1 PERKIN

Nitrone dipolar cycloaddition routes to piperidines and indolizidines. Part 9.† Formal synthesis of (−)-pinidine and total synthesis of (−)-histrionicotoxin, (+)-histrionicotoxin and (−)-histrionicotoxin 235A‡

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Received (in Cambridge, UK) 8th January 2002, Accepted 8th April 2002
First published as an Advance Article on the web 28th May 2002

An intramolecular hydroxylamine-alkyne cyclisation is used for the enantioselective synthesis of the cyclic nitrones **36** and **44**. We have demonstrated the use of a novel nitrone protection strategy by cycloaddition of styrene to the cyclic nitrone **44** in the synthesis of the spirocyclic core of the histrionicotoxin family of alkaloids. Deprotection by dipolar cycloreversion of the styrene adduct (the bicyclic isoxazolidine **39**) and *in situ* intramolecular dipolar cycloaddition of a pendant (*Z*)-α,β-unsaturated nitrile to the intermediate nitrone **50** gave the isoxazolidine **51** in high yield with a surprising degree of regioselectivity compared with the corresponding (*Z*)-enyne **36**. The method is amenable to the synthesis of both enantiomers **51** and **62** of the tricyclic core structure which can be converted by way of the common intermediates (*e.g.* **53** and *ent*-**53**) respectively into the natural configuration of alkaloids (−)-histrionicotoxin **1** and (−)-histrionicotoxin 235A **65** as well as the unnatural (+)-histrionicotoxin **63**.

Introduction

(−)-Histrionicotoxin (HTX) **1** was isolated by Daly and co-workers in 1971 from the skin of the Colombian poison arrow frog *Dendrobates histrionicus*.[1] Since then, a further 15 alkaloids in the same family have been isolated from various frogs of the family *Dendrobatidae*.[2,3] The later members of the family vary only in the length and degree of unsaturation present in the two side chains (Fig. 1).

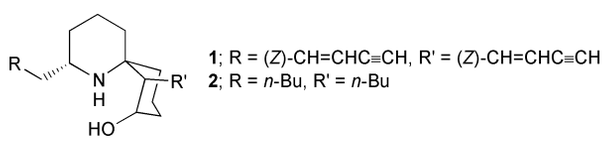


Fig. 1 Histrionicotoxin **1** and perhydrohistrionicotoxin **2**.

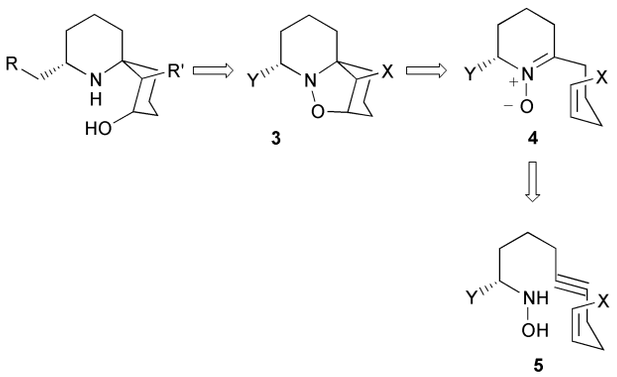
The unique spirocyclic piperidine core and two *cis*-enyne side chains of the parent alkaloid make it highly synthetically challenging. There have been many reports of syntheses of the non-natural perhydrohistrionicotoxin (PHTX) **2**.[4] However, before the preliminary communication[5] of the present work, HTX **1** had only been prepared twice previously. The first synthesis by the group of Kishi[6] was of the racemate and the second by Stork and Zhao[7] afforded the laevorotatary natural enantiomer. A formal synthesis has subsequently been reported by Stockman[8] in which the racemic spirocyclic core bis-nitrile **53** was prepared by an elegant tandem cyclisation–dipolar cycloaddition strategy which depended heavily on the key observations disclosed in our preliminary communication.[5] The histrionicotoxin alkaloids show intense selective inhibition of the nicotinic acetylcholine receptors and this activity has led to their use as an important probe in neurophysiology.[9–11] Natural scarcity (*ca.* 180 μg per frog skin), the restriction on export of the skins from their native Colombia, and the fact that frogs raised in captivity do not produce the alkaloids are excellent reasons for the search for an efficient synthesis. In this paper we provide a solution to this problem which makes available both enantiomers **1** and **63**, as well as demonstrating the potential for the synthesis of all the known HTX alkaloids.§

