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Amidyls in radical cascades. The total synthesis of (±)-aspidospermidine and (±)-13-deoxyserratine

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This paper is dedicated with much affection to Professor William B. Motherwell

Abstract

Concise routes to aspidospermidine and 13-deoxyserratine are described, hinging on a cascade starting from an amidyl radical and allowing the construction of the key indolizidine cores in one step.
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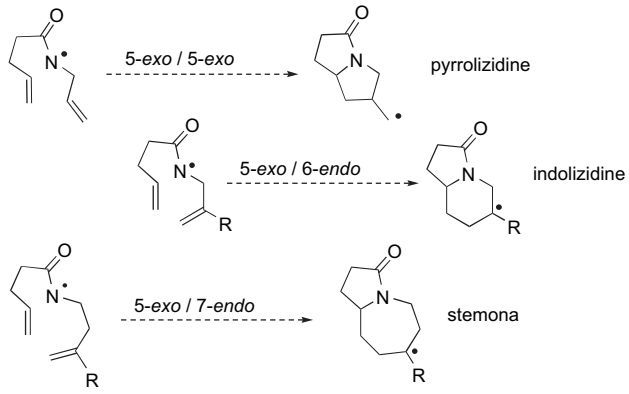
1. Introduction

The use of radical reactions in organic synthesis became widespread about three decades ago yet, despite this popularity, most of the synthetic applications have involved carbon centred radicals, while heteroatom based radicals remained essentially just curiosities.[1] This limited attention stems in part from a lack of convenient and general methods for generating these species, and perhaps a certain absence of a feel regarding their reactivity.

We and others recently developed a number of processes for creating nitrogen-centred radicals, which, when captured by internal olefins, give rise to various types of nitrogen containing heterocycles.[2–4] Thus, pyrrolizidine, indolizidine and related structures commonly found in many alkaloid families can be constructed by employing radical cascades involving, for example, an amidyl radical, as shown in Scheme 1.[5] Depending on the nature of R and the length of the tether, [3,3,0], [4,3,0], and even [5,3,0] azabicyclic motifs can be readily assembled by this approach. The first two correspond to the core motif of the ubiquitous pyrrolizidine and indoline alkaloids, whereas the last, relatively rare, combination is found in the stemona alkaloids (Fig. 1).



Scheme 1.

We have implemented strategies based on such cascades for the synthesis of aspidospermidine **1** and 13-deoxyserratine **2**, both of which contain a key indolizidine subunit.[5] As will be apparent in the present, more detailed account of this work, the method we ultimately adopted for generating the key nitrogen centred radical relies on the cleavage of hydroxamic acid benzoates with stannyl radicals. This method can be

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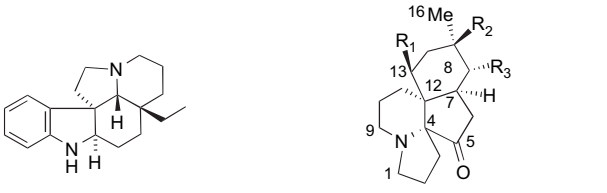


Aspidospermidine **1**

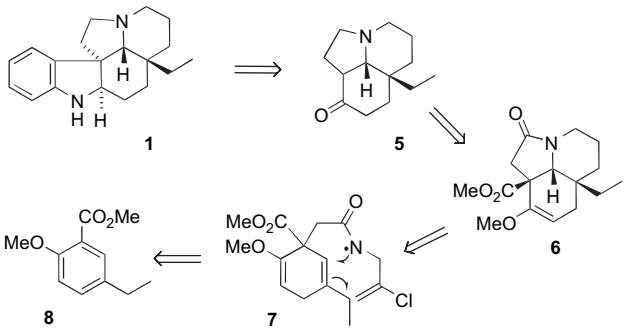
13-Deoxyserratine **2**, R_1= R_3= H, R_2=OH
Serratine **3**, R_1= OH, R_2=OH, R_3= H
Serratinine **4**, R_1= OH, R_2= H, R_3= OH

Figure 1.

adapted to produce a number of other synthetically useful nitrogen radicals, in particular iminyls and amidinyls.[3j,q]

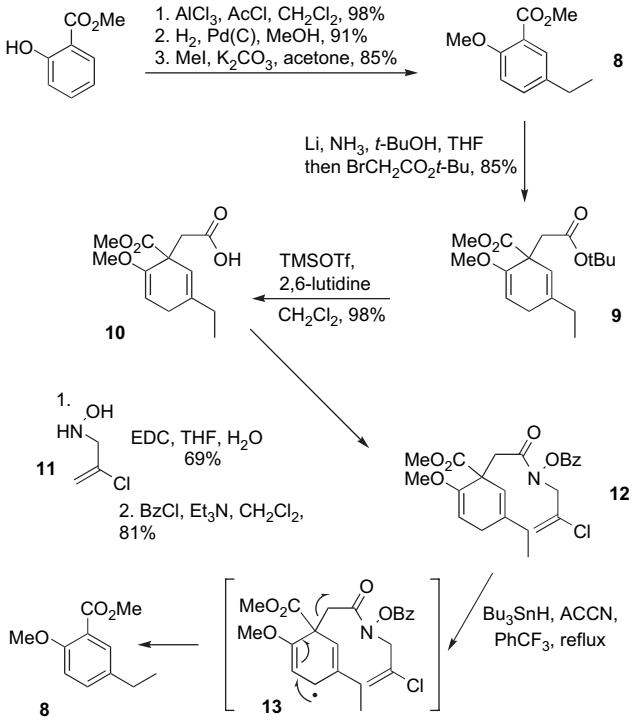
2. Results and discussion

The aspidosperma family of indole alkaloids have inspired many synthetic strategies for the construction of the pentacyclic framework, in particular aspidospermidine **1**, the parent compound.[6] Our proposed synthesis of this alkaloid is outlined in Scheme 2; it hinges on a 5-*exo*/6-*endo* cascade starting with amidyl radical **7** to provide the key tricyclic system **5**, via intermediate **6**. Compound **5** had already been converted into aspidopermidine by the known Fischer indole reaction, initially by Stork[6a] and later by other groups. We envisaged, based on a literature precedent,[7] that placing the chlorine atom on the side chain in intermediate **7** would inhibit the 5-*exo* closure and favour a 6-*endo* in the second cyclisation. This chlorine atom would then be removed by adding an extra equivalent of tributyl stannane. Finally, the required cyclohexadiene radical precursor would be prepared starting from a simple aromatic precursor **8** by an alkylative Birch reduction.



Scheme 2.

The desired precursor for the amidyl radical cyclisation was synthesised as shown in Scheme 3. Birch reduction and alkylation of ester **8** with *tert*-butylbromoacetate formed cyclohexadiene **9**. Numerous conditions for the cleavage of the *tert*-butyl ester also resulted in destruction of the enol ether. Finally, TMSOTf and 2,6-lutidine cleanly provided the required acid **10**, which was coupled to chloroallyl hydroxylamine **11** using EDC, followed by benzoylation to give hydroxamic benzoate **12**. However, we were disappointed to find that when **12** was treated with tributyltin hydride and 1,1′-azobis(cyclohexanecarbonitrile) (ACCN) in refluxing α,α,α-trifluorotoluene



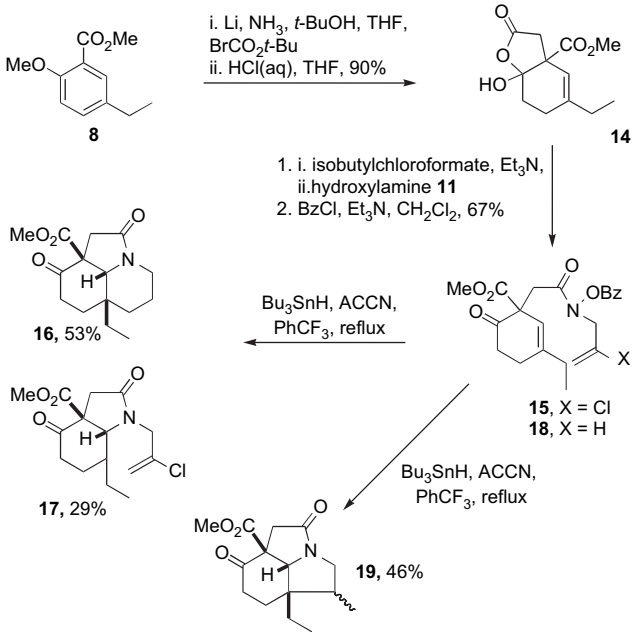
Scheme 3.

(a useful replacement for benzene), no amidyl radical cyclisation to give compound **6** took place: aromatisation occurred instead to give benzoate ester **8**. Thus, ironically, the key radical cyclisation just removed, in one fell swoop, the side chain we had painstakingly attached. Presumably, this is the result of abstraction of a doubly allylic hydrogen by a tributyltin radical or by radicals derived from the initiator to give cyclohexadienyl radical **13**, which aromatises through C–C bond scission. Such fragmentations are well precedented in the literature and have been exploited in ingenious radical sequences.[8]

Our wish to keep the enol ether group as a masked ketone in the cyclisation product **6** stemmed from the subsequent need to reduce the lactam carbonyl selectively in order to attain Stork's intermediate **5**. However, the unexpected and untoward fragmentation mentioned above thwarted our initial plans. We were therefore forced to hydrolyse the methyl enol ether first, in order to prevent the undesired abstraction of a doubly allylic hydrogen and subsequent fragmentation from occurring. As for the hurdle of the later reduction step, we hoped to overcome it by exploiting the presence of the methyl ester to sterically shield the ketone and allow perhaps the selective reduction of the lactam.

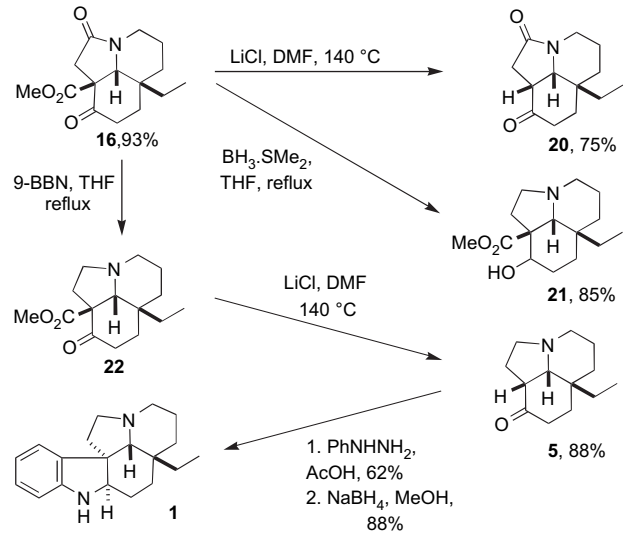
By treating the crude Birch reduction product with aqueous hydrochloric acid in THF, deprotection of both the *tert*-butyl ester and methyl enol ether groups readily took place to give the carboxylic acid, which existed mostly in the lactol form **14** (Scheme 4). This compound was converted into the new benzoate ester radical precursor **15** by the same procedure as above. Pleasingly, the amidyl radical formed upon treatment of **15** with tributyltin hydride and ACCN underwent 5-*exo* cyclisation in useful yield. The major product of the reaction was

tricycle **16**, where the desired 6-*endo* cyclisation had followed. The minor product (29%) was the monocyclised derivative **17**. It is interesting to note that, under the same conditions, analogue **18**, lacking a chlorine atom, suffered two consecutive 5-*exo* ring closures to furnish derivative **19** with a pyrrolizidine structure in 46% yield. The chlorine substituent is therefore necessary for regiocontrol.



