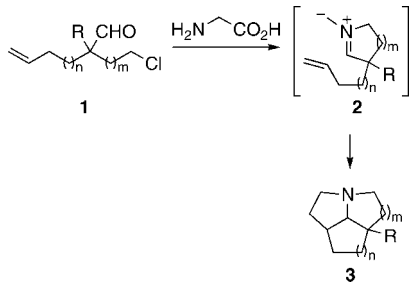
SCHEME 2. Strategy for Combined Cyclization−Cycloaddition



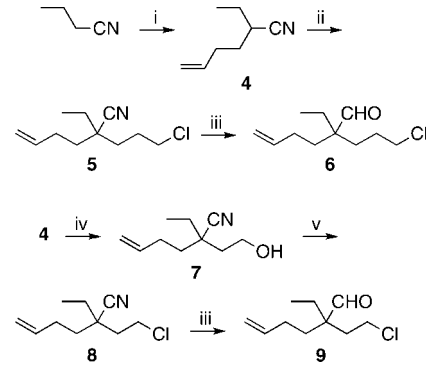
decarboxylation.[9,10] With a tethered alkyl halide as part of the aldehyde substrate, it should be possible to use the more readily available primary amino acids $H_2NCH(R)CO_2H$ as the amine component. Condensation would give an imine and cyclization would then give the required iminium ion and hence azomethine ylide after decarboxylation. Combining this process with an intramolecular cycloaddition reaction should allow three new rings to be formed in one step. By varying the chain lengths between the dipolarophile and the aldehyde and between the alkyl halide and the aldehyde, we have been able to compare the efficiency and stereoselectivity of this cyclization−cycloaddition cascade for the preparation of a range of different ring sizes in the tricyclic amine products.

Results and Discussion

A simple method to prepare aldehydes bearing an alkyl halide and an alkene dipolarophile was required to test the desired chemistry. We chose the aldehydes **1**, which should lead, after condensation with a primary amine (to give an imine), cyclization onto the alkyl halide (to give an iminium ion), and decarboxylation, to the azomethine ylides **2** (Scheme 2). Intramolecular dipolar cycloaddition of the azomethine ylides **2** should then give rise to the fused tricyclic amine products **3**. We anticipated that terminal unactivated alkenes would be suitable dipolarophiles due to the intramolecular nature of the reaction.[1]

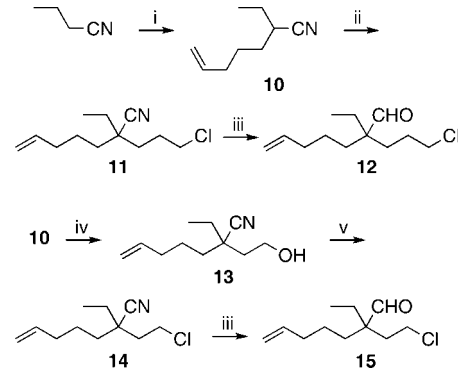
To avoid any potential complication with enolization or enamine formation, we selected substrate **1**, R = Et. This required a method to prepare an aldehyde with an α-quaternary center. We found that an excellent method to achieve this was the alkylation of the anion derived from butanenitrile. The small size and high polar-inductive effect of the nitrile group contribute to its ability to effect successful deprotonation and alkylation to give quaternary centers.[11] Hence, treatment of butanenitrile with LDA followed by alkylation with 4-bromo-1-butene gave the product **4** (Scheme 3). Deprotonation of nitrile **4** with LDA followed by alkylation with 1-bromo-3-chloropropane gave the nitrile **5** in high yield. Reduction of the nitrile **5** with DIBAL-H (with acidic workup to hydrolyze the imine) gave the aldehyde **6**. To investigate the effect of decreasing the tether length between the aldehyde and alkyl halide, we attempted the alkylation of the anion derived from the nitrile **4** with 1-bromo-2-chloroethane. However, this alkylation gave only a low yield of an inseparable mixture of the desired product

SCHEME 3. Preparation of the Aldehydes 6 and 9[a]



[a] Key: (i) LDA (0.5 equiv), THF, −78 °C, 1 h, then 4-bromo-1-butene (0.25 equiv), 80%; (ii) LDA (2 equiv), THF, −78 °C, 1 h, then 1-bromo-3-chloropropane, 95%; (iii) DIBAL-H (1.2 equiv), CH_2Cl_2, −78 °C, then $HCl_{(aq)}$, 87% for **6**, 85% for **9**; (iv) LDA (0.5 equiv), THF, −78 °C, 1 h, then 2-bromoethyl trimethylsilyl ether (0.25 equiv), then $HCl_{(aq)}$, 78%; (v) NCS, PPh_3, THF, rt, 4 h, 95%.

SCHEME 4. Preparation of the Aldehydes 12 and 15[a]



[a] Key: (i) LDA (0.5 equiv), THF, −78 °C, 1 h, then 5-bromo-1-pentene (0.25 equiv), 99%; (ii) LDA (2 equiv), THF, −78 °C, 1 h, then 1-bromo-3-chloropropane, 96%; (iii) DIBAL-H (1.2 equiv), CH_2Cl_2, −78 °C, then $HCl_{(aq)}$, 89% for **12**, 87% for **15**; (iv) LDA (0.5 equiv), THF, −78 °C, 1 h, then 2-bromoethyl trimethylsilyl ether (0.25 equiv), then $HCl_{(aq)}$, 96%; (v) NCS, PPh_3, THF, rt, 4 h, 86%.

(**8**) and the starting nitrile **4**. To circumvent this problem, alkylation was achieved using 2-bromoethyl trimethylsilyl ether (with HCl workup) to give the alcohol **7**. Conversion of the alcohol to the chloride **8** was best carried out using *N*-chlorosuccinimide and triphenylphosphine. Finally, reduction with DIBAL-H gave the aldehyde **9**. Hence, this methodology allowed ready access to the (racemic) substrates **6** and **9** (akin to **1**, R = Et, $n = 1$, $m = 2$ or 1).

In the same way, the homologous aldehyde **12** was prepared from butanenitrile by alkylation with 5-bromo-1-pentene (to give **10**) and then with 1-bromo-4-chlorobutane (to give **11**), followed by DIBAL-H reduction. The aldehyde **15** was prepared from the nitrile **10** by alkylation with 2-bromoethyl trimethylsilyl ether (to give **13**), followed by chlorination (to give **14**) and DIBAL-H reduction (Scheme 4).

We were then ready to test the key cyclization−cycloaddition cascade chemistry with the four substrates **6**, **9**, **12**, and **15**. Heating the aldehyde **6** with glycine in toluene gave the desired tricyclic product **16** in high yield (Scheme 5). Only a single diastereoisomer was formed, and the relative stereochemistry was confirmed by ^{1}H NMR spectroscopy. With alanine and phenylalanine, the products **17** and **18** were obtained respectively as single (racemic) stereoisomers (relative stereochemistry confirmed by ^{1}H NMR spectroscopy). Using glycine ethyl ester,

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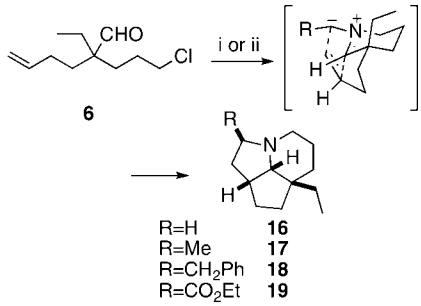
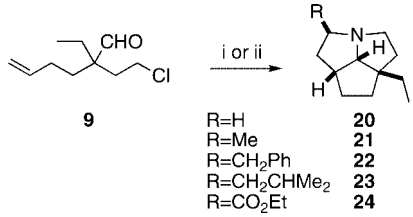
SCHEME 5. Cyclization−Cycloaddition of the Aldehyde 6[a]



[a] Key: (i) $H_2NCH(R)CO_2H$, PhMe, heat, 18−36 h, **16** 82%, **17** 78%, **18** 60%; (ii) $Cl\cdot H_3NCH_2CO_2Et$, PhMe, $^iPr_2NEt$, heat, 2 h, **19** 72%.

SCHEME 6. Cyclization−Cycloaddition of the Aldehyde 9[a]



[a] Key: (i) $H_2NCH(R)CO_2H$, PhMe, heat, 18 h, **20** 77%, **21** 85%, **22** 85%, **23**, 78%; (ii) $Cl\cdot H_3NCH_2CO_2Et$, PhMe, $^iPr_2NEt$, heat, 16 h, **24** 81%.

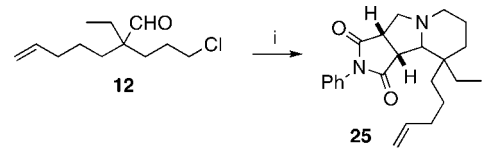
the product **19** was formed in good yield. The stereochemistry of the product **19** was confirmed by reduction of the ethyl ester, conversion to the *p*-bromobenzoate ester, and X-ray crystal structure analysis of the HCl salt.[7] Clearly, there is a preference for cycloaddition through one ylide geometry, as depicted in Scheme 5. The cyclization−cycloaddition cascade gives the all-cis stereochemistry of the products **16**−**19**, as might be expected from the restricted conformation in which the transition state for the cycloaddition has two fused five-membered rings. The synthesis of the tricyclic product **16** represents a novel entry to the core ring system of the alkaloid (±)-scandine.[12]

The aldehyde **9** was heated with several amino acids (glycine, alanine, phenylalanine, and leucine) and with glycine ethyl ester to give the tricyclic products **20**−**24** (Scheme 6). In all cases, the yields of the tricyclic products were high, and only a single (racemic) stereoisomer was detected. These represent some of the most efficient examples of this chemistry, with complete reaction in only a few hours (although a time of 18 h was normally allowed) and high yields (77−85%) for the formation of three rings, four new σ-bonds, and three new stereocenters. The stereochemistry of the product **22** was determined by X-ray crystallographic analysis after conversion to the *N*-oxide and formation of the HCl salt. The stereochemistry of the product **24** was confirmed by X-ray crystallographic analysis after reduction of the ethyl ester, conversion to the *p*-bromobenzoate ester, and formation of the HCl salt. In all cases (products **16**−**24**), the all-cis fused stereoisomer was formed. In the ^1H NMR spectrum, the coupling constant across the fused five-membered rings (doublet for the ring-junction NCH proton) was small ($J \leq 9$ Hz).