We have made extensive use of the intramolecular 1,3-dipolar cycloaddition of *C*- and *N*-alkenyl nitrones in the synthesis of alkaloids in recent years.[12–23] Our discovery of the tandem hydroxylamine-alkyne cyclisation to form cyclic nitrones which could be trapped by an intramolecular 1,3-dipolar cycloaddition of a pendant dipolarophile[14,22] led us to the design of the present approach to histrionicotoxin (Scheme 1). Thus cyclisation of the hydroxylamino-alkyne **5** was expected to produce the cyclic nitrone **4** which would undergo intramolecular dipolar cycloaddition to afford the adduct **3**. This tricyclic core structure is potentially a common precursor to all the known histrionicotoxins. In the ideal plan all the stereocentres of the tricyclic core would be established by the induced diastereoselectivity arising from the control exerted by the single sp^3 stereocentre in the starting hydroxylamine **5**.

† Part 8. See Ref. 22.
‡ This manuscript is dedicated to the sixtieth birthday of Professor L. Tietze.

§ Some examples have recently been communicated. See ref. 62.

 DOI: 10.1039/b200328g



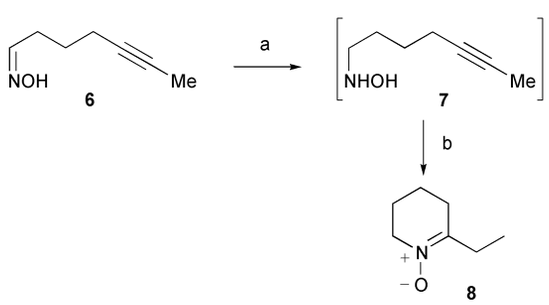
Scheme 1 Retrosynthetic strategy.

A major consideration in developing this strategy was the lack of precedent for the required regioselectivity in the intramolecular dipolar cycloaddition of the nitrone **4**.[24–30] We describe here the results of our model studies towards the tandem hydroxylamine-alkyne–dipolar cycloaddition approach to HTX and the application of a modified approach to the successful total synthesis of the alkaloids (−)-HTX, (+)-HTX and (−)-HTX **235A**.

Results and discussion

Model cyclisation studies

We first examined the model cyclisation of the non-terminal alkyne, hept-5-ynylhydroxylamine **7**, prepared by sodium cyanoborohydride reduction of the corresponding oxime **6**. Formation of the nitrone **8** occurred in 94% overall yield after the reaction mixture had been heated in refluxing toluene for 2 hours (Scheme 2). This is consistent with our general observ-

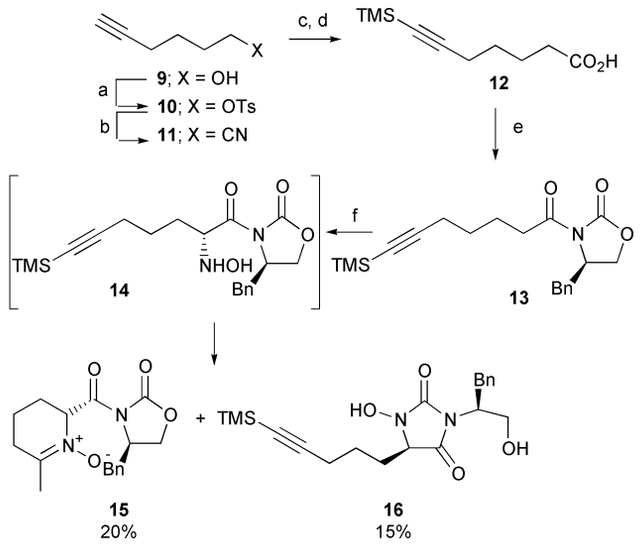


Scheme 2 *Reagents and conditions:* a, $NaBH_3CN$, MeOH, pH 3–4; b, PhMe, 110 °C, 2 h, 94%.