Scheme 4.

Tricycle **16** could be decarboxylated with lithium chloride in DMSO to give tricyclic ketone **20** (Scheme 5), which has previously been converted into aspidospermidine[1a,q,w] in a sequence requiring protection of the ketone for reduction of the amide, and then subsequent Fischer indole reaction. However, as mentioned above, we hoped that the ester in **16** would provide sufficient steric shielding of the ketone group to allow selective reduction of the lactam. In case of success, this will result in a shorter and better synthesis of the target alkaloid.

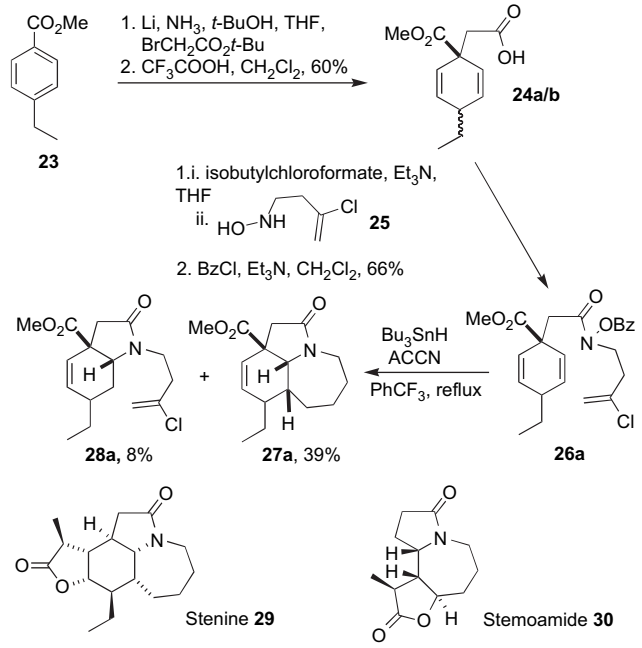


Scheme 5.

Treatment with borane–dimethylsulfide complex gave only the undesired alcohol **21**, the product of reduction of both the lactam and the ketone (Scheme 5). In contrast, the much bulkier 9-BBN cleanly and selectively effected the reduction of the lactam to give tricyclic ketoester **22** in 93% yield.[9] Finally, decarboxylation of the β-keto ester supplied Stork's intermediate **5**, which was converted into aspidosperidine **1** through a Fischer indole reaction with phenyl hydrazine followed by sodium borohydride reduction.

The cascade starting with amidyl radicals thus provides access to both indolizidine and pyrrolizidine skeletons by a 5-*exo* cyclisation followed by either a 5-*exo* or 6-*endo* cyclisation. This second cyclisation is directed 6-*endo* versus 5-*exo* by the presence or absence of the chlorine on the alkene. An extension of this work would be to investigate the analogous system involving 5-*exo* followed by 7-*endo* cyclisation, which would generate the 5,7 system found in the *Stemona* alkaloids.

The precursor for the desired radical cascade, benzoate **26a**, was prepared in a similar way to cyclohexadiene **9**, used above in the synthesis of aspidospermidine. Thus, Birch reduction and alkylation of methyl *p*-ethyl benzoate **23** followed by hydrolysis of the *tert*-butylester gave an equal mixture of two diastereomeric acids **24a/b**, which could be separated by crystallisation of their benzylamine salts, even though the relative stereochemistry of each could not be determined by NOE experiments (Scheme 6). Coupling of one of these diastereomers with homoallyl hydroxylamine **25** and treatment with benzoyl chloride provided radical precursor **26a**. Upon treatment of this compound with tributyltin hydride and ACCN, a relatively clean reaction ensued to give **27a** as the major product along with lesser amounts of bicyclic derivative **28a**.

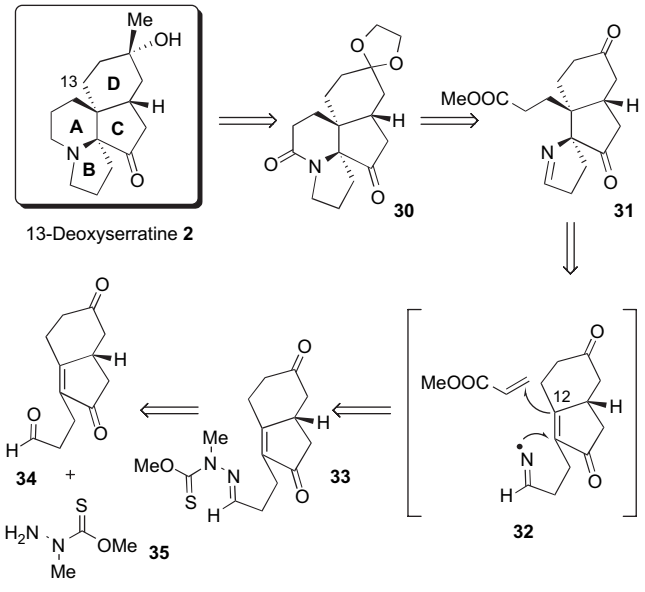


Scheme 6.

It is thus possible to accomplish a 5-*exo* followed by 7-*endo* cyclisation and to assemble three of the four rings of stenine, **29**, in only four steps from methyl *p*-ethyl benzoate **23**. Only one isomer was obtained in the cyclisation and is very likely that indicated for **27a** in Scheme 6, according to molecular models, but this has not been totally ascertained yet. Another example of a stemona alkaloid, stemonamide **30**, is displayed in the same scheme.

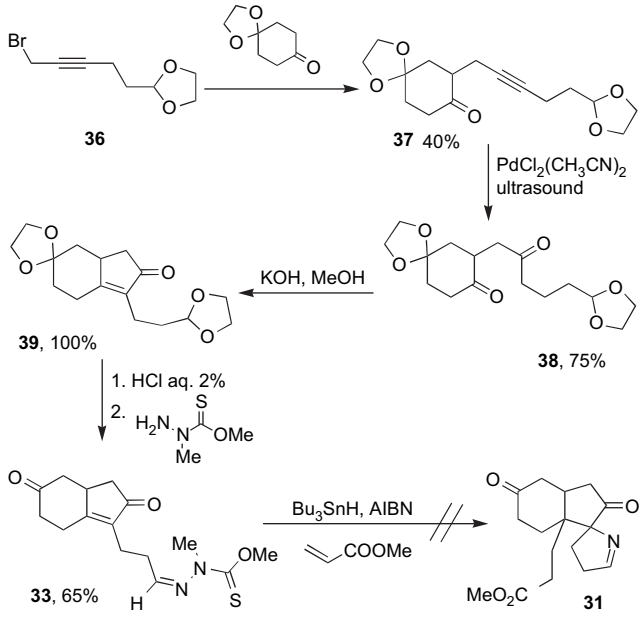
The second target that we explored belongs to the *Lycopodium* alkaloids,[10] a family with a fascinating structural complexity that has yielded challenging synthetic targets in recent years. In the serratinane subgroup, with the exception of (±)-serratinine **4**,[11] and the corresponding 8-deoxy derivative,[12] each of which has previously been synthesised by a long and low yielding route, not much attention has been paid to other alkaloids of this structural family. So far, only one approach to serratine **3**[10,13] has been reported by Livinghouse and co-workers.[14]

In principle, the indolizidine framework of serratine **3** could also be constructed by a cascade of radical cyclisations starting with a nitrogen centred radical. In the first instance, however, we aimed for the slightly less complex (±)-13-deoxyserratine **2**. Our initial synthetic plan towards 13-deoxyserratine is outlined in Scheme 7 and relies on the obtention of lactam **30** by cyclisation of tricyclic ester **31** upon selective reduction of the imine group. The formation of intermediate **31** would result from ring closure of iminyl radical **32** and capture of the ensuing carbon radical at C-12 with methyl acrylate. We had shown that such sequences were indeed possible on simpler structures.[2a] The iminyl radical would be generated from the thiosemicarbazone precursor **33**, itself made by simple condensation of hydrazide **35** with aldehyde **34**.[3k,l]



Scheme 7.

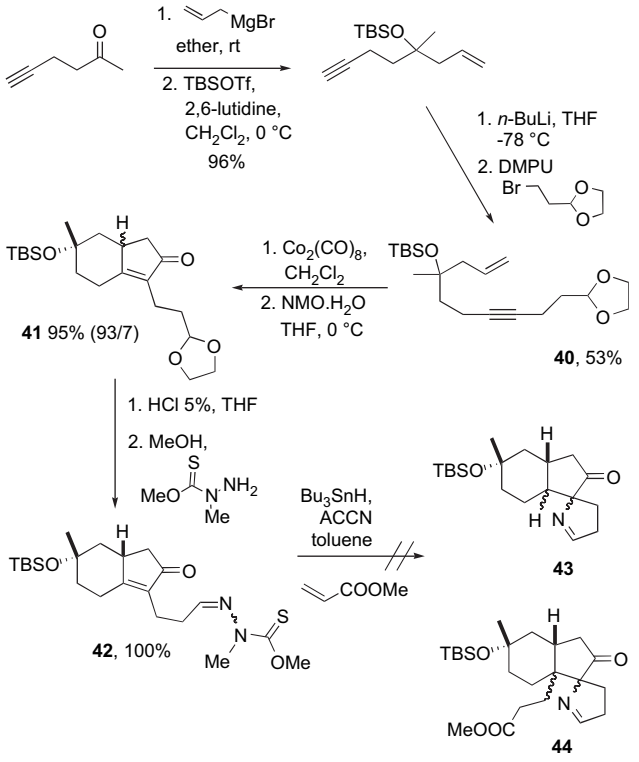
For the synthesis of hydrazone **33**, we followed the classical approach depicted in Scheme 8. Thus, alkylation of mono-protected 1,4-cyclohexanedione with known[15] propargyl bromide **36** gave keto-alkyne **37** in modest yield. Palladium catalysed regioselective hydration of the triple bond[16] delivered smoothly diketone **38**, which was subjected to a Robinson type annelation using methanolic potassium hydroxide to provide cyclopentenone **39** in quantitative yield. Acid hydrolysis of the acetal group furnished intermediate aldehyde **34**. This was not isolated but condensed in situ with hydrazide **35** to give iminyl radical precursor **33** in 65% yield. Unfortunately, all our attempts to induce ring closure and capture with methyl acrylate using the usual stannane techniques met with complete failure. No evidence even for occurrence of the first cyclisation step could be adduced by spectroscopic analysis of the crude reaction mixtures.