For comparison, the aldehydes **12** and **15** were heated with the amino acid glycine; however, no tricyclic products were

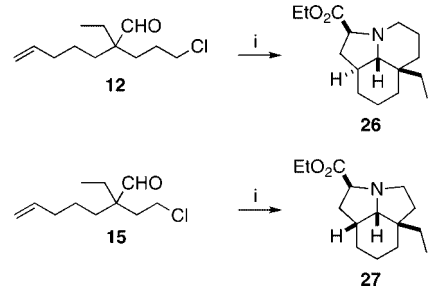
(12) (a) Bernauer, K.; Englert, G.; Vetter, W.; Weiss, E. *Helv. Chim. Acta* **1969**, *52*, 1886–1905. (b) Daudon, M.; Mehri, M. H.; Plat, M. M.; Hagaman, E. W.; Schell, F. M.; Wenkert, E. *J. Org. Chem.* **1975**, *40*, 2838–2839. (c) Cannon, J. R.; Croft, K. D.; Matsuki, Y.; Patrick, V. A.; Toia, R. F.; White, A. H. *Aust. J. Chem.* **1982**, *35*, 1655–1664. (d) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598–2610. (e) Denmark, S. E.; Cottell, J. J. *Adv. Synth. Catal.* **2006**, *348*, 2397–2402.

SCHEME 7. Cyclization−Intermolecular Cycloaddition of the Aldehyde 12[a]



[a] Key: (i) $H_2NCH_2CO_2H$, *N*-phenylmaleimide, PhMe, heat, 12 h, **25** 76%.

SCHEME 8. Cyclization−Cycloaddition of the Aldehydes 12 and 15[a]

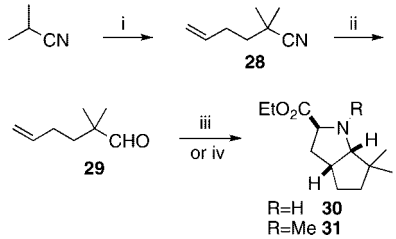


[a] Key: (i) $Cl\cdot H_3NCH_2CO_2Et$, PhMe, $^iPr_2NEt$, heat, 2 h, **26** 74%, **27** 51%.

obtained. In both cases, a mixture of products was formed, and ^1H NMR spectroscopic studies indicated the presence of the unreacted alkene. The mass spectra of the inseparable mixture showed that the products were isomers of the desired tricyclic amines, and this suggested that the initial imine formation and cyclization to give the azomethine ylide had been successful but that the subsequent intramolecular cycloaddition onto the terminal alkene was disfavored in comparison to alternative reaction pathways. This was confirmed by treating the aldehyde **12** with glycine in the presence of the dipolarophile *N*-phenylmaleimide, which gave a mixture of stereoisomers of the cycloadducts **25** (Scheme 7).

This intermolecular cycloaddition result shows that the azomethine ylides derived from the aldehydes **12** and **15** were being formed. The extra methylene unit between the alkene dipolarophile and the azomethine ylide in these substrates (in comparison with **6** and **9**) must be sufficient to disfavor cycloaddition. Cycloaddition was, however, possible with the electron-deficient dipolarophile *N*-phenylmaleimide. We therefore considered whether changing the electronics of the ylide or dipolarophile would promote intramolecular cycloaddition. We were pleased to find that heating aldehydes **12** and **15** with glycine ethyl ester did give the desired tricyclic products **26** and **27** (Scheme 8). These products were each formed as a single diastereoisomer. The coupling constant between the ring junction protons in the ^1H NMR spectrum of product **26** ($J = 12$ Hz) suggested these protons adopt a trans relationship. Reduction of the ethyl ester **26**, conversion to the *p*-bromobenzoate ester, and X-ray crystal structure analysis of the HCl salt confirmed this assignment.[7] However, the product **27** has the all-cis stereochemistry, akin to previous examples (Scheme 5 and 6). This was determined by ^1H NMR spectroscopy ($J = 6$ Hz for the ring junction protons) and by NOESY of the HCl salt of the *p*-bromobenzoate ester (formed after reduction and acylation of the ethyl ester **27**). The switch in the stereochemistry with the product **26** can be ascribed to the reduced conformational rigidity and the presence of two chair-shaped rings in the transition state for cycloaddition that favor a trans-fused ring product.

SCHEME 9. Mechanistic Studies Using the Aldehyde 29[a]



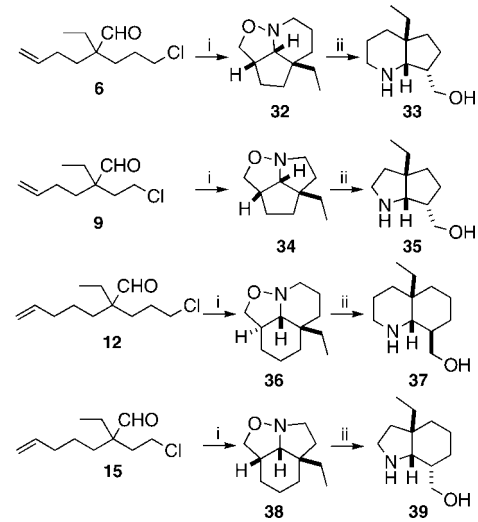
[a] Key: (i) LDA (0.5 equiv.), THF, −78 °C, 1 h, then 4-bromo-1-butene (0.25 equiv.), 80%; (ii) DIBAL-H (1.2 equiv), CH_2Cl_2, −78 °C, then $HCl_{(aq)}$, 65%; (iii) Cl·$H_3NCH_2CO_2Et$, PhMe, $^iPr_2NEt$, heat, 24 h, **30** 21% + recovered **29**; (iv) HCl·$MeNHCH_2CO_2Et$, PhMe, $^iPr_2NEt$, heat, 12 h, **31** 70%.

The cascade process for the formation of the tricyclic amine products could involve one of at least two reaction pathways. Condensation of the amino acid (or ester) with the aldehyde could be followed either by cyclization and then azomethine ylide formation and cycloaddition or by azomethine ylide formation and cycloaddition then cyclization. Work by Pearson and co-workers suggests that, with their substrates, cyclization precedes intermolecular cycloaddition.[8a] To test this, we prepared the aldehyde **29**, lacking the alkyl halide required for cyclization, using the same methodology as before (alkylation of isobutyronitrile to give **28** then DIBAL-H reduction). We anticipated that, should cycloaddition precede cyclization, this substrate would undergo imine formation and cycloaddition with glycine ethyl ester at least as fast as substrate **6** (product **19** formed in high yield in 2 h). However, after heating for 2 h, only starting aldehyde **29** was recovered and the reaction required 24 h to provide a low yield of the bicyclic product **30** (Scheme 9). For comparison, heating the aldehyde **29** with *N*-methylglycine ethyl ester gave a good yield of the bicyclic product **31** in much shorter reaction time (12 h for completion). These results support a mechanism (for Schemes 5, 6, and 8) in which cyclization occurs to form the cyclic azomethine ylide prior to cycloaddition.

The results above describe the formation of cyclic azomethine ylides and their intramolecular cycloaddition to give tricyclic amine products. Cycloaddition of nitrone ylides is well-known onto unactivated dipolarophiles,[13] and we therefore tested the feasibility of this chemistry by addition of hydroxylamine hydrochloride to the aldehydes **6**, **9**, **12**, and **15** (Scheme 10). In all cases, good yields of the tricyclic products **32**, **34**, **36**, and **38** were obtained, each as a single diastereoisomer. The most efficient of these reactions seems to be the formation of product **34** with all five-membered rings, although all of the possible five- and six-membered ring products are accessible. Reduction with zinc and acetic acid promoted cleavage of the *N*−*O* bond to give the bicyclic amino alcohol products **33**, **35**, **37**, and **39**. The relative stereochemistry was confirmed by conversion of the amino alcohols **33**, **37**, and **39** to their bis-*p*-bromobenzoyl derivatives (using *p*-BrC_6H_4COCl, Et_3N, DMAP, CH_2Cl_2) and X-ray crystal structure analysis. The relative stereochemistry of the cycloadducts matches that obtained for the cyclization−cycloaddition with azomethine ylides.

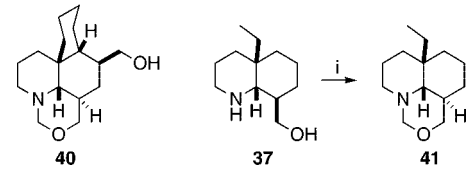
Recently, a new alkaloid called myrioneurinol with activity against malaria was isolated from the leaves of *Myrioneuron*

SCHEME 10. Nitrone Cycloadditions[a]



[a] Key: (i) Cl·H_3NOH, PhMe, $^iPr_2NEt$, heat, 2−18 h, **32** 64%, **34** 89%, **36** 67%, **38** 47%; (ii) Zn, AcOH, H_2O, 70 °C, 1−2 h, **33** 98%, **35** 92%, **37** 97%, **39** 97%.

SCHEME 11. Cyclization To Give the Core Ring System of Myrioneurinol[a]



[a] Key: (i) $(CH_2O)_n$, PhMe, TsOH, heat, 2 h, **41** 100%.

nutans.[14] The structure of this alkaloid **40** contains a 1,3-oxazine ring that could be derived from a hydroxymethyl-substituted quinolizidine ring system. Hence, we treated the amino alcohol **37** with paraformaldehyde and *p*-toluenesulfonic acid to obtain, in quantitative yield, the (racemic) tricyclic product **41** (Scheme 11). The product **41** has three of the rings of the natural product myrioneurinol.

We were interested to determine if our cascade cyclization−cycloaddition chemistry would be amenable to the use of an alkyne as the dipolarophile. This would lead to a dihydropyrrole product that could provide a means to allow further functionalization or conversion to the pyrrole.