ation that hydroxylamine-alkyne cyclisations onto terminal and silyl-substituted acetylenes are much faster than cyclisations onto other non-terminal alkynes.[19,22] This observation is analogous to those of Ciganek [31] and Black [32] in the Cope–House cyclisation [33] of alkenyl hydroxylamines.

An enantioselective synthesis of HTX **1** would require the (*S*)-hydroxylamino-alkyne derivative (*e.g.* **40**) from which all other stereocentres could then be induced diastereoselectively. Whilst a number of methods for the enantioselective synthesis of hydroxylamines exist (*e.g.* oxidation of amines,[34] nucleophilic displacement of triflates,[35]¶ addition of organometallics to nitrones [36–39] and oximes [40]) it was decided to mimic the enolate hydroxylamination protocol of Oppolzer,[41] but using an Evans oxazolidinone auxiliary. The terminally silylated heptynoic acid **12** was prepared in 4 steps from commercially available hex-5-yn-1-ol **9** as shown in Scheme 3, and was then coupled to the Evans benzyl oxazolidinone auxiliary [42] by a mixed anhydride method. Attempted electrophilic hydroxylamination of the

¶ The IUPAC name for triflate is trifluoromethanesulfonate.



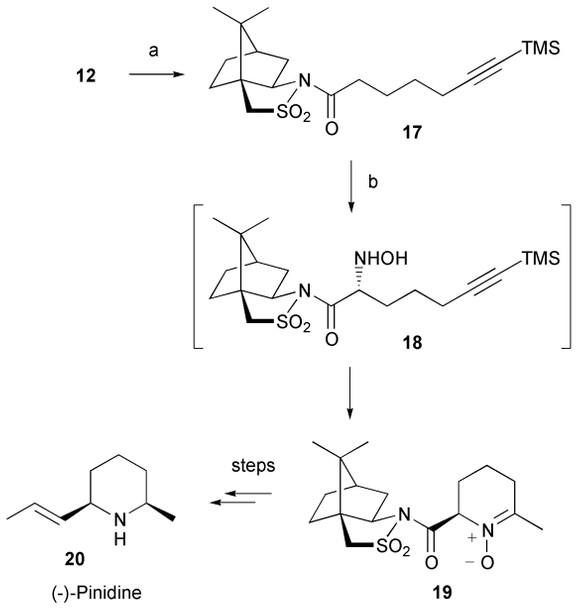
Scheme 3 *Reagents and conditions:* a, TsCl, pyridine, 0 °C, 16 h, 99%; b, NaCN, DMSO, 2 h, 90%; c, i. NaOH, EtOH, ii. HCl (aq), 97%; d, i. *n*-BuLi, THF, −78 °C, ii. TMSCl, −78 °C ⟶ rt, iii. HCl (aq), 78%; e, i. Me_3CCOCl, Et_3N, Et_2O, −78 °C, ii. X_c-Li, THF, −78 °C ⟶ 0 °C, 73%; f, i. NaHMDS, THF, −78 °C, ii. 1-chloro-1-nitrosocyclohexane, iii. HCl (aq), iv. $NaHCO_3$ (aq), 1 h. X_c = (*R*)-4-Benzyloxazolidin-2-one.

sodium enolate of the *N*-acyloxazolidinone **13** using 1-chloro-1-nitrosocyclohexane followed by acid hydrolysis of the nitrone intermediate, base extraction (to release the intermediate hydroxylamine **14**) and stirring at 25 °C for 1 hour to induce the Cope–House cyclisation was unsatisfactory, giving the required nitrone **15** in poor yield, along with the by-product **16**, resulting from attack on the carbonyl of the auxiliary by the hydroxylamine **14**. Evans has noted similar side reactions with related amines,[43] and clearly the more demanding cyclisation conditions required for a non-terminal alkyne would be incompatible with the Evans auxiliary. The diastereoselectivity of the hydroxylamination reaction was assumed to follow the usual reactivity pattern of the Evans auxiliaries,[44] and was shown by ^{1}H NMR spectroscopy to be >95 : 5. Given the above mentioned problems this approach was abandoned in favour of the Oppolzer camphorsultam auxiliary.[41,45]