Scheme 8.

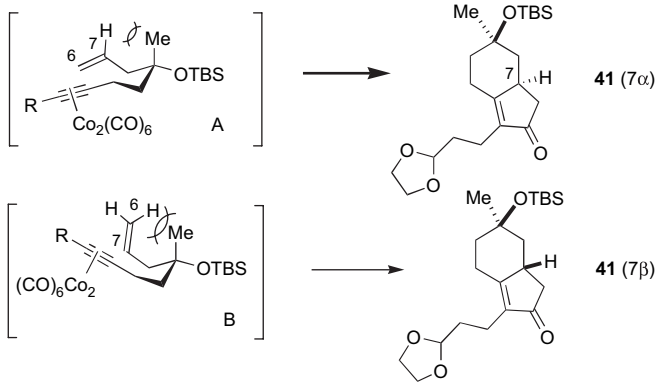
In parallel, we examined a far more efficient three-step route to an advanced precursor exploiting the formidable Pauson–Khand reaction.[17] This second synthetic plan is summarised in Scheme 9. Thus, enyne **40**, made in two trivial steps from 1-hexyn-5-one, underwent smooth conversion into cyclopentenone **41**, after treatment of the intermediate alkyne–cobalt complex with *N*-methyl morpholine *N*-oxide.[18] The formation of 5/6 ring combination, as compared with bicyclic 5/5 systems, is relatively uncommon using the Pauson–Khand reaction.[17] The high efficiency in our case is presumably the result of a favourable Thorpe–Ingold effect exerted by the substituents on the carbon bearing the protected tertiary alcohol.

The high diastereoselectivity (93/7) observed in the Pauson–Khand reaction, as determined by analysis of the ^{1}H NMR spectra, may be explained by considering the relative stability of the intermediates leading to **41** (7α) and **41** (7β), in the light of earlier studies in the literature.[19] The preferred conformers for the alkyne–$Co(CO)_6$ complex can be regarded as **A** and **B**, in which the TBSO group points in a pseudo-equatorial position. A weaker repulsion between H(7) and the axial-like methyl group would be expected in conformer **A**,



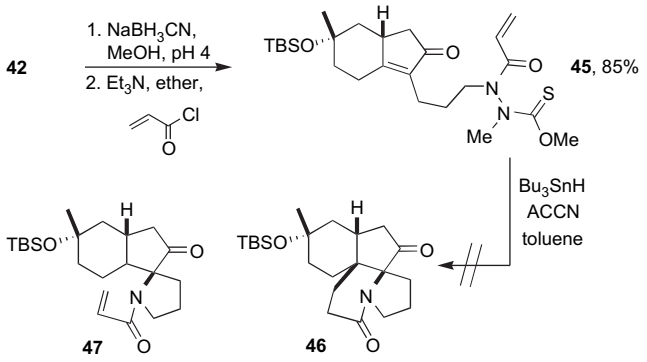
Scheme 9.

in comparison with the one between H(6) and the axial-like methyl group in conformer **B**, thus favouring cyclisation through conformer **A** (Scheme 10).



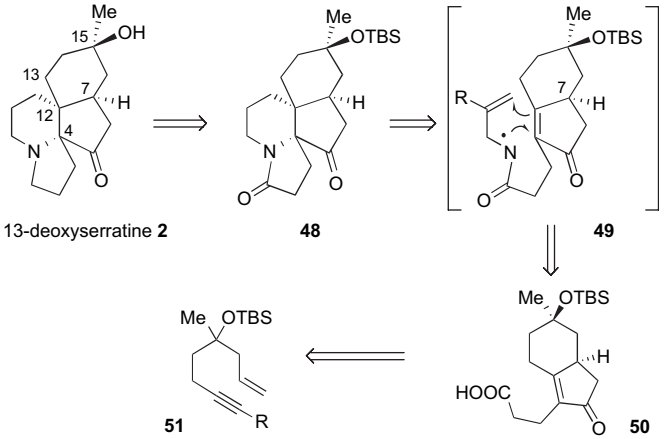
Scheme 10.

The major isomer **41** (7α) was easily converted into thiosemicarbazone **42** in quantitative yield. However, we were again disappointed to find that slow addition of tributyl stannane to a mixture of **42** and methyl acrylate did not accomplish the desired transformation and no cyclic imine **43** or **44** could be detected. Faced with this second setback, we decided to try starting with an amidyl radical and to render intramolecular the second ring closure. To this end, thiosemicarbazone **42** was reduced with sodium cyanoborohydride under mildly acidic conditions and the intermediate hydrazide acylated with acryloyl chloride to furnish **45** in good overall yield (Scheme 11). In this case, too, treatment with stannane did not provide the desired tetracyclic compound **46** or even tricyclic derivative **47**.



Scheme 11.

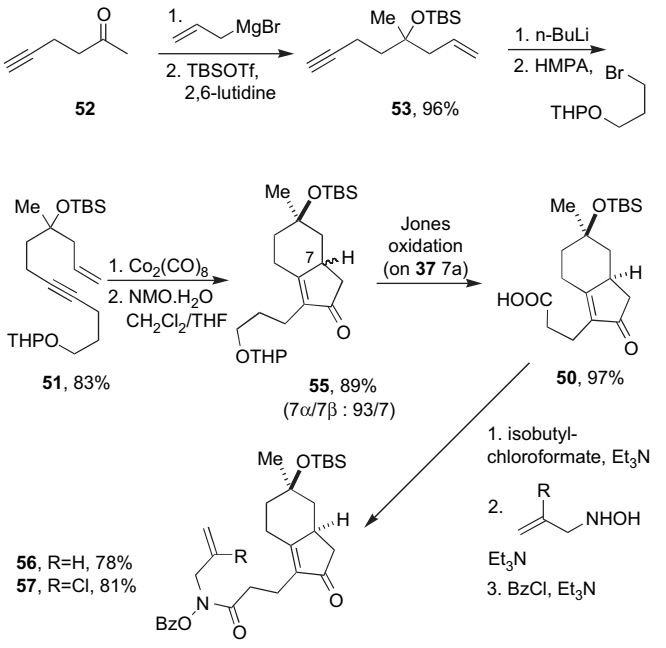
In the final attempt to access our elusive target, we considered accelerating the ring closure of the amidyl radical by placing the carbonyl group inside the ring being formed (cf. **49** in Scheme 12) instead of outside as in the last approach. The former variant was shown by Newcomb and colleagues to cyclise at least one order of magnitude faster.[20] To access the corresponding amidyl radical, however, it proved easier to prepare the hydroxamic acid benzoate precursor, as for aspidospermidine, rather than the thiosemicarbazide methodology we had been using so far. Our synthetic plan, outlined in Scheme 12, hinges on two key steps allowing the stereocontrolled introduction of the four stereogenic centres at C(4), C(7), C(12) and C(15). The same diastereoselective Pauson–Khand reaction[17] would allow an easy access to the key bicyclo [4.3.0] nonenone intermediate **50** starting from the very simple enyne **51**. The concave shape of this molecule would then control the stereochemistry in the cascade sequence involving amidyl radical **49** to give keto-lactam **48** and thence (±)-13-deoxyserratine **2**.



Scheme 12.

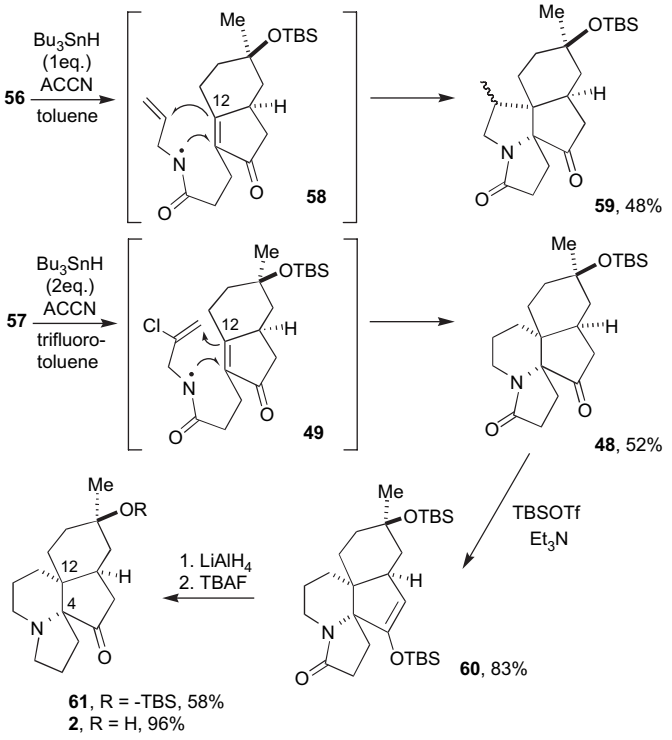
Practically, this was achieved by the reaction sequence pictured in Scheme 13: 4-hexyne-2-one **52** was alkylated with allylmagnesium bromide and the resulting tertiary alcohol

protected as the silyl ether alkyne **53** in 96% yield using *tert*-butyldimethylsilyl trifluoromethanesulfonate. Subsequent deprotonation with *n*-BuLi followed by alkylation with 2-(3-bromopropoxy)tetrahydro-2*H*-pyran furnished precursor **51** for the Pauson–Khand reaction. Exposure of the alkyne–$Co(CO)_6$ complex derived from **51** with *N*-methyl morpholine oxide hydrate[18] resulted in a rapid conversion into the desired bicyclo [4.3.0] nonenone **55** in 89% isolated yield, as a 93:7 mixture of epimers at the level of C-7. Submitting the major isomer to Jones oxidation finally led to the formation of the key intermediate acid **50** (64% overall from **52**).



Scheme 13.

The synthesis of the corresponding *O*-benzoyl *N*-allyl- and *N*-2-chloroallyl-hydroxamic acids, **56** and **57**, was accomplished in the same manner as for the aspidospermidine precursors without isolation of the intermediates. Slow addition of Bu_3SnH and ACCN to a refluxing solution of **56** in toluene furnished the undesired pyrrolizidine structure **59** in 48% yield via a 5-*exo*/5-*exo* cyclisation cascade starting with radical **58** (Scheme 14). This result was not unexpected, but we were nevertheless hoping that steric hindrance around the tertiary radical, derived from the first 5-*exo* cyclisation and localised at C-12, would favour a subsequent 6-*endo* mode without the need to place a directing chlorine atom on the allylic side chain of the hydroxylamine moiety. In contrast, treatment of the chlorinated analogue **57** with 2 equiv of Bu_3SnH in α,α,α-trifluorotoluene under dilute conditions indeed resulted in the formation of the desired indolizidinone **48** as the major product (52%) possessing the correct serratine skeleton (Scheme 14). To complete the synthesis, it was necessary to reduce the lactam without affecting the more reactive ketone. Various reagents that could possibly accomplish this task directly were tried but with little success. The ketone was therefore protected as a *tert*-butyldimethylsilyl-enol-ether **60** and the lactam moiety then reduced with $LiAlH_4$.[21] Finally, deprotection of both the alcohol and ketone using TBAF provided (±)-13-deoxyserratine **2** in 48% yield for the last three steps.