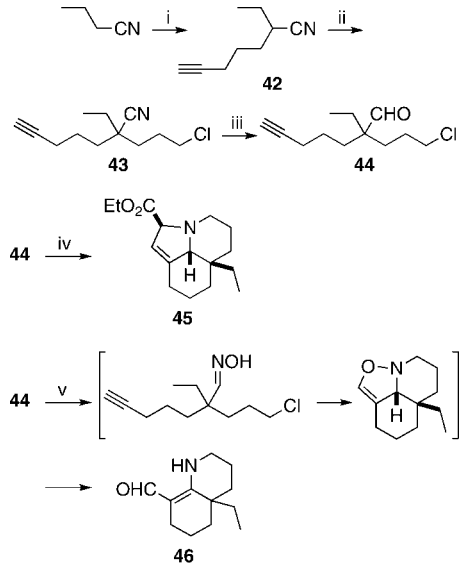
Initial studies in the use of an alkyne as the dipolarophile are described in Scheme 12. 5-Bromo-1-pentyne was prepared from the corresponding tosylate (itself prepared from the alcohol)[15] by addition of lithium bromide. This bromide was volatile and was used directly in the alkylation of butanenitrile to give the nitrile **42**. Alkylation of the nitrile **42** gave the nitrile **43** together with a small amount of the internal alkyne (in which both the nitrile and the alkyne had been alkylated with 1-bromo-3-chloropropane). Reduction with DIBAL-H gave the aldehyde **44**. Heating this aldehyde with glycine ethyl ester gave a single diastereoisomer of the product **45**. The relative stereochemistry was confirmed by ^1H NMR NOESY and is consistent with the previous examples (in which there is a preference for cycloaddition through the S-shaped ylide geometry). The product **45**

(13) (a) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235–3285. (b) Koumbis, A. E.; Gallos, J. K. *Curr. Org. Chem.* **2006**, *7*, 585–628. (c) Ruck-Braun, K.; Freysoldt, T. H. E.; Wierschem, F. *Chem. Soc. Rev.* **2005**, *34*, 507–516. (d) Osborn, H. M. I.; Gemmell, N.; Harwood, L. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2419–2438.

(14) Pham, V. C.; Jossang, A.; Sévenet, T.; Nguyen, V. H.; Bodo, B. *Tetrahedron* **2007**, *63*, 11244–11249.

(15) Atkinson, R. S.; Grimshire, M. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1215–1224.

SCHEME 12. Preparation and Cycloaddition of the Aldehyde 44[a]



[a] Key: (i) LDA (0.5 equiv), THF, −78 °C, 1 h, then 5-bromo-1-pentyne (0.25 equiv), 64%; (ii) LDA (2 equiv), THF, −78 °C, 1 h, then 1-bromo-3-chloropropane, 63%; (iii) DIBAL-H (1.2 equiv), CH_2Cl_2, −78 °C, then $HCl_{(aq)}$, 64%; (iv) $Cl^{-}H_3NCH_2CO_2Et$, PhMe, $^{i}Pr_2NEt$, heat, 18 h, **45** 65%; (v) $Cl^{-}H_3NOH$, PhMe, $^{i}Pr_2NEt$, 60 °C to give the oxime, which was heated in PhMe, 18 h, **46** 38%.

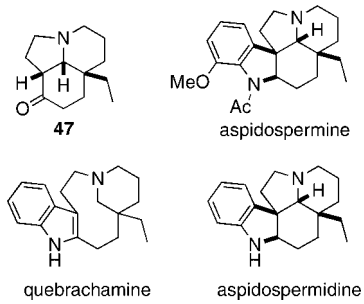


FIGURE 1. *Aspidosperma* alkaloid targets.

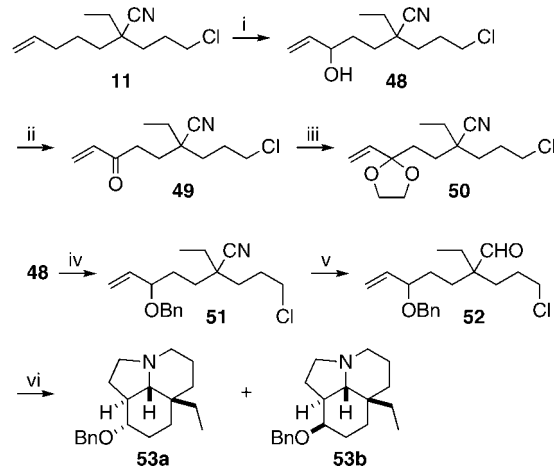
was unstable and oxidizes slowly to the pyrrole. Treatment of the aldehyde **44** with hydroxylamine gave the intermediate oxime (which could be isolated in 83% yield), which was heated in toluene to give the product **46** (Scheme 12). This product arises from the expected cyclization−cycloaddition cascade, followed by rearrangement of the dihydroisoxazole to the vinylogous amide **46**. Although the use of glycine was unsuccessful, this chemistry shows that cyclization−cycloaddition using glycine ethyl ester or hydroxylamine is feasible with a terminal alkyne as the dipolarophile.

The tricyclic fused ring system **26** (Scheme 8) is found in many alkaloids, particularly those of the *Aspidosperma* family. Stork and Dolfini published the first synthesis of aspidospermine and quebrachamine (Figure 1).[16] In their classic synthesis, the ketone **47** was prepared in approximately 13 steps and was converted to aspidospermine and quebrachamine using a Fischer indole synthesis followed by reduction. Later, the same ketone was used to prepare aspidospermidine.[17] Many other syntheses

(16) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872–2873.

(17) (a) Gnecco, D.; Vázquez, E.; Galindo, A.; Terán, J. L.; Orea, L.; Bernès, S.; Enríquez, R. G. *ARKIVOC* **2003**, *xi*, 185–192. (b) Iyengar, R.; Schildknegt, K.; Morton, M.; Aubé, J. *J. Org. Chem.* **2005**, *70*, 10645–10652. (c) Callier-Dublanchet, A. C.; Cassayre, J.; Gagosz, F.; Quiclet-Sire, B.; Sharp, L. A.; Zard, S. Z. *Tetrahedron* **2008**, *64*, 4803–4816.

SCHEME 13. Initial Route to the Nitrile 50 and Cyclization−Cycloaddition of the Aldehyde 52[a]

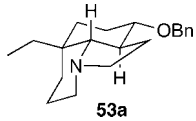


[a] Key: (i) SeO_2 (2 equiv), *t*-BuOOH (5 equiv), salicylic acid (cat.), CH_2Cl_2, heat, 20 h, **48** 75%, **49** 9%; (ii) Dess−Martin periodinane (1.5 equiv), CH_2Cl_2, 0 °C to rt, 3 h, 100%; (iii) $HOCH_2CH_2OH$, PPTS, PhMe, heat, 18 h, ∼40%; (iv) NaH, BnBr, THF, 50 °C, 50 min, 98%; (v) DIBAL-H (1.3 equiv), CH_2Cl_2, −78 °C, then $HCl_{(aq)}$, 82%; (vi) $H_2NCH_2CO_2H$ (4 equiv), PhMe, heat, 48 h, 34% (**53a/53b** 85:15).

or formal syntheses of these alkaloids have been reported.[18] We wondered whether our chemistry would be amenable to a synthesis of these alkaloids via the ketone **47**. One problem to be addressed was the fact that the azomethine ylide derived from the aldehyde **12** and glycine ethyl ester gives the product **26**, in which an ester substituent is present in the tricyclic target, whereas attempted cycloaddition with glycine failed (Schemes 7 and 8). One way to circumvent this problem may be to activate the alkene dipolarophile to cycloaddition, either as the enone or vinyl sulfone. Another aspect was the stereochemistry of the cycloadduct, which favors the cis−trans stereoisomer (**26**) rather than the all-cis stereoisomer required in **47**. However, epimerization of the ketone **47** is known via retro-Mannich reaction,[18] so the stereochemical outcome of the cycloaddition should not in fact be an issue.

Initially, we carried out an allylic oxidation of compound **11** with selenium dioxide and *tert*-butyl hydroperoxide (Scheme 13). The major product was the desired allylic alcohol **48** (dr 1:1), together with some of the (separable) overoxidized product (ketone **49**) and some starting material (**11**). Oxidation of the allylic alcohol **48** to the ketone **49** was quantitative using the Dess−Martin periodinane reagent. Attempted reduction of the nitrile **49** using DIBAL-H gave only the allylic alcohol **48**. Reduction of the nitrile **48** gave a mixture of products, which were assumed to be diastereomeric lactols. We therefore protected the ketone **49** to give the acetal **50**. However, this step occurred in variable yield (typically less than 40%), and no improvement was obtained under modified conditions with

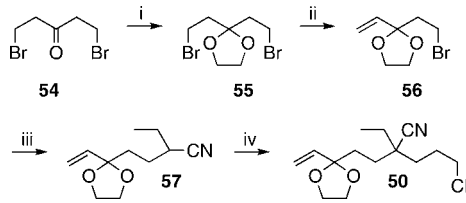
(18) For recent references, see: (a) Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 995–1002. (b) Toczko, M. A.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 2642–2645. (c) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628–4641. (d) Marino, J. P.; Rubio, M. B.; Cao, G.; de Dios, A. *J. Am. Chem. Soc.* **2002**, *124*, 13398–13399. (e) Fukuda, Y.; Shindo, M.; Shishido, K. *Org. Lett.* **2003**, *5*, 749–751. (f) Tanino, H.; Fukuishi, K.; Ushiyama, M.; Okada, K. *Tetrahedron* **2004**, *60*, 3273–3282. (g) Banwell, M. G.; Smith, J. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2613–2618. (h) Banwell, M. G.; Lupton, D. W. *Org. Biomol. Chem.* **2005**, *3*, 213–215. (i) Banwell, M. G.; Lupton, D. W.; Willis, A. C. *Aus. J. Chem.* **2005**, *58*, 722–737. (j) Pearson, W. H.; Aponick, A. *Org. Lett.* **2006**, *8*, 1661–1664. (k) Pereira, J.; Barlier, M.; Guillou, C. *Org. Lett.* **2007**, *9*, 3101–3103.