Acylation of (−)-(2*R*)-10,2-camphorsultam with the activated derivative of the acid **12** using the mixed anhydride method was followed by electrophilic hydroxylamination to form the hydroxylamine **18** which underwent cyclisation to give the required nitrone **19** in good yield (Scheme 4) with no evidence of formation of the other diastereomer as determined by ^{1}H NMR spectroscopy. The stereochemistry of the hydroxylamine **18** was assigned according to the precedent of Oppolzer.[41] The nitrone **19** is also an intermediate in Oppolzer's synthesis of (−)-pinidine **20**,[46] and accordingly the approach described here constitutes a formal synthesis of this alkaloid. The Oppolzer hydroxylamination strategy was accordingly adopted for the synthesis of HTX.

Tandem cyclisation studies

With these initial encouraging results in hand, we embarked upon the attempted synthesis of a hydroxylamine precursor for our tandem cyclisation–cycloaddition reaction. Previous work by Gössinger,[25] Tufariello,[24] and Grigg [26–30] had shown the regiochemical outcome of the required intramolecular cycloaddition reaction to be a fine balance of steric and electronic effects. The terminal olefin substituent (X in the precursor **4** in Scheme 1) suffers from steric interactions akin to the 1,3-diaxial interactions of a cyclohexane chair in the transition state **21** leading to the required 6,6,5-adduct **23** (Fig. 2), and these interactions are absent in the transition state **22** leading to the regioisomeric 6,5,5-adduct **24**; this balance determines the outcome of the



Scheme 4 *Reagents and conditions:* a, i. Me_3CCOCl, Et_3N, Et_2O, −78 °C ⟶ 0 °C, ii. (−)-Aux*-Li, THF, 69%; b, i. NaHMDS, THF, −78 °C, ii. 1-chloro-1-nitrosocyclohexane, iii. HCl (aq), iv. $NaHCO_3$ (aq), v. CH_2Cl_2, rt, 1 h, 85%. (−)-Aux* = (−)-*S*-camphor-10,2-sultam.

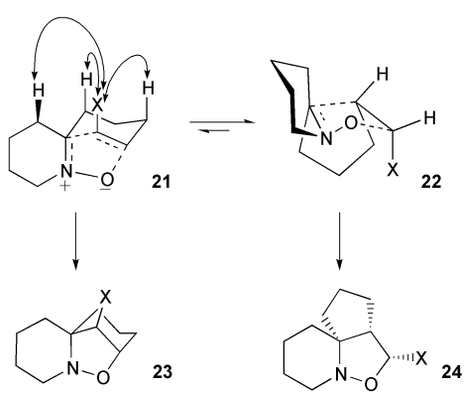
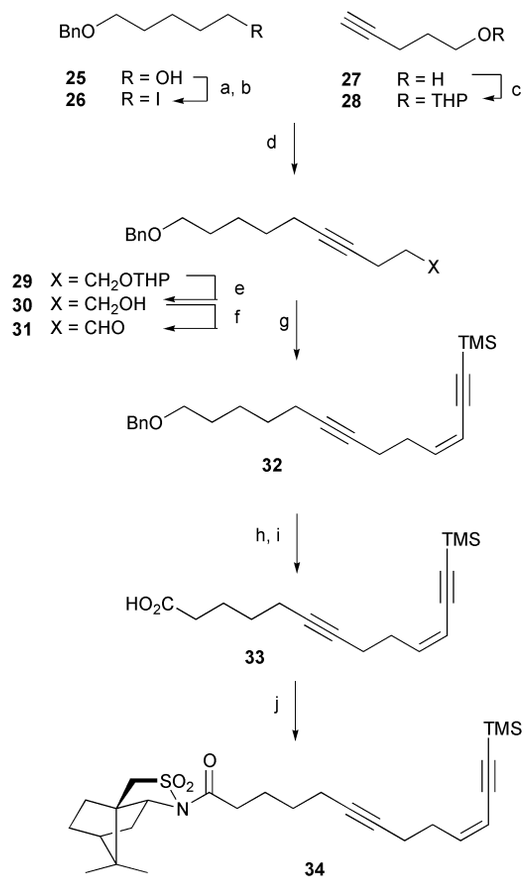