Scheme 14.

We thus have in hand a concise (10 steps) and efficient (12% overall yield) synthesis of (±)-13-deoxyserratine **2**. It is worth stressing that the use of an amidyl radical intermediate has allowed us to create *in one step* the two adjacent quaternary centres at C(4) and C(12) with the correct relative stereochemistry. The presence of these centres in serratine and related alkaloids such as serratinine has considerably hampered previous approaches. The concise access to both (±)-aspidospermidine **1** and (±)-13-deoxyserratine **2** showcases the considerable potential for nitrogen centred radicals for the total synthesis of various families of alkaloids.

3. Experimental

3.1. General conditions

All reactions were carried out under an inert atmosphere. Commercial reagents were used as-received without further purification. All products were purified by using silica gel (SDS, Silice 60 A. C. C. 40–63 μm) or by crystallisation. Analytical TLC was carried out on Merck silica gel plates using short wave (254 nm) UV light, 1% aq $KMnO_4$ solution to visualise components. NMR spectra were recorded in $CDCl_3$ using a Bruker AMX400 operating at 400 MHz for ^1H and 100 MHz for ^{13}C. The chemical shifts are expressed in parts per million (ppm) referenced to residual chloroform. ^1H NMR data are reported as follows: δ, chemical shift; multiplicity (recorded as: s,

singlet; br s, broad singlet; d, doublet; t, triplet; q, quadruplet; qt, quintuplet; ht, heptuplet; dd, double doublet; ddd, double double doublet; dddd, double double double doublet; dt, double triplet; ddt, double double triplet; dq, double quadruplet; tt, triple triplet; td; triple doublet; tdd, triple double doublet; m, multiplet), coupling constants (*J* are given in hertz, Hz) and integration. Infrared absorption spectra were recorded as thin films or as solutions in CCl_4 with a Perkin–Elmer 1600 Fourier Transform Spectrophotometer. Mass spectra were recorded with an HP 5989B mass spectrometer via direct introduction for chemical positive ionisation (CI) using ammonia as the reagent gas. Melting points were determined by Reichert microscope apparatus and were uncorrected. HRMS were performed on JEOL JMS-GcMate II, GC/MS system spectrometer. Microanalyses were performed by the Service de Microanalyse, Institut de Chimie des Substances Naturelles, CNRS, F-91198, Gif-sur-Yvette.

3.1.1. Methyl 5-ethyl-2-methoxybenzoate (**8**)

To a solution of methyl 5-ethyl-2-hydroxybenzoate (1.8 g, 10 mmol) in acetone (50 mL) at room temperature were added potassium carbonate (2 g, 15 mmol) and methyl iodide (1.3 mL, 20 mmol). After 6 h, the reaction mixture was concentrated then diluted with diethyl ether and water. The organic phase was separated and the aqueous phase was extracted with diethyl ether. The combined organic phases were dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. The residue was purified by flash chromatography (1:9 ethyl acetate/hexanes) to yield the title compound as a colourless oil (1.65 g, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, d, J=2.8 Hz), 7.23 (1H, dd, J=6.2, 2.8 Hz), 6.80 (1H, d, J=6.2 Hz), 3.84 (6H, s), 2.63 (2H, q, J=7.4 Hz), 1.32 (3H, t, J=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 158.6, 133.2, 131.8, 130.1, 113.8, 113.5, 56.4, 52.4, 33.6, 15.2; IR (thin film) ν_{max} 3027, 2940, 1680, 1437, 1260, 1102 cm^{-1}; MS (CI): *m*/z (%) 195 $[M+H]^+$, 212 $[M+NH_3]^+$; HRMS (EI) calcd for $C_{11}H_{14}O_3$ $[M]^+$ 194.0943, found 194.0937.

3.1.2. (±)-Methyl 5-ethyl-2-methoxy-1-(tert-butoxycarbonylmethyl)cyclohexa-2,5-diene carboxylate (**9**)

To a solution of the ester **8** (5.0 g, 25.6 mmol) in THF (8.8 mL), *tert*-butanol (2.1 mL) and ammonia (250 mL) at −40 °C was added lithium (448 mg, 74 mmol, 3 equiv). A permanent blue colour resulted and after 5 min, *tert*-butylbromoacetate (7.3 mL, 49.4 mmol, 1.9 equiv) was added slowly. After a further 5 min the ammonia was allowed to evaporate at room temperature. The residue was neutralised with 2 M HCl and the aqueous layer was extracted with diethyl ether. The combined organic phases were dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. The residue was purified by flash chromatography (1:5 diethyl ether/hexanes) to yield the title compound **9** as a colourless oil (5.36 g, 21.8 mmol, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33–5.31 (1H, m), 4.81 (1H, t, J=3.5 Hz), 3.64 (3H, s), 3.52 (3H, s), 2.80–2.72 (3H, m), 2.67 (1H, dd, J=22.0, 3.7 Hz), 2.01 (2H, qd, J=7.9, 3.5 Hz), 1.34 (9H, s), 1.00 (3H, t, J=7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 169.9, 152.3, 139.4, 119.2, 93.5, 79.8, 54.4, 52.5, 50.9, 41.9, 29.5, 28.9, 27.9, 12.0; IR (thin film) ν_{max} 3040, 2951, 1752, 1739, 1638, 1392, 1208, 1093 cm^{-1}; MS (CI): *m*/z (%) 311 $[M+H]^+$, 328 $[M+NH_3]^+$; HRMS (EI) calcd for $C_{17}H_{26}O_5$ $[M]^+$ 310.1780, found 310.1793.

3.1.3. (±)-2-(1-(Methoxycarbonyl)-5-ethyl-2-methoxycyclohexa-2,5-dienyl)acetic acid (**10**)

To a solution of the *tert*-butyl ester **9** (438 mg, 1.5 mmol) in dichloromethane (15 mL) at 0 °C was added 2,6-lutidine (700 μL, 3.2 mmol) and trimethylsilyltrifluoromethanesulfonate (700 μL, 3.4 mmol). After 1 h, water was added, the aqueous phase was acidified and extracted with dichloromethane. The combined organic phases were dried over anhydrous magnesium sulfate and the solvent was removed in vacuo to leave acid **10** as a colourless oil (372 mg, 98%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.2 (1H, br s), 5.40–5.36 (1H, m), 4.85 (1H, t, J=3.5 Hz), 3.69 (3H, s), 3.55 (3H, s), 3.01 (1H, d, J=14.9 Hz), 2.82 (1H, d, J=14.9 Hz), 2.77 (2H, s), 2.07 (2H, qd, J=7.3, 3.5 Hz), 1.03 (3H, t, J=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 157.1, 139.5, 131.1, 119.4, 93.5, 65.7, 54.6, 51.6, 41.7, 29.0, 27.6, 11.3; IR (thin film) ν_{max} 3051, 2936, 1746, 1692, 1408, 1361, 1207, 1104 cm^{-1}; MS (CI): *m*/z (%) 255 $[M+H]^+$, 272 $[M+NH_3]^+$; HRMS (EI) calcd for $C_{13}H_{18}O_5$ $[M]^+$ 254.1154, found 254.1142.

3.1.4. (±)-Methyl 1-[(N-2-chloroallyl-N-benzyloxycarbomoyl)methyl]-5-ethyl-2-methoxy-cyclohexa-2,5-diene carboxylate (**12**)

A solution of the acid **10** (960 mg, 4.02 mmol) and *N*-(2-chloroallyl) hydroxylammonium trifluoroacetate[22] (1.83 g) in THF (18 mL) and water (18 mL) was adjusted to pH 5. EDC (1.30 g, 6.78 mmol, 1.7 equiv) was added, and the resulting mixture was stirred at room temperature for 2 h. The mixture was diluted with diethyl ether, the aqueous phase was separated and extracted with diethyl ether, and the combined organic extracts were washed with water. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. The residue was purified by flash chromatography (1:5 diethyl ether/hexanes) to yield the hydroxylamine (960 mg, 2.79 mmol, 69%). This hydroxylamine (800 mg, 2.33 mmol) was dissolved in dichloromethane (44 mL), and triethylamine (3.3 mL, 20 mmol, 10 equiv) and benzoyl chloride (1.16 mL, 10 mmol, 4.3 equiv) were added at room temperature. The mixture was stirred at room temperature for 15 min then was washed with water. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. The residue was purified by flash chromatography (3:7 diethyl ether/hexanes) to yield the title compound **12** as a colourless oil (810 mg, 1.88 mmol, 81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (2H, d, J=7.2 Hz), 7.66 (1H, t, J=7.2 Hz), 7.51 (2H, t, J=7.6 Hz), 5.53 (1H, s), 5.43 (1H, s), 5.37 (1H, s), 4.84 (1H, s), 4.64 (1H, d, J=16.4 Hz), 4.50 (1H, d, J=16.4 Hz), 3.67 (3H, s), 3.50 (3H, s), 3.20 (1H, d, J=15.6 Hz), 2.85–2.74 (3H, m), 2.07 (2H, q, J=7.6 Hz), 1.04 (3H, t, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 170.8, 164.1, 152.1, 139.5, 135.5, 134.4, 130.1 (2 aromatic

C+1C), 128.8, 119.3, 115.4, 94.0, 54.6, 53.3, 52.6, 50.3, 37.8, 29.2 (2C), 12.1; IR (thin film) ν_{max} 2963, 1766, 1735, 1640, 1452, 1219 cm^{-1}; MS (CI): *m*/z (%) 448 $[M+H]^+$.

3.1.5. Methyl 5-ethyl-2,3,3a,6,7,7a-hexahydro-7a-hydroxy-2-oxobenzofuran-3a-carboxylate (**14**)

To a solution of the ester **8** (3.00 g, 15.4 mmol) in ammonia (150 mL), THF (5.3 mL) and *tert*-butanol (1.3 mL) at −40 °C was added lithium (270 mg, 44.8 mmol, 3 equiv). A permanent blue colour resulted and after 5 min, *tert*-butylbromoacetate (7.3 mL, 49.4 mmol, 3.2 equiv) was added slowly. After a further 5 min, ammonia was allowed to evaporate at room temperature, then THF (100 mL) and hydrochloric acid (2 M, 100 mL) were added. The reaction mixture was stirred for an additional 2 h, then hydrochloric acid (6 M, 50 mL) was added. After a further 4 h, the reaction mixture was diluted with water and diethyl ether. The organic phase was separated, the aqueous phase was extracted with diethyl ether and the combined organic extracts were dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the residue was purified by flash chromatography (1:1 diethyl ether/hexanes) to provide the title compound **14** as a colourless oil (3.31 g, 13.9 mmol, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (1H, s), 3.72 (3H, s), 3.47 (1H, d, *J*=17.2 Hz), 2.48 (1H, d, *J*=17.2 Hz), 2.38−2.08 (4H, m), 2.02 (2H, q, *J*=7.2 Hz), 0.98 (3H, t, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 170.9, 143.4, 118.4, 54.8, 52.9, 38.2, 29.7, 26.0, 11.8 (two quaternary C could not be observed); IR (thin film) ν_{max} 3409, 2965, 1769, 1738, 1434, 1281, 1238 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{16}O_5$ $[M]^+$ 240.0978, found 240.1002.