53a

FIGURE 2. Conformation of the cycloadduct **53a**.

SCHEME 14. Alternative Route to the Nitrile 50[a]

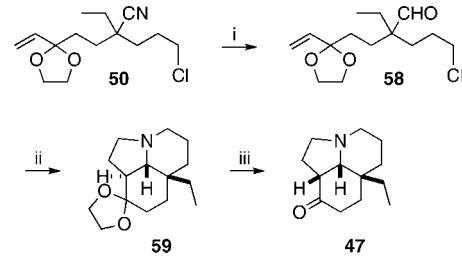


[a] Key: (i) $HOCH_2CH_2OH$, TsOH, PhH, heat, 6 h, 86%; (ii) *t*-BuOK (1.5 equiv), THF−PhMe (1:1), 0 °C to rt, 1 h, 82%; (iii) butanenitrile (4 equiv.), LDA (2 equiv), THF, −78 °C, 1 h, then bromide **56**, 88%; (iv) LDA (2 equiv), THF, −78 °C, 1 h, then 1-bromo-3-chloropropane, 96%.

the bis-TMS ether of ethylene glycol.[19] We therefore studied some alternative protecting groups and prepared the benzyl ether **51** from the alcohol **48**. With the failure in the key cyclization−cycloaddition of the related substrate **12** with glycine, we were not anticipating successful reaction with the aldehyde **52**, derived from **51**. We therefore initially attempted to activate the alkene dipolarophile by cross metathesis with phenyl vinyl sulfone. However, this was unsuccessful using the allylic alcohol **48** or the allylic ether **51** (or the corresponding *O*-TBDPS and *O*-Ac derivatives). To check the feasibility of carrying out the cascade chemistry, the substrate **52** was heated with glycine and we were pleasantly surprised to find that this was partly successful. The aldehyde **52** is a mixture (1:1) of two (inseparable) diastereomers, and therefore, cyclization−cycloaddition should lead to a mixture of the stereoisomeric products **53**. However, only two stereoisomers of **53** were obtained. These were separable, and both indicated, by ^{1}H NMR spectroscopy, that the ring junction protons were trans related (J ∼12 Hz for each). The major stereoisomer (29% yield) was assigned as isomer **53a**, on the basis of the multiplicity and coupling constants for the proton on the ring attached to the benzyloxy group (C*H*OBn), which showed a triple doublet (J 10 and 4 Hz). This implies that the benzyloxy group is in the equatorial position (Figure 2). Presumably, cycloaddition of the other diastereomer of the aldehyde **52** is less favorable, as it places the benzyloxy group in the axial position (the ^{1}H NMR spectrum for C*H*OBn of **53b** shows a broad quartet, J 2.5 Hz), and this explains the lower yield (5%) of the stereoisomer **53b**.

We were therefore intrigued to test the cyclization−cycloaddition cascade with the aldehyde derived from the acetal **50**. We reasoned that a better route to the nitrile **50** would be by direct alkylation of butanenitrile with the bromide **56** (Scheme 14). This bromide was prepared from the known dibromoketone **54**, itself prepared in two steps from ethyl bromopropionate using a Kulinkovich reaction and ring-opening of the resulting cyclopropanol with *N*-bromosuccinimide.[20] Treatment of the dibromide **54** with ethylene glycol gave the acetal **55** in high yield, together with a small amount (7% yield) of the alkene **56**. Treatment of the dibromide **55** with *t*-BuOK promoted elimination to give the alkene **56**. None of the dieliminated product was observed despite using an excess of the base. With the bromide **56** in hand, we were able to prepare the nitrile **50** by two successive high-yielding alkylations in the same way as the other substrates described above. This route was therefore preferable for the formation of the nitrile **50**.

SCHEME 15. Cyclization−cycloaddition of the Aldehyde 55[a]



[a] Key: (i) DIBAL-H (1.2 equiv), CH_2Cl_2, −78 °C, then oxalic acid (0.5 M), 82%; (ii) $H_2NCH_2CO_2H$, PhMe, CSA (0.1 equiv), heat, 18 h, 79%; (iii) HCl (2 M), THF, heat, 1 h, 88%.

Reduction of the nitrile **50** with DIBAL-H followed by aqueous HCl workup gave a mixture of the aldehyde **58** and the aldehyde in which the acetal had been hydrolyzed to the enone. Prolonged exposure to aqueous HCl did promote complete hydrolysis of the acetal, but the enone−aldehyde was unstable and could not be isolated. Reduction of the nitrile **50** followed by aqueous oxalic acid workup gave the desired aldehyde **58** in high yield, without hydrolysis of the acetal (Scheme 15). Although this substrate was similar to the aldehyde **12**, which had failed to undergo cycloaddition with glycine, it is possible that the acetal group could influence this transformation. Hence, we attempted the cyclization−cycloaddition on heating with glycine. After several hours, there appeared to be a small amount of product being formed. Addition of 10 mol % of camphor sulfonic acid (CSA) enhanced the formation of this product, which was isolated after the mixture was heated for 18 h. We were pleased to find that the product was the cyclic amine **59**, which was formed in 79% yield as a single diastereoisomer. The relative stereochemistry is the same as that found for the formation of the tricyclic product **26** and was confirmed by X-ray crystal structure analysis of **59**.[7] The ability of the substrate **58** to undergo the desired cycloaddition reaction must be due to the presence of the acetal, particularly in its protonated form. The protonated acetal (or transient oxonium ion) could act as an electron-withdrawing group to activate the alkene sufficiently to interact with the azomethine ylide. Simple hydrolysis of the acetal then gave the ketone **47**, in which the stereocenter α to the ketone had epimerized. This chemistry therefore completes a short synthesis (seven steps from dibromide **54**) of the Stork−Dolfini ketone.

The total synthesis of the alkaloids aspidospermine, quebrachamine, and aspidospermidine was carried out using the ketone **47** (Scheme 16). This followed the literature procedures.[16,17] Hence, treatment of ketone **47** with 2-methoxyphenylhydrazine in EtOH gave the intermediate hydrazone that was heated in acetic acid. After partial purification through a short silica column, the crude mixture was dissolved in THF and treated with $LiAlH_4$ (45 °C for 16 h) and then acetylated to give the alkaloid (±)-aspidospermine (29% yield over the four steps). Heating the ketone **47** with phenylhydrazine in benzene then evaporation of the solvent and heating in acetic acid, followed by evaporation of the solvent and heating with KBH_4 in methanolic KOH, resulted in the formation of (±)-quebrachamine (39% yield over the three steps). Similarly, heating

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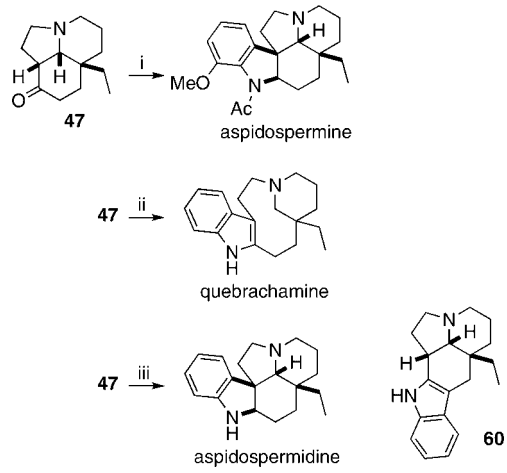
(20) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675–1686.

SCHEME 16. Completion of the Total Synthesis of the *Aspidosperma* Alkaloids[a]



[a] Key: (i) 2-MeOC$_6$H$_4$NHNH$_2$, EtOH, rt, 3 h, then AcOH, 95 °C, 1 h, then LiAlH$_4$, THF, 50 °C, then Ac$_2$O, pyridine, 22%; (ii) PhNHNH$_2$, PhH heat, 2.5 h, then AcOH, 95 °C, 3 h, then KBH$_4$, KOH, MeOH, 39%; (iii) PhNHNH$_2$, PhH heat, 2.5 h, then AcOH, 95 °C, 2.5 h, then LiAlH$_4$, THF, heat, 13 h, 42% (+ 8% of **60**).

the ketone **47** with phenylhydrazine in benzene then in acetic acid, followed by evaporation of the solvent and heating with LiAlH$_4$ in THF, resulted in the formation of (±)-aspidospermidine (42% yield over the 3 steps), together with a small amount (8% yield) of the regioisomeric indole **60**.[17]

Conclusions

Tricyclic amines can be prepared in one step from acyclic precursors using a cascade of tandem reactions involving condensation of an aldehyde with a primary amine, cyclization (by *N*-alkylation), deprotonation, or decarboxylation to give an azomethine ylide (or nitrone), followed by intramolecular dipolar cycloaddition. The reactions are, in all the cases described here, completely regioselective and stereoselective. The cycloaddition necessarily forms a 5-membered ring. The other two rings may be 5- or 6-membered, and all combinations of these are amenable, depending on the length of the tethers [between the aldehyde and the alkene (or alkyne) dipolarophile, and between the aldehyde and the alkyl chloride] in the substrates. Simple amino acids such as glycine, alanine, and phenylalanine and derivatives such as glycine ethyl ester and also hydroxylamine can be used successfully, although when the tether to the dipolarophile produces a 6-membered ring then glycine was unsuccessful. The chemistry was applied to the synthesis of the core ring systems of the alkaloids (±)-scandine and (±)-myrioneurinol and the total syntheses of the alkaloids (±)-aspidospermine, (±)-quebrachamine and (±)-aspidospermidine.

Experimental Section

Experimental procedures and spectroscopic data have been reported previously for the compounds **4**−**6**, **10**−**12**, **16**−**19**, **26**, **32, 36**, **47**, **50**, and **54**−**60**.[7]

Experimental procedures and spectroscopic data for the compounds **13**−**15**, **25**, **27**−**31**, **33**, **37**−**39**, and **51**−**53** are reported in the Supporting Information.

As representative examples, experimental procedures and spectroscopic data are reported below for the compounds **7**−**9**, **20**−**24**, **34**−**35**, **41**−**46**, and **48**−**49**.