Fig. 2 Transition states leading to the 6,6,5- (**23**) and 6,5,5-adducts (**24**).

cycloaddition. Gössinger had decided on the basis of a limited number of experiments that the adduct derived from transition state **22** was the kinetic product, whereas that arising from the alternative transition state **21** would be realised under conditions of thermodynamic control.[25]

It is predicted that the required 6,6,5-adduct **23** would be favoured by a small, electron-withdrawing terminal alkene substituent X. On the basis of steric A-values,[47] and useful functionality for elaboration of the side chains of the final product, we examined the dipolar cycloaddition with a trimethylsilylenyne as the terminal substituent on the dipolarophile. Accordingly, the *N*-acyl sultam **34** was synthesised as shown in Scheme 5. Tosylation of commercially available 5-benzyloxypentan-1-ol **25** and subsequent Finkelstein reaction[48] of the tosylate gave the iodide **26** in high yield. Alkylation of the lithio-derivative of the THP-protected pent-4-yn-1-ol **28** in THF at 50 °C with the iodide **26** gave the differentially protected diol in high yield. Removal of the THP group using Amberlyst-15® in methanol and subsequent Swern oxidation[49] afforded the stable aldehyde **31**, which could be stored indefinitely at −18 °C. Olefination according to the Yamamoto procedure[50,51] gave the required TMS-enyne **33** as a 20 : 1 (*Z*–*E*) mixture of isomers as determined by ^{1}H NMR spectroscopy.‖ Selective cleavage of the benzyl ether in the presence of both alkene and alkyne functionalities was readily achieved using the boron trichloride–

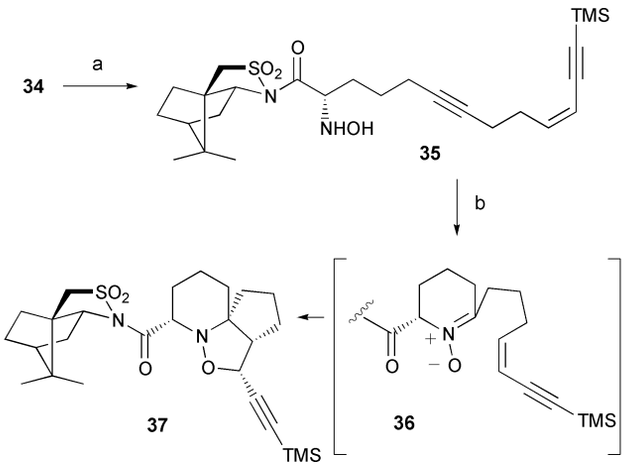


Scheme 5 *Reagents and conditions:* a, TsCl, Et_3N, DMAP, CH_2Cl_2; b, NaI, Me_2C=O, 87% (2 steps); c, 3,4-dihydro-2*H*-pyran, Amberlyst®-15, CH_2Cl_2, 96%; d, i. **28**, *n*-BuLi, THF, −78 °C, ii. **26**, THF, 50 °C, 3 days, 82%; e, Amberlyst®-15, MeOH, 100%; f, DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, 94%; g, i. 3-TBDMS-1-TMS-prop-1-yne, *t*-BuLi; ii. $Ti(O^iPr)_4$; iii. **31**, THF, 76%; h, $BCl_3{\cdot}SMe_2$, CH_2Cl_2, 0 °C, 85%; i, CrO_3–H_2SO_4, Me_2C=O, 90%; j, i. Me_3CCOCl, Et_3N, THF, 0 °C; ii. Aux*-Li, THF, 86%. Aux* = (+)-(*R*)-camphor-10,2-sultam.