3.1.6. Synthesis of radical precursor (**15**)

To a solution of the acid **14** (200 mg, 0.84 mmol) in THF (11 mL) at 0 °C were added triethylamine (146 μL, 1.04 mmol, 1.2 equiv) and isobutylchloroformate (125 μL, 0.96 mmol, 1.1 equiv). The reaction mixture was stirred for 15 min, then additional triethylamine (282 μL, 2.00 mmol, 2.4 equiv) was added followed by a solution of *N*-(2-chloroallyl) hydroxylammonium trifluoroacetate[22] (400 mg) in THF (2 mL). After 2 h the reaction mixture was diluted with diethyl ether and was washed with 2 M hydrochloric acid. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. The residue was dissolved in dichloromethane (7 mL), and triethylamine (490 μL, 3.48 mmol, 4.4 equiv) and benzoyl chloride (300 μL, 2.59 mmol, 3 equiv) were added. After 15 min, the reaction mixture was washed with water and the organic phase was separated and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the residue was purified by flash chromatography (3:10 diethyl ether/hexanes) to provide the title compound **15** as a colourless oil (255 mg, 0.56 mmol, 67%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (2H, d, *J*=7.6 Hz), 7.56 (1H, t, *J*=7.2 Hz), 7.49 (2H, t, *J*=7.6 Hz), 5.42 (1H, s), 5.36 (1H, s), 5.32 (1H, s), 4.56 (1H, d, *J*=16.4 Hz), 4.47 (1H, d, *J*=16.4 Hz), 3.63 (3H, s), 3.18 (1H, d, *J*=17.2 Hz), 3.03 (1H, d, *J*=17.2 Hz), 2.85−2.76 (1H, m), 2.64−2.56 (1H, m), 2.55−2.48 (1H, m), 2.46−2.38 (1H, m), 2.09 (2H, q, *J*=7.6 Hz), 1.01 (3H, t, *J*=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 170.7, 170.5, 163.9, 144.3, 135.0, 134.6, 130.0, 128.8, 126.2, 119.8, 115.6, 56.5, 53.2, 52.7, 38.0, 37.2, 30.0, 28.5, 11.9; IR (thin film) ν_{max} 2965, 1767, 1739, 1717, 1688, 1452, 1434, 1228 cm^{-1}; MS (CI): *m*/z (%) 434 $[M+H]^+$, 451 $[M+NH_3]^+$.

3.1.7. Methyl 6a-ethyl-nonahydro-2,9-dioxo-1H-pyrrolo[3,2,1-ij]quinoline-9a-carboxylate (**16**)

To a degassed solution of **15** (120 mg, 0.20 mmol) in trifluorotoluene (5 mL) was added a solution of tributyltin hydride (126 μL, 0.46 mmol, 2.3 equiv) and ACCN (10 mg, 0.041 mmol, 0.02 equiv) in trifluorotoluene (5 mL) over a period of 12 h. The solvent was removed in vacuo and the residue was purified by flash chromatography (diethyl ether) to provide the tricycle **16** as a colourless oil (35 mg, 0.106 mmol, 53%) and the bicycle **17** as a colourless oil (18 mg, 0.057 mmol, 29%). Data for tricycle **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (1H, d, *J*=12.8 Hz), 3.82 (1H, d, *J*=2.4 Hz), 3.74 (3H, s), 3.14 (1H, d, *J*=17.2 Hz), 2.71 (1H, d, *J*=17.2 Hz), 2.63 (1H, ddd, *J*=16.4, 14.8, 6.4 Hz), 2.58−2.50 (1H, m), 2.42 (1H, ddd, *J*=16.4, 4.8, 2.4 Hz), 2.02 (1H, t, *J*=14.4, 4.8 Hz), 1.75 (1H, d, *J*=13.6 Hz), 1.65 (2H, qd, *J*=7.6, 7.6 Hz), 1.69−1.50 (3H, m), 1.38−1.30 (1H, m), 0.90 (3H, t, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4, 171.5, 171.5, 69.1, 57.4, 53.3, 40.7, 38.0, 34.9, 34.8, 32.9, 28.6, 24.8, 18.7, 6.8; IR (thin film) ν_{max} 2952, 1704, 1434 cm^{-1}; MS (CI): *m*/z (%) 280 $[M+H]^+$, 297 $[M+NH_3]^+$; HRMS (EI) calcd for $C_{15}H_{21}O_4N$ $[M]^+$ 279.1471, found 279.1464. Data for bicycle **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (1H, t, *J*=2.0 Hz), 5.00 (1H, t, *J*=2.0 Hz), 4.41 (1H, s), 4.32 (1H, d, *J*=16.0 Hz), 3.78 (3H, s), 3.68 (1H, d, *J*=16.0 Hz), 3.21 (1H, d, *J*=16.8 Hz), 3.10 (1H, d, *J*=16.8 Hz), 2.65 (1H, ddd, *J*=16.8, 8.4, 5.6 Hz), 2.33 (1H, ddd, *J*=16.8, 7.2, 4.8 Hz), 2.00−1.88 (3H, m), 1.71 (2H, dq, *J*=14.4, 7.6 Hz), 0.98 (3H, t, *J*=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 170.2, 169.4, 150.7, 108.2, 69.7, 59.7, 53.4, 46.5, 45.8, 41.0, 35.8, 31.6, 28.7, 8.4; IR (thin film) ν_{max} 2929, 1714, 1434, 1242 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{20}O_4NCl$ $[M]^+$ 313.1081, found 313.1074.

3.1.8. (±)-(4S,6aR)-6a-Ethyl-hexahydro-1H-pyrrolo-[3,2,1-ij]quinoline-2,9(9aH)-dione (**20**)

A solution of the ester **16** (10 mg, 0.036 mmol) and lithium chloride (3 mg, 0.072 mmol, 2 equiv) in DMF (145 μL) was heated to 140 °C overnight. The mixture was cooled, diluted with dichloromethane and was washed with water. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. The residue was purified by flash chromatography (6:4 diethyl ether/hexanes) and the title compound **20** was isolated as a colourless solid (6 mg, 0.027 mmol, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (1H, d, *J*=12.8 Hz), 3.42 (1H, dd, *J*=6.4, 2.0 Hz), 2.96 (1H, d, *J*=17.2 Hz), 2.88 (1H, dd, *J*=9.2, 6.4 Hz), 2.57−2.48 (1H, m), 2.47−2.31 (2H, m), 2.28 (1H, d, *J*=17.2 Hz), 2.01 (1H, td, *J*=13.6, 5.6 Hz), 1.90−1.80 (2H, m), 1.62−1.25 (5H, m), 0.97 (3H, t, *J*=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1,

174.5, 65.8, 42.5, 40.5, 35.4, 34.1, 33.0, 32.6, 29.2, 24.0, 18.8, 6.9; IR (thin film) ν_{max} 2952, 1704, 1434 cm^{-1}; MS (CI): *m*/z (%) 222 $[M+H]^+$, 239 $[M+NH_3]^+$; HRMS (EI) calcd for $C_{13}H_{19}O_2N$ $[M]^+$ 221.1416, found 221.1418.

3.1.9. (±)-(4R,6aR,9aS)-Methyl 6a-ethyl-nonahydro-9-hydroxy-1H-pyrrolo[3,2,1-ij]quinoline-9a-carboxylate (21)

To a solution of the lactam **16** (10 mg, 36 μmol) in THF (216 μL) was added borane–dimethylsulfide complex (36 μL, 2 M in THF, 72 μmol, 2 equiv). The reaction mixture was brought to reflux for 1 h, cooled and methanol was added. The solvent was removed in vacuo and the residue was purified by flash chromatography (1:1 diethyl ether/hexanes) to yield the title compound **21** as a colourless oil (8.2 mg, 30.7 μmol, 85%): ^1H NMR (400 MHz, $CDCl_3$) δ 3.70 (3H, s), 3.70–3.60 (1H, m), 3.17–3.10 (1H, m), 2.99 (1H, d, J=10.8 Hz), 2.30–2.20 (3H, m), 1.98–1.86 (2H, m), 1.86–1.77 (2H, m), 1.77–1.62 (2H, m), 1.50–1.37 (3H, m), 1.25 (1H, d, J=11.2 Hz), 1.10–0.98 (2H, m), 0.76 (3H, t, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 76.1, 74.3, 53.9, 53.3, 53.3, 51.7, 35.6, 33.1, 32.7, 29.6, 28.8, 26.6, 21.5, 7.0; IR (thin film) ν_{max} 3400, 2934, 1708, 1443 cm^{-1}; MS (CI): *m*/z (%) 268 $[M+H]^+$; HRMS (EI) calcd for $C_{15}H_{25}O_3N$ $[M]^+$ 267.1835, found 267.1828.

3.1.10. (±)-(4R,6aR,9aS)-Methyl 6a-ethyl-nonahydro-9-oxo-1H-pyrrolo[3,2,1-ij]quinoline-9a-carboxylate (22)

To a solution of the lactam **16** (35 mg, 0.106 mmol) in THF (500 μL) was added 9-BBN (464 μL, 0.5 M in THF, 0.23 mmol, 2.2 equiv) and the mixture was brought to reflux. After 1 h, the mixture was cooled, ethanolamine was added and the solvent was removed in vacuo. The residue was treated with hexane and the solid was filtered and washed with hexane. The filtrate was evaporated and the residue was purified by flash chromatography (3:7 diethyl ether/hexanes) to yield the title compound **22**, which was isolated as a colourless oil (26 mg, 0.098 mmol, 93%): ^1H NMR (400 MHz, $CDCl_3$) δ 3.71 (3H, s), 3.01 (2H, td, J=8.8, 2.8 Hz), 2.86–2.79 (1H, m), 2.72 (1H, td, J=14.4, 6.0 Hz), 2.49 (1H, s), 2.40–2.25 (2H, m), 2.23–2.16 (1H, m), 1.94–1.80 (2H, m), 1.72–1.60 (2H, m), 1.52–1.44 (2H, m), 1.40–1.10 (3H, m), 0.89 (3H, t, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 173.8, 77.2, 62.5, 53.2, 52.7, 52.6, 36.4, 35.8, 32.5, 29.8, 29.2, 27.3, 21.0, 7.1; IR (thin film) ν_{max} 2936, 1734, 1716, 1447 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{23}O_3N$ $[M]^+$ 265.1678, found 265.1673.