2-Ethyl-2-(2-hydroxyethyl)hex-5-enenitrile 7. *n*-Butyllithium (29.0 mL, 72.6 mmol, 2.5 M in hexanes) was added to diisopropylamine (10.8 mL, 76.7 mmol) in THF (73 mL) at −78 °C. After 20 min, nitrile **4** (5.11 g, 41.5 mmol) was added dropwise. After 20 min, 2-bromoethyl trimethylsilyl ether (11.1 mL, 72.6 mmol) was added, and the mixture was allowed to warm to room temperature over 18 h. Aqueous HCl (2 M, to pH 2) was added, and then the mixture was stirred for 1 h. The mixture was extracted with Et$_2$O (3 × 75 mL), dried (MgSO$_4$), and evaporated. Purification by column chromatography, eluting with hexane−EtOAc (9:1 to 1:1), gave the nitrile **13** (6.94 g, 94%) as an oil: R_f 0.18 [hexane−EtOAc (3:1)]; ν_{max}/cm^{-1} 3435, 2975, 2945, 2930, 2235, 1645; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 5.81 (1H, ddt, *J* 17.0, 10.5, 6.5 Hz, CH), 5.12−4.99 (2H, m, CH$_2$), 3.89−3.82 (2H, m, CH$_2$), 2.14−2.06 (2H, m, CH$_2$), 1.88 (2H, t, *J* 7.0 Hz, CH$_2$), 1.73−1.66 (4H, m, 2 × CH$_2$), 1.04 (3H, t, *J* 7.5 Hz, CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 135.9, 122.5, 114.6, 58.1, 38.4, 36.9, 34.3, 28.4, 27.6, 7.7; HRMS (CI) found MH$^+$ 168.1387, C$_{10}$H$_{18}$NO requires MH$^+$ 168.1388; LRMS *m*/*z* (CI) 185 (3, MNH$_4^+$), 168 (100, MH$^+$).

2-Ethyl-2-(2-chloroethyl)hex-5-enenitrile 8. *N*-Chlorosuccinimide (1.23 g, 9.2 mmol) in THF (25 mL) was added dropwise to triphenylphosphine (2.44 g, 9.2 mmol) in THF (24 mL) at room temperature, followed by addition of the alcohol **7** (1.46 g, 8.76 mmol) in THF (14.5 mL). After 4 h, the solvent was evaporated, H$_2$O (10 mL) was added, and the mixture was extracted with Et$_2$O (3 × 30 mL). The organic layers were washed with H$_2$O (15 mL), dried (MgSO$_4$), and evaporated. Purification by column chromatography, eluting with hexane−EtOAc (98:2), gave the nitrile **8** (1.55 g, 95%) as an oil: R_f 0.41 [hexane−EtOAc (95:5)]; ν_{max}/cm^{-1} 2980, 2940, 2230, 1645; ^{1}H NMR (300 MHz, CDCl$_3$) δ = 5.80 (1H, ddt, *J* 17.0, 10.5, 6.5 Hz, CH), 5.13−5.00 (2H, m, CH$_2$), 3.67−3.59 (2H, m, CH$_2$), 2.25−2.14 (2H, m, CH$_2$), 2.12−2.04 (2H, m, CH$_2$), 1.73−1.64 (4H, m, 2 × CH$_2$), 1.05 (3H, t, *J* 7.5 Hz, CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 136.9, 122.9, 116.3, 40.8, 39.8, 39.0, 35.4, 29.5, 28.9, 9.0; HRMS (CI) found MH$^+$ 186.1046, C$_{10}$H$_{17}$N^{35}Cl requires MH$^+$ 186.1049; LRMS *m*/*z* (CI) 205 (15, MNH$_4^+$ (35Cl)), 203 (100, MNH$_4^+$ (37Cl)), 186 (2, MH$^+$ (35Cl)).

2-(2-Chloroethyl)-2-ethylhept-6-enal 9. DIBAL-H (11.7 mL, 11.7 mmol, 1.0 M in hexanes) was added dropwise to the nitrile **8** (1.45 g, 7.8 mmol) in CH$_2$Cl$_2$ (38 mL) at −78 °C. After 1.5 h, aqueous HCl (10 mL, 1 M) was added, and the mixture was allowed to warm to room temperature. Further aqueous HCl (10 mL, 1 M) was added, and the mixture was extracted with Et$_2$O (6 × 50 mL), dried (MgSO$_4$), and evaporated. Purification by column chromatography, eluting with hexane−EtOAc (98:2), gave the aldehyde **9** (1.25 g, 85%) as an oil: R_f 0.47 [hexane−EtOAc (95:5)]; ν_{max}/cm^{-1} 2975, 2965, 2935, 1725, 1645; ^{1}H NMR (300 MHz, CDCl$_3$) δ = 9.45 (1H, s, CH), 5.77 (1H, ddt, *J* 17.0, 10.5, 6.5 Hz, CH), 5.08−4.96 (2H, m, CH$_2$), 3.45 (2H, dd, *J* 7.0 Hz, CH$_2$), 2.07−1.89 (4H, m, 2 × CH$_2$), 1.68−1.54 (4H, m, 2 × CH$_2$), 0.84 (3H, t, *J* 7.5 Hz, CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ = 205.6, 138.0, 115.7, 52.4, 40.3, 34.9, 32.6, 31.2, 28.1, 24.9, 8.2; HRMS (ES) found MH$^+$ 189.1040, C$_{10}$H$_{17}$OCl requires MH$^+$ 189.1046; LRMS *m*/*z* (ES) 191 (5, MH$^+$ (37Cl)), 189 (100, MH$^+$ (35Cl)).

(5a*SR*,7a*RS*,7b*SR*)-5a-Ethyloctahydrocyclopenta[*gh*]pyrrolizine 20. The aldehyde **9** (495 mg, 2.6 mmol) and glycine (788 mg, 10.5 mmol) were heated under reflux in PhMe (26 mL). After 18 h, the mixture was cooled to room temperature and filtered, and the solid was washed with CH$_2$Cl$_2$ (20 mL). The organic layer was evaporated and purified by column chromatography, eluting with CH$_2$Cl$_2$−MeOH−NH$_3$ (95:5:0.1), to give the cycloadduct **20** (334 mg, 77%) as an oil: R_f 0.15 [CH$_2$Cl$_2$−MeOH−NH$_3$ (95:5:0.1)]; ν_{max}/cm^{-1} 2965, 2880, 1465; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 3.23 (1H, d, *J* 7.5 Hz, CH), 2.89 (1H, dt, *J* 11.0, 6.0 Hz, CH), 2.77 (1H, dt, *J* 11.0, 6.5 Hz, CH), 2.66−2.55 (2H, m, 2 × CH), 2.49−2.39 (1H, m, CH), 1.77−1.65 (2H, m, 2 × CH), 1.61−1.27 (8H, m, 8 × CH), 0.83 (3H, t, *J* 7.5 Hz, CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ = 79.8, 54.4, 52.3, 43.3, 34.8, 34.4, 30.3, 30.1, 30.0,

9.2; HRMS (ES) found MH^+ 166.1595, $C_{11}H_{20}N$ requires MH^+ 166.1596; LRMS *m/z* (ES) 166 (100, MH^+).

(2*RS*,5a*SR*,7a*RS*,7b*SR*)-5a-Ethyl-2-methyloctahydrocyclopenta[*gh*]pyrrolizine 21. The aldehyde **9** (500 mg, 2.6 mmol) and alanine (954 mg, 10.6 mmol) were heated under reflux in PhMe (25 mL). After 18 h, the mixture was cooled to room temperature and filtered, and the solid was washed with CH_2Cl_2 (20 mL). The organic layer was evaporated and purified by column chromatography, eluting with CH_2Cl_2−MeOH−NH_3 (97:3:0.1), to give the cycloadduct **21** (405 mg, 85%) as an oil: R_f 0.25 [CH_2Cl_2−MeOH−NH_3 (95:5:0.1)]; ν_{max}/cm^{-1} 2960, 2940, 2935, 2875, 1460; ^1H NMR (400 MHz, $CDCl_3$) δ = 3.34 (1H, d, *J* 7.5 Hz, CH), 2.87−2.71 (2H, m, 2 × CH), 2.67 (1H, ddd, *J* 11.0, 7.0, 4.0, CH), 2.42 (1H, quintet d, *J* 7.5, 2.0 Hz, CH), 1.76−1.67 (1H, m, CH), 1.63−1.18 (9H, m, 9 × CH), 1.00 (3H, d, *J* 6.0 Hz, CH_3), 0.83 (3H, t, *J* 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 80.2, 58.2, 55.1, 51.2, 42.2, 38.5, 35.2, 34.2, 30.5, 30.4, 20.1, 9.2; HRMS (ES) found MH^+ 180.1759, $C_{12}H_{22}N$ requires MH^+ 180.1752; LRMS *m/z* (ES) 180 (100, MH^+).

(2*SR*,3*RS*,5a*SR*,7a*RS*,7b*SR*)-2-Benzyl-5a-ethyloctahydrocyclopenta[*gh*]pyrrolizine 22. The aldehyde **9** (540 mg, 2.9 mmol) and phenylalanine (1.91 g, 11.4 mmol) were heated under reflux in PhMe (29 mL). After 18 h, the mixture was cooled to room temperature and filtered, and the solid was washed with CH_2Cl_2 (20 mL). The organic layer was evaporated and purified by column chromatography, eluting with CH_2Cl_2−MeOH−NH_3 (98:2:0.1), to give the cycloadduct **22** (642 mg, 85%) as an oil: R_f 0.35 [CH_2Cl_2−MeOH−NH_3 (95:5:0.1)]; ν_{max}/cm^{-1} 2940, 2865, 1465; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.22−7.17 (2H, m, 2 × CH), 7.13−7.08 (3H, m, 3 × CH), 3.38 (1H, d, *J* 7.5 Hz, CH), 2.90−2.78 (3H, m, 3 × CH), 2.62 (1H, ddd, *J* 11.0, 6.5, 4.5 Hz, CH), 2.51−2.36 (2H, m, 2 × CH), 1.71−1.62 (1H, m, CH), 1.57−1.38 (6H, m, 6 × CH), 1.38−1.27 (2H, m, 2 × CH), 1.21−1.10 (1H, m, CH), 0.82 (3H, t, *J* 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.3, 128.1, 127.2, 124.9, 80.4, 65.6, 55.0, 51.7, 42.3, 41.8, 36.7, 35.2, 34.3, 30.3, 30.2, 9.2; HRMS (ES) found MH^+ 256.2053, $C_{18}H_{26}N$ requires MH^+ 256.2065; LRMS *m/z* (ES) 256 (100, MH^+).