3.1.11. (±)-(4S,6aR)-6a-Ethyl-octahydro-9aH-pyrrolo[3,2,1-ij]quinolin-9-one (5)

A solution of the ester **22** (16 mg, 0.060 mmol) and lithium chloride (5 mg, 0.120 mmol, 2 equiv) in DMF (242 μL) was heated to 140 °C for 3 h. The mixture was cooled, diluted with dichloromethane and was washed with water. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. The residue was purified by flash chromatography (6:4 diethyl ether/hexanes) and the title compound **5** was isolated as a colourless oil (11 mg, 0.053 mmol, 88%): ^1H NMR (400 MHz, $CDCl_3$) δ 3.04–2.97 (2H, m), 2.66 (1H, ddd, J=9.2, 5.2, 2.0 Hz), 2.45–2.20 (3H, m), 1.98–1.85 (3H, m), 1.79 (1H, dd, J=10.8, 2.0 Hz), 1.76–1.57 (3H, m), 1.52–1.45 (2H, m), 1.37–1.26 (2H, m), 1.10 (1H, td, J=13.2, 4.4 Hz), 0.93 (3H, t, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 73.6, 53.3, 53.0, 48.2, 36.9, 34.8, 32.9, 30.3, 30.1, 26.1, 21.3, 7.2; IR (thin film) ν_{max} 2931, 1712, 1448 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{21}ON$ $[M]^+$ 207.1623, found 207.1614.

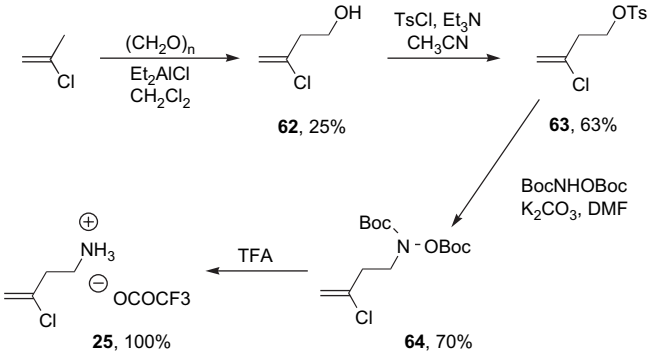
3.1.12. (±)-Dehydroaspidospermidine

The title compound was prepared according to the procedure of Gnecco et al.[6w] (±)-(4*S*,6a*R*)-6a-Ethyl-octahydro-9a*H*-pyrrolo[3,2,1-*ij*]quinolin-9-one **5** (8.0 mg, 39 μmol) was converted into the title compound (6.7 mg, 0.024 mmol, 62%). All spectral data corresponded to that quoted in Ref. 6w.

3.1.13. (±)-Aspidospermidine (1)

The title compound was prepared according to the procedure of Gnecco et al.[6w] Dehydroaspidospermidine (4.0 mg, 14 μmol) was converted into the title compound (3.4 mg, 12.3 μmol, 88%). All spectral data corresponded to that quoted in Ref. 6w.

The synthesis of hydroxylamine **25** follows the sequence in Scheme 15.



Scheme 15.

3.1.14. 3-Chlorobut-3-enol (62)

To a solution of paraformaldehyde (1.17 g) and 2-chloropropene (3 g, 2.70 mL, 39 mmol) in dichloromethane (94 mL) at 0 °C was added diethylaluminium chloride (39 mL, 1.0 M in hexanes, 39 mmol, 1 equiv). The reaction mixture was stirred overnight then was quenched by addition of saturated aqueous ammonium chloride. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The solvent was removed in vacuo and the residue was purified by flash chromatography (2:3 diethyl ether/hexanes) to yield 3-chlorobut-3-enol as a colourless oil (1.05 g, 9.9 mmol, 25%): ^1H NMR (400 MHz, $CDCl_3$) δ 5.24 (1H, d, J=0.8 Hz), 5.22 (1H, d, J=0.8 Hz), 3.79 (2H, t, J=6.0 Hz), 2.55 (2H, t, J=6.0 Hz), 2.36 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 114.5, 59.4, 42.2; IR (thin film) ν_{max} 3358, 2957, 1636 cm^{-1}; HRMS (EI) calcd for C_4H_7OCl $[M]^+$ 106.0186, found 106.0185.

*3.1.15. 3-Chlorobut-3-enyl-4-methylbenzenesulfonate (**63**)*

To a solution of 3-chlorobut-3-enol (1.05 g, 9.9 mmol) and DMAP (catalytic) in acetonitrile (9.9 mL) and triethylamine (2.0 mL) was added *p*-toluenesulfonyl chloride (2.79 g, 14.6 mmol, 1.5 equiv). The mixture was stirred at room temperature for 2 h, then was diluted with diethyl ether and washed with saturated aqueous sodium hydrogen carbonate then 2 M HCl. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. The residue was purified by flash chromatography (1:4 diethyl ether/hexanes) and the tosylate was isolated as a colourless oil (1.61 g, 6.2 mmol, 63%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (2H, d, J=8.0 Hz), 7.32 (2H, d, J=8.0 Hz), 5.19 (1H, s), 5.18 (1H, s), 4.17 (2H, t, J=6.4 Hz), 2.62 (2H, t, J=6.4 Hz), 2.41 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 136.6, 132.6, 129.9, 127.7, 115.4, 66.5, 38.4, 21.5; IR (thin film) ν_{max} 1637, 1598, 1360, 1177 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{13}O_3SCl$ $[M]^+$ 260.0274, found 260.0280.

*3.1.16. N-(3-Chloro-3-propenyl)[N,O-bis(tert-butyl-oxycarbonyl)] hydroxylamine (**64**)*

To a solution of the tosylate (1.61 g, 6.2 mmol) and *N*,*O*-bis-(*tert*-butyl-oxycarbonyl) hydroxylamine (1.45 g, 6.25 mmol) in DMF (6.4 mL) was added potassium carbonate (920 mg). The reaction mixture was stirred for 24 h, then was diluted with diethyl ether and was washed with water. The organic phase was separated and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the residue was purified by flash chromatography (1:9 diethyl ether/hexanes) to yield the title compound as a colourless oil (1.45 g, 4.36 mmol, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (1H, d, J=1.2 Hz), 5.20 (1H, d, J=1.2 Hz), 3.80 (2H, br s), 2.62 (2H, t, J=6.8 Hz), 1.50 (9H, s), 1.45 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 152.1, 138.9, 114.4, 84.9, 47.9, 36.9, 28.0, 27.5; IR (thin film) ν_{max} 2981, 1785, 1719, 1395, 1370 cm^{-1}; MS (CI): *m*/z (%) 322 $[M+H]^+$, 339 $[M+NH_3]^+$; HRMS (EI) calcd for $C_{14}H_{25}O_5NCl$ $[M+H]^+$ 322.1421, found 322.1431.

*3.1.17. N-(3-Chloro-3-propenyl)-hydroxylammonium trifluoroacetate (**25**)*

A solution of *N*-(3-chloro-3-propenyl)[*N*,*O*-bis(*tert*-butyl-oxycarbonyl)] hydroxylamine (740 mg, 2.3 mmol) in dichloromethane (4.4 mL) was treated with trifluoroacetic acid (1.89 mL). The reaction mixture was stirred at room temperature for 6 h, then the solvent was removed in vacuo to yield the title compound **25** as a colourless oil (550 mg, 2.3 mmol, 100%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (2H, s), 3.53 (2H, t, J=7.2 Hz), 2.84 (2H, t, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 116.9, 49.0, 33.1.

*3.1.18. 2-(1-(Methoxycarbonyl)-4-ethylcyclohexa-2,5-dienyl)acetic acid (**24a**/**b**)*

To a solution of methyl *p*-ethyl benzoate **23** (5.8 g, 0.035 mol) in ammonia (341 mL), THF (12 mL) and *t*-BuOH (2.86 mL) at −40 °C was added lithium (614 mg, 0.102 mol, 3 equiv). The mixture was stirred at the same temperature for 15 min, then *tert*-butylbromoacetate (16 mL, 0.108 mol, 3.1 equiv) was added. After a further 15 min, ammonia was allowed to evaporate, the residue was neutralised with 2 M HCl and the aqueous layer was extracted with diethyl ether. The combined organic phases were dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. The residue was dissolved in dichloromethane (50 mL) and was treated with trifluoroacetic acid (10 mL) at room temperature. After 2 h the solvent was removed and the title compound was purified by flash chromatography (3:10 diethyl ether/hexanes with 0.05% acetic acid) yielding the mixture of diastereomers **24a/b** (3.0 g, 0.0134 mol, 38%). The mixture of diastereomeric acids was dissolved in isopropanol and benzylamine (1.44 g, 1.46 mL, 1 equiv) was added. Crystallisation gave separation of the diastereomeric salts, which were dissolved in ethyl acetate and washed with 2 M HCl to recover the free acid. **24a**: ^{1}H NMR (400 MHz, C_6D_6) δ 5.94 (2H, dd, J=10.2, 2.0 Hz), 5.55 (2H, dd, J=10.2, 3.2 Hz), 3.35 (3H, s), 2.74 (2H, s), 2.49–2.44 (1H, m), 1.18 (2H, qd, J=7.6, 6.0 Hz), 0.68 (3H, t, J=7.6 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 177.2, 173.9, 131.2, 127.1, 52.5, 46.6, 45.3, 37.1, 28.2, 10.8; IR (thin film) ν_{max} 2962, 1732, 1434 cm^{-1}; MS (CI): *m*/z (%) 225 $[M+H]^+$, 242 $[M+NH_3]^+$, MS HRMS (EI) calcd for $C_{12}H_{15}O_4$ $[M-H]^+$ 223.0970, found 223.0970; **24b**: ^{1}H NMR (400 MHz, C_6D_6) δ 5.74–5.66 (4H, m), 3.58 (3H, s), 2.66 (2H, s), 2.57–2.52 (1H, m), 0.98 (2H, qd, J=7.6, 6.0 Hz), 0.48 (3H, t, J=7.6 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 175.9, 173.7, 131.1, 127.0, 53.5, 52.3, 46.5, 37.0, 28.4, 10.7; IR (thin film) ν_{max} 2962, 1731, 1434 cm^{-1}; MS (CI): *m*/z (%) 225 $[M+H]^+$, 242 $[M+NH_3]^+$; MS HRMS (EI) calcd for $C_{12}H_{16}O_4$ $[M]^+$ 224.1049, found 224.1060.