Amine **22** was oxidized and converted to its HCl salt according to:

(2*SR*,3*RS*,5a*SR*,7a*RS*,7b*SR*)-2-Benzyl-5a-ethyloctahydrocyclopenta[*gh*]pyrrolizine 3-Oxide Hydrochloride Salt. To the amine **22** (225 mg, 0.88 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added *m*-CPBA (395 mg, 1.76 mmol) in one portion. After 1 h, the mixture was allowed to warm to room temperature and the solvent was evaporated. Purification by column chromatography, eluting with CH_2Cl_2−MeOH−NH_3 (95:5:0.1), gave the *N*-oxide as an oil which crystallized on standing. To the *N*-oxide in Et_2O (5 mL) was added HCl (3.0 mL, 1.0 M in Et_2O) before the solvent was evaporated to give the HCl salt (267 mg, 99%) as a solid which recrystallized from CH_2Cl_2−Et_2O−petroleum ether as cubes: mp 183 °C dec; ν_{max}/cm^{-1} 2965, 2935, 2435, 1575, 1460; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.33−7.23 (5H, m, ArH), 4.67 (1H, d, *J* 8.5 Hz, CH), 4.49−4.41 (1H, m, CH), 4.08−4.01 (1H, m, CH), 3.63−3.55 (2H, m, 2 × CH), 3.04−2.96 (1H, m, CH), 2.91 (1H, dd, *J* 13.5, 9.0 Hz, CH), 2.51−2.44 (1H, m, CH), 2.26−2.19 (1H, m, CH), 1.98−1.75 (4H, m, 4 × CH), 1.72−1.60 (3H, m, 3 × CH), 1.51−1.42 (1H, m, CH), 0.95 (3H, t, *J* 7.5 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 135.8, 129.4, 129.0, 127.4, 95.2, 76.7, 65.5, 54.6, 40.4, 35.1, 34.5, 34.2, 33.2, 30.5, 30.1, 9.7; HRMS (ES) found M^+ − Cl, 272.2007, $C_{18}H_{26}NO$ requires M^+ − Cl 272.2014; LRMS *m/z* (ES) 256 (100, M^+ − Cl). Anal. Cald for $C_{18}H_{26}ClNO$: C, 70.22; H, 8.51; N, 4.55; Cl, 11.52. Found: C, 69.93; H, 8.51; N, 4.43; Cl, 11.76.

X-ray crystal structure analysis: Detailed results are deposited at the Cambridge Crystallographic Data Centre. Structure No. CCDC-694397.

(2*RS*,5a*SR*,7a*RS*,7b*SR*)-5a-Ethyl-2-isobutyloctahydrocyclopenta[*gh*]pyrrolizine 23. The aldehyde **9** (395 mg, 2.1 mmol) and leucine (1.11 g, 8.4 mmol) were heated under reflux in PhMe (21 mL). After 18 h, the mixture was cooled to room temperature and filtered, and the solid was washed with CH_2Cl_2 (20 mL). The organic layer was evaporated and purified by column chromatography, eluting with CH_2Cl_2−MeOH−NH_3 (97:3:0.1), to give the cycloadduct **23** (359 mg, 78%) as an oil: R_f 0.27 [CH_2Cl_2−MeOH−NH_3 (95:5:0.1)]; ν_{max}/cm^{-1} 2945, 2865, 1465; ^1H NMR (400 MHz, $CDCl_3$) δ = 3.31 (1H, d, *J* 7.5 Hz, CH), 2.85 (1H, ddd, *J* 11.5, 9.0, 6.5 Hz, CH), 2.74−2.63 (2H, m, 2 × CH), 2.48−2.36 (1H, quintet, *J* 7.5 Hz, CH), 1.77−1.63 (2H, m, 2 × CH), 1.59−1.26 (9H, m, 9 × CH), 1.25−1.18 (1H, m, CH), 1.13 (1H, ddd, *J* 13.5, 8.5, 6.0 Hz, CH), 0.82 (9H, apparent t, *J* 6.5 Hz, 3 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 80.1, 61.5, 54.9, 51.9, 45.2, 42.3, 37.1, 35.3, 34.5, 30.6, 30.4, 24.9, 22.5, 21.6, 9.2; HRMS (ES) found MH^+ 222.2223, $C_{15}H_{28}N$ requires MH^+ 222.2222; LRMS *m/z* (ES) 222 (100, MH^+).

(2*SR*,5a*SR*,7a*RS*,7b*SR*)-5a-Ethyloctahydrocyclopenta[*gh*]pyrrolizine-2-carboxylic Acid Ethyl Ester 24. The aldehyde **9** (387 mg, 2.05 mmol), glycine ethyl ester hydrochloride (434 mg, 3.08 mmol), and *N*,*N*-diisopropylethylamine (1.08 mL, 6.15 mmol) were heated under reflux in PhMe (21 mL). After 12 h, the mixture was cooled to room temperature, evaporated, and purified by column chromatography, eluting with CH_2Cl_2−MeOH (97:3), to give the cycloadduct **24** (396 mg, 81%) as an oil: R_f 0.22 [CH_2Cl_2−MeOH (95:5)]; ν_{max}/cm^{-1} 2965, 2935, 2870, 1740; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.24−4.14 (2H, m, CH_2), 3.56 (1H, d, *J* 7.5 Hz, CH), 3.48 (1H, dd, *J* 9.0, 6.5 Hz, CH), 3.05 (1H, ddd, *J* 11.5, 8.0, 6.5 Hz, CH), 2.78 (1H, ddd, *J* 11.5, 6.5, 5.0 Hz, CH), 2.58 (1H, m, CH), 2.05 (1H, ddd, *J* 12.5, 9.5, 7.5 Hz, CH), 1.95−1.79 (2H, m, 2 × CH), 1.69 (1H, ddd, *J* 12.0, 6.5, 5.0 Hz, CH), 1.61−1.29 (6H, m, 6 × CH), 1.27 (3H, t, *J* 7.0 Hz, CH_3), 0.90 (3H, t, *J* 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.2, 80.4, 65.8, 59.7, 54.8, 52.4, 42.9, 34.9, 34.8, 34.3, 30.2, 30.0, 13.3, 9.1; HRMS (ES) found MH^+ 238.1806, $C_{14}H_{24}NO_2$ requires MH^+ 238.1807; LRMS *m/z* (ES) 238 (100, MH^+).

Ester **24** was reduced and converted to its *p*-bromobenzoyl derivative according to:

4-Bromobenzoic Acid (2*SR*,5a*SR*,7a*RS*,7b*SR*)-5a-Ethyloctahydrocyclopenta[gh]pyrrolizin-2-ylmethyl Ester. $LiAlH_4$ (2.76 mL, 2.76 mmol, 1.0 M in THF) was added to the ester **24** (285 mg, 1.20 mmol) in THF (10 mL) at −5 °C, and the mixture was allowed to warm to room temperature. After 10 min, the mixture was cooled to 0 °C, and saturated aqueous sodium hydrogen carbonate solution (1.5 mL) was added. The mixture was filtered through Celite, washed with CH_2Cl_2 (3 × 15 mL), dried ($MgSO_4$), and evaporated to give the alcohol (201 mg, 86%), which was used without further purification. To this alcohol (200 mg, 1.02 mmol) in CH_2Cl_2 (10 mL) were added DMAP (63 mg, 0.51 mmol) and 4-bromobenzoyl chloride (459 mg, 2.05 mmol) at 0 °C. Triethylamine (0.43 mL, 3.07 mmol) was added dropwise, and the mixture was allowed to warm to room temperature. After 18 h, saturated aqueous sodium hydrogen carbonate (20 mL) was added. The mixture was extracted with EtOAc (3 × 15 mL) and then CH_2Cl_2 (3 × 15 mL), and the organic portions were dried ($MgSO_4$), filtered, and evaporated. Purification by column chromatography, eluting with EtOAc, gave ester (337 mg, 87%) as an oil: R_f 0.15 [EtOAc]; ν_{max}/cm^{-1} 2935, 2865, 1720; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.89 (2H, d, *J* 9.0 Hz, ArH), 7.56 (2H, d, *J* 9.0 Hz, ArH), 4.30−4.19 (2H, m, 2 × CH), 3.49 (1H, d, *J* 7.0 Hz, CH), 3.22−3.14 (1H, m, CH), 3.06 (1H, ddd, *J* 11.5, 8.5, 6.5 Hz, CH), 2.89 (1H, ddd, *J* 11.5, 7.0, 5.0 Hz, CH), 2.56 (1H, br quin, *J* 7.0 Hz, CH), 1.88−1.79 (2H, m, 2 × CH), 1.77−1.17 (8H, m, 8 × CH), 0.89 (3H, t, *J* 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.7, 130.7, 130.1, 128.2, 127.0, 80.8, 68.2, 62.1, 54.8, 52.8, 42.1, 35.2, 34.7, 34.5, 30.5, 30.2, 9.2; HRMS (ES) found MH^+ 378.1059, $C_{19}H_{25}NO_2{}^{79}Br$ requires MH^+ 378.1069; LRMS *m/z* (ES) 380 (100, MH^+ (81Br)), 378 (100, MH^+ (79Br)).

To a stirred solution of this ester (127 mg, 0.37 mmol) in CH_2Cl_2 (1 mL) was added HCl (4 mL, 1 M solution in Et_2O, 4.0 mmol). After 5 min, the solvent was evaporated to give the hydrochloride

salt (140 mg, 100%), which recrystallized from CH_2Cl_2−Et_2O−petroleum ether as cubes: mp 184−186 °C; ν_{max}/cm^{-1} 2965, 2930, 2365, 1720; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.10 (1H, br s, NH), 7.95 (2H, d, *J* 8.5 Hz, ArH), 7.59 (2H, d, *J* 8.5 Hz, ArH), 4.99−4.90 (1H, m, CH), 4.84 (1H, br d, *J* 11.5 Hz, CH), 4.36 (1H, br t, *J* 6.0 Hz, CH), 3.87 (2H, br s, 2 × CH), 3.26 (1H, br s, CH), 2.93−2.83 (1H, m, CH), 2.25−1.98 (4H, m, 4 × CH), 1.90−1.42 (6H, m, 6 × CH), 0.94 (3H, t, *J* 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.3, 131.1, 130.5, 128.0, 126.8, 81.1, 64.0, 61.8, 54.3, 52.0, 41.3, 35.0, 33.2, 33.0, 29.5, 29.4, 8.9; HRMS (ES) found MH$^+$ 378.1059, $C_{19}H_{25}NO_2{}^{79}Br$ requires MH$^+$ 378.1069; LRMS *m*/*z* (ES) 380 (100, MH$^+$ (81Br)), 378 (100, MH$^+$ (79Br)); Anal. Calcd for $C_{19}H_{26}BrClNO_2$: C, 55.02; H, 6.08; N, 3.38; Br, 19.26; Cl, 8.55. Found: C, 54.75; H, 6.02; N, 3.16; Br, 19.23; Cl, 8.54.

X-ray crystal structure analysis: Detailed results are deposited at the Cambridge Crystallographic Data Centre. Structure No. CCDC-694395.

(2a*SR*,4a*SR*,6b*SR*)-4a-Ethyloctahydro-1-oxa-6a-azacyclopenta[*cd*]pentalene 34. The aldehyde **9** (385 mg, 2.04 mmol), hydroxylamine hydrochloride (213 mg, 3.06 mmol), and *N*,*N*-diisopropylethylamine (1.08 mL, 6.12 mmol) were heated under reflux in toluene (20 mL). After 2 h, the solvent was evaporated, and the residue was purified by column chromatography, eluting with EtOAc, to give cycloadduct **34** (303 mg, 89%) as an oil: R_f 0.20 (EtOAc); ν_{max}/cm^{-1} 2955, 2865, 2855; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.66 (1H, dd, *J* 9.0, 6.0 Hz, CH), 3.55 (1H, dd, *J* 9.0, 2.5 Hz, CH), 3.48 (1H, d, *J* 9.0 Hz, CH), 3.26 (1H, ddd, *J* 13.0, 6.5, 3.5 Hz, CH), 3.02−2.86 (2H, m, 2 × CH), 1.89−1.80 (1H, m, CH), 1.79−1.70 (1H, m, CH), 1.65−1.29 (6H, m, 6 × CH), 0.84 (3H, t, *J* 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 80.8, 70.2, 54.9, 54.7, 48.9, 35.6, 33.4, 30.0, 29.7, 9.1; HRMS (ES) found MH$^+$ 168.1388, $C_{10}H_{18}NO$ requires MH$^+$ 168.1388; LRMS *m*/*z* (ES) 168 (100, MH$^+$).

[(3a*SR*,6*RS*,6a*SR*)-3a-Ethyloctahydrocyclopenta[*b*]pyrrol-6-yl]methanol 35. Zn powder (353 mg, 5.40 mmol) was added to the hydroxylamine **34** (215 mg, 1.29 mmol) in AcOH/H_2O (1:2, 8 mL), and the mixture was heated to 70 °C. After 30 min, the mixture was cooled to room temperature, filtered, and washed with CH_2Cl_2. The solvent was evaporated, and ammonia solution (10 mL) and CH_2Cl_2 (20 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), dried ($MgSO_4$), and evaporated to give the amino alcohol **35** (201 mg, 92%) as an oil: ν_{max}/cm^{-1} 3240, 2935, 2865, 1460, 1395, 1025; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.96 (1H, dd, *J* 11.5, 2.0 Hz, CH), 3.94 (1H, br s, NH), 3.70 (1H, dd, *J* 11.5, 4.0 Hz, CH), 3.30 (1H, d, *J* 6.0 Hz, CH), 2.91 (1H, dt, *J* 10.5, 6.5 Hz, CH), 2.83 (1H, dt, *J* 10.5, 6.5 Hz, CH), 1.92−1.80 (2H, m, 2 × CH), 1.61 (2H, td, *J* 6.5, 2.5 Hz, 2 × CH), 1.61−1.40 (5H, m, 5 × CH), 0.89 (3H, t, *J* 7.5 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 71.9, 63.0, 55.3, 47.4, 44.4, 39.2, 36.4, 33.3, 26.8, 10.1; HRMS (EI) found M$^+$ 169.1466, $C_{10}H_{19}NO$ requires M$^+$ 169.1467; LRMS *m*/*z* (ES) 170 (100, MH$^+$).

(6a*SR*,9a*RS*,9b*SR*)-6a-Ethyloctahydro-2-oxa-3a-azaphenalene 41. The amino alcohol **37** (233 mg, 1.18 mmol) and TsOH·H_2O (11 mg, 0.06 mmol) in $CHCl_3$ (7.5 mL) were heated under reflux. After 5 h, the mixture was allowed to cool to room temperature, and H_2O (6 mL) and potassium carbonate (1 g) were added. The mixture was extracted with CH_2Cl_2 (2 × 15 mL), and the organic layer was dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petroleum ether−EtOAc (9:1), gave the oxazine **41** (245 mg, 100%) as an oil: R_f 0.22 [petroleum ether−EtOAc (9:1)]; ν_{max}/cm^{-1} 2920, 2845, 1460; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.44 (1H, dd, *J* 10.5, 0.5 Hz, CH), 4.40 (1H, d, *J* 10.5 Hz, CH), 3.86 (1H, ddd, *J* 12.0, 4.0, 0.5 (CH), 3.19 (1H, td, *J* 12.0, 3.5 Hz, CH), 3.15 (1H, t, *J* 11.0 Hz, CH), 2.61 (1H, br dd, *J* 11.0, 5.0 Hz, CH), 2.33 (1H, d, *J* 11.0 Hz, CH), 2.30−2.21 (1H, m, CH), 1.95−1.87 (1H, m, CH), 1.79−1.69 (1H, m, CH), 1.59 (1H, td, *J* 13.5, 4.0 Hz, CH), 1.55−1.34 (5H, m, 5 × CH), 1.25−1.09 (3H, m, 3 × CH), 0.76 (3H, t, *J* 7.5 Hz, CH_3), 0.72 (1H, dd, *J* 12.0, 3.5 Hz, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 87.0, 73.5, 66.8, 44.7, 36.0, 34.8, 30.3, 28.5, 27.7, 24.7, 21.4, 20.6, 7.0; HRMS (ES) found MH$^+$ 210.1853, $C_{13}H_{24}NO$ requires MH$^+$ 210.1858; LRMS *m*/*z* (ES) 210 (100, MH$^+$).

2-Ethylhept-6-ynenitrile 42. *n*-Butyllithium (16.56 mL, 35.6 mmol, 2.5 M in hexanes) was added to diisopropylamine (5.26 mL, 37 mmol) in THF (40 mL) at −78 °C. After 10 min, butyronitrile (6.2 mL, 71.2 mmol) was added dropwise. After 10 min, the 5-bromo-1-pentyne (2.4 g, 18 mmol) was added, and the mixture was allowed to warm to room temperature. After 1 h, saturated aqueous ammonium chloride solution (30 mL) was added, and the mixture was extracted with Et_2O (3 × 50 mL). The organic layers were combined, dried ($MgSO_4$), and evaporated. Purification by column chromatography, eluting with petroleum ether−EtOAc (97:3), gave the nitrile **42** (1.5 g, 64%) as an oil: R_f 0.50 [petroleum ether−EtOAc (19:1)]; ν_{max}/cm^{-1} 3295, 2960, 2235, 1460; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.52 (1H, quin, *J* 7.0 Hz, CH), 2.28 (2H, td, *J* 6.5, 2.5 Hz, CH_2), 1.99 (1H, t, *J* 2.5 Hz, CH), 1.85−1.60 (6H, m, 3 × CH_2), 1.10 (3H, t, *J* 7.5 Hz CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ = 121.8, 84.1, 69.2, 32.9, 30.8, 25.8, 25.5, 18.0, 11.5; HRMS (EI) found M$^+$ 135.1048, $C_9H_{13}N$ requires M$^+$ 135.1054; LRMS *m*/*z* (EI) 135 (10, M$^+$), 107 (100).

2-(3-Chloropropyl)-2-ethylhept-6-ynenitrile 43. In the same way as the nitrile **42**, *n*-butyllithium (13.3 mL, 33.3 mmol, 2.5 M in hexanes), diisopropylamine (4.6 mL, 35.8 mmol), nitrile **42** (2.9 g, 21.5 mmol), and 1,3-bromochloropropane (3.29 mL, 33.3 mmol) gave, after purification by column chromatography, eluting with petroleum ether−EtOAc (97:3), the nitrile **43** (2.9 g, 63%) as an oil: R_f 0.40 [petroleum ether−EtOAc (19:1)]; ν_{max}/cm^{-1} 3250, 2985, 2235, 1460; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.60 (2H, t, *J* 6.5 Hz, CH_2), 2.26 (2H, td, *J* 6.5, 2.5 Hz, CH_2), 2.00 (1H, t, *J* 2.5 Hz, CH) 1.95−1.87 (2H, m, 2 × CH), 1.75−1.60 (8H, m, 8 × CH), 1.03 (3H, t, *J* 7.5 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 123.3, 83.2, 69.3, 44.6, 40.5, 34.5, 33.0, 28.9, 27.5, 23.2, 18.4, 8.6; HRMS (EI) found M$^+$ 211.1129, $C_{12}H_{18}NCl$ requires M$^+$ 211.1122; LRMS *m*/*z* (EI) 211 (15, M$^+$), 67 (100).