*3.1.19. Synthesis of radical precursor (**26a**)*

To a solution of the acid **24a** (35 mg, 0.16 mmol) in THF (2.2 mL) at 0 °C were added triethylamine (27.1 μL, 0.17 mmol, 1.1 equiv) and isobutylchloroformate (23.0 μL, 0.17 mmol, 1.1 equiv). The reaction mixture was stirred for 15 min, then additional triethylamine (52.4 μL, 0.33 mmol, 2.1 equiv) was added followed by a solution of the *N*-(3-chloro-3-butenyl) hydroxylammonium trifluoroacetate **25** (36 mg) in THF (2 mL). After 2 h, the reaction mixture was diluted with diethyl ether and was washed with 2 M hydrochloric acid. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. The residue was dissolved in dichloromethane (1.2 mL), and triethylamine (91.1 μL, 0.54 mmol, 3.4 equiv) and benzoyl chloride (56.1 μL, 0.40 mmol, 2.5 equiv) were added. After 15 min, the reaction mixture was washed with water and the organic phase was separated and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the residue was purified by flash chromatography (3:10 diethyl ether/hexanes) to provide the title compound **26a** as a colourless oil (36 mg, 0.083 mmol, 52%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (2H, d, J=7.6 Hz), 7.67 (1H, t, J=7.2 Hz), 7.52 (2H, t, J=7.6 Hz), 5.89–5.73 (4H, m), 5.26 (1H, s), 5.24 (1H, s), 4.02 (2H, t, J=6.4 Hz), 3.73 (3H, s), 2.67–2.60 (5H, m), 1.50–1.40 (2H, m), 0.83–0.75 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 170.6, 164.1, 139.1, 134.6, 130.8, 130.0,

129.8, 126.6, 126.5, 114.4, 52.6, 46.3, 45.7, 43.1, 38.6, 36.5, 27.7, 10.4; IR (thin film) ν_{max} 2962, 1766, 1727, 1684, 1451 cm^{-1}; MS (CI): *m*/z (%) 432 $[M+H]^+$, 468 $[M+NH_3]^+$.

3.1.20. (4R,7aR)-Methyl 10-ethyl-1,2,3,4,4,6,7,7a,10,10a-decahydro-6-oxoazepino[3,2,1-hi]indole-7a-carboxylate (**27a**)

To a degassed solution of **26a** (36 mg, 0.083 mmol) in trifluorotoluene (2 mL) was added a solution of tributyltin hydride (52.3 μL, 0.19 mmol, 2.3 equiv) and ACCN (4.1 mg, 0.017 mmol, 0.02 equiv) in trifluorotoluene (2 mL) over a period of 12 h. The solvent was removed in vacuo and the residue was purified by flash chromatography (diethyl ether) to provide the tricycle **27a** as a colourless oil (9 mg, 0.032 mmol, 39%) and the bicycle **28a** as a colourless oil (2 mg, 6.4 μmol, 8%). Data for tricycle **27a**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.74–5.68 (2H, m), 3.93 (1H, d, J=10.8 Hz), 3.88 (1H, ddd, J=11.2, 7.6, 5.2 Hz), 3.72 (3H, s), 3.09–3.02 (1H, m), 2.98 (1H, d, J=16.8 Hz), 2.48 (1H, d, J=16.8 Hz), 2.19 (1H, d, J=14.8 Hz), 2.05–1.87 (3H, m), 1.70–1.52 (3H, m), 1.30–1.23 (2H, m), 1.15–1.02 (1H, m), 0.85 (3H, t, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 172.3, 133.2, 125.7, 64.1, 53.0, 50.7, 42.5, 42.3, 41.4, 40.4, 33.3, 26.6, 25.3, 24.5, 9.3; IR (thin film) ν_{max} 2929, 1734, 1692, 1437 cm^{-1}; MS (CI): *m*/z (%) 278 $[M+H]^+$; HRMS (EI) calcd for $C_{16}H_{23}O_3N$ $[M]^+$ 277.1678, found 277.1667.

3.1.21. 4-Methyloct-1-en-7-yn-4-ol

To a solution of 5-hexyn-2-one **52** (2.28 g, 23.7 mmol) in dry ether under argon was added allylmagnesium bromide (1.0 M in ether, 26 mL, 26 mmol) and the reaction mixture was stirred at room temperature for 15 min. Saturated aqueous ammonium chloride was added and the mixture was extracted with ether. The combined organic layer was dried over magnesium sulfate, filtered and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, heptane–EtOAc, 90:10) to give the title compound (5.73 g, 96%) as a colourless oil: ^1H NMR (200 MHz, $CDCl_3$) δ 5.85 (1H, m), 5.14 (2H, m), 2.32 (2H, td, J=7.3, 2.5 Hz), 2.24 (2H, d, J=8.1 Hz), 1.98 (1H, t, J=2.5 Hz), 1.86 (1H, s), 1.74 (2H, t, J=7.3 Hz), 1.19 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 133.6, 119.1, 84.9, 71.9, 68.6, 46.5, 40.0, 26.4, 13.2; IR (thin film) ν_{max} 3405, 3304, 3076, 2976, 2929, 2117, 1639, 1438, 1376, 1115 cm^{-1}; MS (CI+ NH_3) *m/z* 156 (MNH_4^+), 138 ($M-OH+NH_3^+$), 121 ($M-OH^+$).

3.1.22. (1-Allyl-1-methyl-pent-4-ynyloxy)-tert-butyl-dimethyl-silane (**53**)

To a solution of 4-methyloct-1-en-7-yn-4-ol (1.55 g, 11.2 mmol) in dry dichloromethane under argon at 0 °C were added 2,6-lutidine (3.26 mL, 28.0 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (2.82 mL, 12.3 mmol) and the reaction mixture was stirred for 30 min. Aqueous 1.0 M HCl was added and the mixture was extracted with ether. The combined organic layer was dried over magnesium sulfate, filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, heptane) to give **53** (2.81 g, 100%) as a colourless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.80 (1H, m), 5.05 (2H, m), 2.26 (2H, td, J=8.2, 2.3 Hz), 2.22 (2H, d, J=7.6 Hz), 1.92 (1H, t, J=2.3 Hz), 1.71 (2H, m), 1.20 (3H, s), 0.87 (9H, s), 0.09 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7, 117.7, 85.3, 74.8, 67.8, 47.2, 41.2, 27.3, 26.0, 18.4, 13.3, −1.9; IR (CCl_4) ν_{max} 3313, 2955, 2929, 2856, 2120, 1640, 1472, 1375, 1254, 1125, 1081, 1042 cm^{-1}; MS (CI+ NH_3) *m/z* 253 (MH^+), 211, 138, 121. Anal. Calcd for $C_{15}H_{28}OSi$: C, 71.36; H, 11.18, found: C, 71.32; H, 11.22.

3.1.23. [1-Allyl-1-methyl-8-(tetrahydro-pyran-2-yloxy)-oct-4-ynyloxy]-tert-butyl-dimethyl-silane (**51**)

To a solution of **53** (1.0 g, 3.96 mmol) in dry THF under argon at −78 °C was added *n*-BuLi (1.53 M in hexanes, 2.84 mL, 4.35 mmol) and the reaction mixture was stirred for 30 min. HMPT (3.5 mL) was added and the mixture was slowly cooled to 0 °C. 2-(3-Bromo-propoxy)-tetrahydropyran was then added and the mixture was stirred for 1 h at 0 °C and 3 h at room temperature. Saturated aqueous ammonium chloride was added and the mixture was extracted with ether. The combined organic layer was dried over magnesium sulfate, filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, heptane–EtOAc, 95:5) to give **51** (1.29 g, 83%) as a colourless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.80 (1H, m), 5.03 (2H, m), 4.60 (1H, dd, J=2.9, 2.9 Hz), 3.90–3.74 (2H, m), 3.53–3.44 (2H, m), 2.20 (2H, d, J=7.6 Hz), 2.28–2.18 (4H, m), 1.77 (2H, t, J=6.4 Hz), 1.85–1.50 (8H, m), 1.18 (3H, s), 0.86 (9H, s), 0.08 (6H, s); ^{13}C NMR (250 MHz, $CDCl_3$) δ 134.8, 117.4, 98.8, 80.9, 79.0, 74.9, 66.1, 62.1, 47.1, 41.8, 30.8, 29.3, 27.3, 25.9, 25.6, 19.6, 18.3, 15.8, 13.5, −1.9; IR (neat) ν_{max} 3076, 2930, 2856, 1640, 1472, 1441, 1374, 1359, 1254, 1159, 1137, 1121, 1077, 1036 cm^{-1}; MS (CI+ NH_3) *m/z* 412 (MNH_4^+). Anal. Calcd for $C_{23}H_{42}O_3Si$: C, 70.00; H, 10.73, found: C, 70.29; H, 10.87.

3.1.24. 6-(tert-Butyl-dimethyl-silanyloxy)-6-methyl-3-[3-(tetrahydro-pyran-2-yloxy)-propyl]-1,4,5,6,7,7a-hexahydro-inden-2-one (**55**)

To a solution of **51** (560 mg, 1.42 mmol) in dichloromethane (7 mL) was added dicobalt octacarbonyl (533 mg, 1.56 mmol) and the black reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with dichloromethane (7 mL) and THF (14 mL), and 4-methylmorpholine *N*-oxide monohydrate (1.9 g, 14.2 mmol) was added. The solution was stirred at room temperature for 1 h, at which time the mixture has turned purple and no cobalt complex was visible by TLC. The mixture was filtered through Celite (washing solvent diethyl ether) and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, heptane–EtOAc, 90:10) to give major isomer **55** (497 mg, 83%) as a colourless oil.

55 (mixture of THP isomers): ^1H NMR (200 MHz, $CDCl_3$) δ 4.44 (1H, m), 3.80–3.70 (1H, m), 3.64–3.54 (1H, m),

3.42–3.34 (1H, m), 3.28–3.17 (1H, m), 2.91 (1H, dddd, J=12.6, 6.5, 5.2, 2.5 Hz), 2.68–2.42 (2H, m), 2.44 (1H, dd, J=18.5, 6.5 Hz), 2.16 (2H, br t, J=7.5 Hz), 2.01 (1H, ddd, J=12.6, 5.2, 2.5 Hz), 1.19 (3H, s), 1.88–1.21 (11H, m), 0.98 (1H, dd, J=12.6, 12.6 Hz), 0.85 (9H, s), 0.05 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.3, 176.2, 136.5, 98.7, 72.3, 66.7, (62.2, 62.3), 48.0, 40.9, 39.8, 35.6, 30.7, 30.2, 28.5, 25.9, 25.4, 24.1, (19.6, 19.7), 19.2, 18.3, −2.0; IR (neat) ν_{max} 2930, 2856, 1699, 1651, 1440, 1373, 1255, 1137, 1035 cm^{-1}; MS (CI+ NH_3) m/z 339 (M−THP+2H$^+$).