2-(3-Chloropropyl)-2-ethylhept-6-ynal 44. In the same way as the aldehyde **9**, DIBAL-H (20 mL, 20 mmol, 1.0 M in hexanes) and the nitrile **43** (2.8 g, 13.3 mmol) gave, after purification by column chromatography, eluting with petroleum ether−EtOAc (97:3), the aldehyde **44** (2.9 g, 64%) as an oil: R_f 0.3 [petroleum ether−EtOAc (19:1)] ν_{max}/cm^{-1} 3300, 2945, 1710, 1460; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.44 (1H, s, CHO), 3.54 (2H, m, CH_2), 2.22 (2H, td, *J* 7.0, 2.5 Hz, CH_2), 1.99 (1H, t, *J* 2.5 Hz, CH) 1.68−1.54 (2H, m, 2 × CH), 1.46−1.36 (8H, m, 8 × CH), 0.83 (3H, t, *J* 7.5 Hz, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ = 206.3, 83.7, 68.9, 51.7, 45.2, 30.5, 28.5, 26.7, 24.7, 22.5, 18.9, 7.8; HRMS (EI) found M$^+$ 214.1124, $C_{12}H_{19}OCl$ requires M$^+$ 214.1125; LRMS *m*/*z* (EI) 215 (5, MH$^+$), 55 (100).

(2*SR*,3a*RS*,6a*SR*)-Ethyl 6a-Ethyl-3,4,5,6,6a,7,8,9-octahydro-2*H*-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylate 45. In the same way as the ester **24**, the aldehyde **44** (0.26 g, (1.2 mmol), glycine ethyl ester hydrochloride salt (0.26 g, 1.85 mmol), and *N*,*N*-diisopropylethylamine (0.65 mL, 3.7mmol) gave, after purification by column chromatography, eluting with petroleum ether−EtOAc (1:4), the ester **45** (0.21 g, 65%) as an oil: R_f 0.30 [petroleum ether−EtOAc (1:4)]; ν_{max}/cm^{-1} 2935, 2865, 1745, 1460; ^{1}H NMR (500 MHz, $CDCl_3$) δ =5.40 (1H, q, *J* 2.5 Hz, CH), 4.21−4.06 (2H, m, CH_2) 3.91 (1H, d, *J* 2.5 Hz, CH), 3.74 (1H, s, CH), 2.90 (1H, d, *J* 11.0 Hz, CH), 2.60 (1H, d, *J* 13.5 Hz, CH), 2.36 (1H, td, *J* 11.0, 3.5 Hz, CH), 2.04−1.88 (4H, m, 4 × CH), 1.80 (1H, qt, *J* 13.0, 3.5 Hz, CH), 1.63−1.53 (1H, m, CH), 1.52−1.36 (4H, m, 4 × CH), 1.26 (3H, t, *J* 7.0 Hz, CH_3), 1.22−1.17 (1H, m, CH), 0.86 (3H, *J* 7.5 Hz, CH_3); (125 MHz, $CDCl_3$) δ = 171.5, 143.9, 117.5, 73.3, 70.5, 60.6, 50.6, 35.3, 34.6, 32.7, 29.7, 26.7, 26.0, 20.0, 14.2, 7.6; HRMS (ES) found M$^+$ 263.1885, $C_{16}H_{25}NO_2$ requires M$^+$ 263.1890; LRMS *m*/*z* (ES) 264 (100, MH$^+$).

4a-Ethyl-1,2,3,4,4a,5,6,7-octahydroquinoline-8-carbaldehyde 46. Hydroxylamine hydrochloride (0.11 g, 1.52 mmol), *N*,*N*-diisopropylethylamine (0.52 mL, 3.0 mmol), and the aldehyde **44**

(0.25 g, 1.2 mmol) were heated to 60 °C in toluene (12 mL). After 3 h, the solvent was evaporated. Purification by column chromatography, eluting with petroleum ether−EtOAc (9:1), gave the oxime (0.19 g, 83%) as a mixture (1:1) of stereoisomers as an oil: R_f 0.30 [petroleum ether−EtOAc (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (0.5H, s, CH), 7.28 (0.5H, s, CH), 3.54 (2H, t, *J* 6.5 Hz, CH_2), 2.20 (2H, td, *J* 6.5, 2.5 Hz, CH_2), 1.99 (1H, t, *J* 2.5 Hz, CH), 1.81−1.36 (10H, m, 10 × CH), 0.85 (3H, t, *J* 7.0 Hz, CH_3); a portion of this oxime (0.18 g, 0.8 mmol) was heated under reflux in PhMe (12 mL). After 16 h, the solvent was evaporated. Purification by column chromatography, eluting with petroleum ether−EtOAc (1:1), gave the aldehyde **46** (60 mg, 38%) as an oil: R_f 0.20 [petroleum ether−EtOAc (1:1)]; ν_{max}/cm^{-1} 2970, 2935, 2235, 1640, 1460; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.90 (1H, s, CHO), 3.40 (1H, m, CH), 3.30 (1H, m, CH), 2.40 (2H, m, 2 × CH), 1.91 (1H, m, CH), 1.78 (1H, dt, *J* 13.0, 4.0 Hz, CH), 1.65 (6H, m, 6 × CH), 1.32 (1H, dt, *J* 13.0, 4.0 Hz, CH), 1.20 (1H, m, CH), 0.81 (3H, t, *J* 7.5 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 188.0, 169.9, 99.0, 40.5, 36.0, 31.2, 28.7, 26.6, 23.2, 18.0, 17.7, 7.0; HRMS (EI) found M$^+$ 193.1467, $C_{12}H_{19}NO$ requires M$^+$ 193.1471; LRMS *m*/*z* (ES) 194 (100, MH$^+$).

2-(3-Chloropropyl)-2-ethyl-5-hydroxyhept-6-enenitrile 48. To the nitrile **11** (2.71 g, 12.6 mmol) in CH_2Cl_2 (125 mL) was added *tert*-butyl hydroperoxide (12.7 mL, 63.4 mmol, 5.0 M in decane), freshly ground selenium dioxide (2.82 g, 25.4 mmol), and salicylic acid (20 mg), and the mixture was heated under reflux. After 20 h, the mixture was cooled to room temperature, evaporated, and partitioned between H_2O (125 mL) and Et_2O (200 mL). The aqueous portion was extracted with Et_2O (2 × 100 mL). The combined organic portions were washed with saturated sodium chloride solution (50 mL), dried ($MgSO_4$), and evaporated. Purification by column chromatography, eluting with petroleum ether−EtOAc (95:5 to 4:1), gave the nitrile **48** (2.18 g, 75%) as a mixture of diastereomers (1:1) as an oil [R_f 0.40 [petroleum ether−EtOAc (4:1)]; ν_{max}/cm^{-1} 3435, 2960, 2235, 1460; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 5.85 (2H, ddd, *J* 17.0, 10.5, 6.0 Hz, 2 × C*H* = CH_2), 5.30−5.08 (4H, m, 2 × CH=C*H*$_2$), 4.16−4.05 (2H, m, 2 × C*H*OH), 3.56 (4H, t, *J* 6.0 Hz, 2 × CH_2Cl), 1.96−1.51 (20H, m, 10 × CH_2), 1.00 (6H, t, *J* 7.5 Hz, 2 × CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ = 140.4, 123.4, 115.5, 72.7, 44.6, 40.5, 33.1, 32.9, 31.4, 31.2, 29.0, 28.8, 27.6, 27.5, 8.6; HRMS (ES) found MNa$^+$ 252.1129, $C_{12}H_{20}$NONa35Cl requires MNa$^+$ 252.1131; LRMS *m*/*z* (ES) 254 (5, MNa$^+$ (37Cl)), 252 (100, MNa$^+$ (35Cl))] and recovered nitrile **11** (320 mg, 12%) and the nitrile **49** (265 mg, 9%), data as below.

2-(3-Chloropropyl)-2-ethyl-5-oxohept-6-enenitrile 49. To the alcohol **48** (1.60 g, 6.96 mmol) in CH_2Cl_2 (35 mL) at 0 °C was added Dess−Martin periodinane (4.43 g, 10.45 mmol) in one portion, and the mixture was allowed to warm to room temperature. After 3 h, aqueous 5% sodium thiosulfate solution (30 mL) was added, the mixture was stirred vigorously for 20 min, and then CH_2Cl_2 (30 mL), K_2CO_3 (5 g), and H_2O (40 mL) were added. The mixture was extracted with CH_2Cl_2 (2 × 40 mL). The organic portions were washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$), and evaporated. Purification by column chromatography, eluting with petroleum ether−EtOAc (9:1), gave the nitrile **49** (1.61 g, 100%) as an oil: R_f 0.54 [petroleum ether−EtOAc (5:1)]; ν_{max}/cm^{-1} 2970, 2230, 1680, 1700, 1460; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 6.38 (1H, dd, *J* 17.5, 10.0 Hz, CH), 6.26 (1H, dd, *J* 17.5, 2.0 Hz, CH), 5.59 (1H, dd, *J* 10.0, 2.0 Hz, CH), 3.57 (2H, t, *J* 6.0 Hz, CH_2Cl), 2.81−2.71 (2H, m, C(O)CH_2), 1.97−1.81 (4H, m, 2 × CH_2), 1.80−1.56 (4H, m, 2 × CH_2), 1.03 (3H, t, *J* 7.5 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.6, 136.1, 128.9, 123.0, 45.5, 40.2, 34.7, 33.0, 29.3, 29.0, 27.3, 8.5; HRMS (ES) found MNa$^+$ 250.0982, $C_{12}H_{18}$NONa^{35}Cl requires MNa$^+$ 250.0972; LRMS *m*/*z* (ES) 252 (2, MNa$^+$ (37Cl)), 250 (100, MNa$^+$ (35Cl)), 228 (5, MH$^+$).

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Supporting Information Available: Procedures and spectroscopic data for compounds **13**−**15**, **25**, **27**−**31**, **33**, **37**−**39**, and **51**−**53**. X-ray crystal structure data for the compounds derived from **22**, **24**, and **39**. NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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