3.1.25. 3-[5-(tert-Butyl-dimethyl-silanyloxy)-5-methyl-2-oxo-3,3a,4,5,6,7-hexahydro-2H-inden-1-yl]-propionic acid (**50**)

To a solution of **55** in acetone (25 mL) at 0 °C was added Jones' solution (2.6 [Cr] M, 1.31 mL, 3.42 mmol) and the solution was stirred for 2 h. Water was added and the mixture extracted with dichloromethane. The organic layer was basified with 1.0 M NaOH until pH 9 and the aqueous layer was separated, acidified with 1.0 M HCl until pH 1 and extracted with ether. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, heptane–EtOAc, 50:50) to give **50** (390 mg, 97%) as a colourless oil, which crystallised with time as a white solid; mp 88–90 °C (heptane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (1H, br s), 3.01 (1H, dddd, J=12.9, 6.5, 5.3, 2.3 Hz), 2.71 (1H, ddd, J=14.0, 4.7, 2.3 Hz), 2.54 (1H, dd, J=18.8, 6.5 Hz), 2.55–2.45 (5H, m), 2.08 (1H, ddd, J=12.9, 5.3, 2.3 Hz), 1.87 (1H, dd, J=18.8, 2.3 Hz), 1.91 (1H, m), 1.33 (1H, ddd, J=13.5, 13.5, 4.7 Hz), 1.26 (3H, s), 1.06 (1H, dd, J=12.9, 12.9 Hz), 0.88 (9H, s), 0.12 (3H, s), 0.11 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1, 178.7, 178.3, 135.0, 72.4, 48.1, 41.0, 39.9, 36.1, 32.4, 30.2, 26.1, 24.4, 18.4, 18.1, −1.9, −2.0; IR (CCl_4) ν_{max} 2955, 2929, 2856, 1708, 1652, 1255, 1098, 1050, 1036 cm^{-1}; MS (CI+ NH_3) m/z 353 (MH$^+$). Anal. Calcd for $C_{19}H_{32}O_4Si$: C, 64.73; H, 9.15, found: C, 64.57; H, 9.13.

3.1.26. N-Benzoyloxy-3-[5-(tert-butyl-dimethyl-silanyloxy)-5-methyl-2-oxo-3,3a,4,5,6,7-hexahydro-2H-inden-1-yl]-N-(2-chloro-allyl)-propionamide (**57**)

To a solution of **50** (200 mg, 0.567 mmol) in THF under argon at 0 °C were added triethylamine (87 μL, 0.624 mmol) and isobutylchloroformate (81 μL, 0.624 mmol) and the reaction mixture was stirred for 10 min. Excess of triethylamine was added (2 mL) and a solution of *N*-(2-chloroallyl)-hydroxylamine (610 mg, 5.68 mmol) in THF was added. The reaction mixture was stirred for 10 min at 0 °C and 30 min at room temperature. Aqueous 1.0 M HCl was added and the mixture was extracted with ether. The separated organic layer was dried over magnesium sulfate, filtered and the solvents were removed under reduced pressure. The residue was taken up in dichloromethane and triethylamine (210 μL, 1.50 mmol) and benzoyl chloride (131 μL, 1.13 mmol) were added. The mixture was stirred for 1 h at room temperature. Water was then added and the mixture was extracted with ether. The separated organic layer was dried over magnesium sulfate, filtered and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, heptane–EtOAc, 85:15) to give **57** (250 mg, 81%) as a colourless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (2H, d, J=7.9 Hz), 7.65 (1H, t, J=7.9 Hz), 7.50 (2H, t, J=7.9 Hz), 5.38 (2H, d, J=9.2 Hz), 4.57 (2H, br s), 2.99 (1H, ddd, J=12.9, 6.5, 5.5 Hz), 2.79 (1H, ddd, J=13.8, 4.6, 2.1 Hz), 2.65–2.45 (5H, m), 2.50 (1H, dd, J=18.0, 6.5 Hz), 2.07 (1H, ddd, J=12.9, 5.5, 2.3 Hz), 1.90 (1H, m), 1.85 (1H, d, J=18.0 Hz), 1.36 (1H, ddd, J=13.4, 13.4, 4.6 Hz), 1.25 (3H, s), 1.09 (1H, dd, J=12.9, 12.9 Hz), 0.88 (9H, s), 0.12 (3H, s), 0.11 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.0, 178.0, 172.9, 164.2, 135.6, 134.9, 134.5, 130.1, 128.9, 126.5, 115.9, 72.4, 53.5, 47.9, 41.0, 39.8, 35.9, 30.2, 30.1, 26.0, 24.4, 18.4, 18.1, −1.9, −2.0; IR (neat) ν_{max} 2929, 2855, 1766, 1694, 1650, 1452, 1254, 1099, 1038, 1006 cm^{-1}; MS (CI+ NH_3) m/z 546 (MH$^+$), 426 (M−BzO+2H$^+$), 390, 322. Anal. Calcd for $C_{29}H_{40}ClNO_5Si$: C, 63.77; H, 7.38, found: C, 63.78; H, 7.45.

3.1.27. 2-(tert-Butyl-dimethyl-silanyloxy)-2-methyl-decahydro-indeno[7a,1-h]indolizine-9,12-dione (**48**)

To a degassed solution of **57** (100 mg, 0.183 mmol) and ACCN (2 mg, 0.009 mmol) in refluxing α,α,α-trifluorotoluene (1.5 mL) was added a degassed solution of Bu_3SnH (103 μL, 0.384 mmol) and ACCN (9 mg, 0.037 mmol) in α,α,α-trifluorotoluene (3 mL) over 8 h. The reaction mixture was then cooled to room temperature and concentrated. The residue was purified by flash column chromatography (silicagel, heptane to heptane–EtOAc 70:30) to give **48** (37 mg, 52%) as a white solid; mp 136–139 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (1H, m), 2.66 (1H, dd, J=20.5, 10.0 Hz), 2.26 (1H, m), 2.44–2.33 (3H, m), 2.13 (1H, m), 2.09 (1H, dd, J=20.5, 3.9 Hz), 1.94–1.82 (3H, m), 1.75–1.67 (2H, m), 1.62 (1H, m), 1.54–1.43 (2H, m), 1.39 (1H, m), 1.29 (3H, s), 1.32–1.28 (1H, m), 1.26 (1H, dd, J=13.5, 13.5 Hz), 0.90 (9H, s), 0.11 (3H, s), 0.10 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 175.5, 74.1, 71.8, 45.9, 38.9, 38.8, 38.6, 38.0, 37.8, 34.4, 31.0, 28.7, 27.2, 26.2, 25.8, 19.3, 18.5, −1.8, −1.9; IR (CCl_4) ν_{max} 2933, 2856, 1748, 1703, 1393, 1253, 1153, 1122, 1106, 1020; MS (CI+ NH_3) m/z 392 (MH$^+$), 260 (M−OTBS$^+$). HRMS (CI+ CH_4) Calcd for $C_{22}H_{38}NO_3Si$ 392.2621, found 392.2626.

3.1.28. 2,12-Bis-(tert-butyl-dimethyl-silanyloxy)-2-methyl-1,3,4,6,7,10,11,13a-octahydro-2H,5H-indeno[7a,1-h]-indolizin-9-one (**60**)

To a solution of **48** (28 mg, 0.071 mmol) in dry dichloromethane (0.8 mL) were added triethylamine (50 μL, 0.357 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (65 μL, 0.286 mmol) and the reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with dichloromethane and saturated aqueous sodium hydrogenocarbonate was added. The organic layer was separated dried over sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, heptane–EtOAc, 80:20)

to give **60** (29 mg, 83%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (1H, d, J=3.5 Hz), 4.05 (1H, m), 2.53–2.31 (3H, m), 2.25–2.15 (2H, m), 1.85–1.57 (6H, m), 1.48–1.23 (4H, m), 1.25 (3H, s), 1.01 (1H, dd, J=12.3, 12.3 Hz), 0.89 (18H, s), 0.18 (3H, s), 0.17 (3H, s), 0.09 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 155.7, 104.4, 73.6, 72.1, 44.9, 43.2, 40.9, 39.2, 39.1, 38.2, 31.4, 31.1, 30.5, 26.6, 26.2, 25.6, 20.5, 17.8, −1.8, −4.6, −5.1; IR (CCl_4) ν_{max} 2930, 2857, 1695, 1644, 1402, 1252, 1100; MS (CI+ NH_3) m/z 507 (MH^+).

3.1.29. 2-(tert-Butyl-dimethyl-silanyloxy)-2-methyl-decahydro-indeno[7a,1-h]indolizin-12-one (*61*)

To a solution of **60** (26 mg, 0.051 mmol) in dry THF (4 mL) was added $LiAlH_4$ (19 mg, 0.514 mmol) and the reaction mixture was heated to reflux for 45 min. The mixture was cooled to 0 °C, diluted with diethyl ether and carefully quenched with water. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, heptane–EtOAc, 70:30) to give the title compound (11 mg, 58%) as a white solid; mp 65–67 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.18 (1H, m), 2.97 (1H, m), 2.72 (1H, td, J=11.0, 4.3 Hz), 2.52 (1H, dd, J=11.0, 11.0 Hz), 2.51 (1H, dd, J=19.8, 9.7 Hz), 2.33 (1H, dddd, J=10.9, 9.7, 5.5, 3.0 Hz), 1.92 (1H, dd, J=19.8, 3.0 Hz), 1.89–1.30 (14H, m), 1.25 (3H, s), 0.89 (9H, s), 0.09 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.2, 75.2, 72.2, 50.4, 47.2, 44.8, 40.0, 38.9, 37.9, 37.2, 34.2, 31.0, 30.2, 26.5, 26.2, 21.9, 19.9, 18.5, −1.7, −1.8; IR (neat) ν_{max} 2930, 2854, 1734, 1471, 1252, 1106, 1058, 1022 cm^{-1}; MS (CI+ NH_3) m/z 378 (MH^+), 246 ($M-OTBS^+$). HRMS (CI+ CH_4) Calcd for $C_{22}H_{40}NO_2Si$ 378.2828, found 392.2825.

3.1.30. 13-Deoxyserratine (*2*)

To a solution of **61** (11 mg, 0.029 mmol) in dry THF (0.8 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 87 μL, 0.087 mmol) and the reaction mixture was heated to reflux for 6 h. Aqueous 1.0 M NaOH was added and the mixture extracted with ether. The separated organic layer was dried over sodium sulfate, filtered and concentrated to give pure **2** (7.2 mg, 96%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 (1H, m), 2.90 (1H, m), 2.64–2.58 (2H, m), 2.58 (1H, dd, J=19.4, 9.9 Hz), 2.48 (1H, m), 2.01 (1H, dd, J=19.4, 4.1 Hz), 1.89–1.25 (14H, m), 1.27 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 76.1, 69.7, 50.9, 47.8, 42.1, 39.4, 36.3, 34.4, 33.7, 30.8, 29.8, 28.3, 27.1, 21.5, 20.0 (the C=O resonance could not be observed); IR (CCl_4) ν_{max} 3612 (OH), 2975, 2930, 2855, 1734 (C=O), 1117; MS (CI+ NH_3) m/z 264 (MH^+), 246 ($M-OH^+$); MS (EI) m/z 263 (M^+, 9), 235 (M^+-28, 38), 136 (100). These fragmentations are in good agreement with those reported by Inubushi and co-workers for serratinine and its derivatives.[23] HRMS (CI+ CH_4) Calcd for $C_{16}H_{26}NO_2$ $[M+H]^+$ 264.1964, found 264.1965.

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