methyl sulfide reagent developed within our group.[52] Jones oxidation[53] of the alcohol was followed by coupling to the sultam auxiliary using the mixed anhydride method as before. Electrophilic hydroxylamination of the acylsultam **34** afforded the required hydroxylamine **35** as a single diastereomer as judged by ^{1}H NMR spectroscopy. The hydroxylamine cyclised on heating to give the intermediate nitrone **36** which underwent intramolecular dipolar cycloaddition to give the tricycle **37** (Scheme 6). Whilst the proof of concept of the tandem process was gratifying (the tandem cyclisation protocol had proceeded in 83% yield to give the product tricycle **37** as a single diastereomer from an acyclic precursor whose existing stereocentre induced the formation of three new stereocentres in a controlled manner), the regiochemical outcome of the dipolar cycloaddition was not that required. Furthermore all attempts at thermal equilibration of the unwanted product **37** at elevated temperatures failed to give any of the desired 6,6,5-adduct (analogous to **3**).

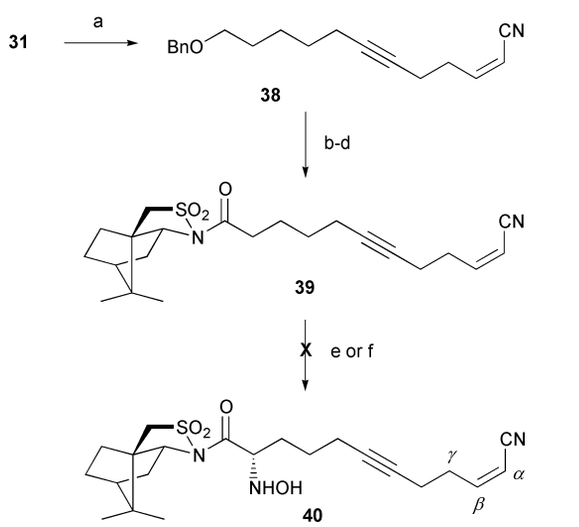
In the light of this result, we decided to change to the apparently smaller and more electron-withdrawing nitrile group as the dipolarophile substituent. Intuitively the HOMO-(nitrone)–LUMO(dipolarophile) interaction would be expected

‖ The selectivity and yield of this reaction appear to depend on the ratio of aldehyde to bis(silylpropyne) used in the reaction: 1.1 eq. of bis-(silylpropyne) gave > 20 : 1 (*Z*–*E*) selectivity, but poor yield (27%); 2.0 eq. of bis(silylpropyne) gave a much improved yield (82%), but poor selectivity (8 : 1, *Z*–*E*); a balance was found with 1.5 eq. of silane, which gave a 20 : 1 (*Z*–*E*) ratio in 76% yield. The reasons for this are unclear.



Scheme 6 *Reagents and conditions:* a, i. NaHMDS, THF, −78 °C, ii. 1-chloro-1-nitrosocyclohexane, iii. HCl (aq), iv. $NaHCO_3$ (aq), 61%; b. PhMe, 110 °C, 83%.

to be more favourable for a nitrile substituent than an alkyne. Hence, exposure of the aldehyde **31** to Yamamoto's modified Peterson conditions for the generation of (*Z*)-enenitriles[50] afforded the required enenitrile as a 7 : 1 (*Z*–*E*) mixture of isomers as estimated by ^{1}H NMR spectroscopy (Scheme 7).



Scheme 7 *Reagents and conditions:* a, i. $TMSCH_2CN$, *n*-BuLi, THF, −78 °C, ii. $B(O^iPr)_3$, iii. **31**, THF, 81%; b, $BCl_3{\cdot}SMe_2$, CH_2Cl_2, 0 °C, 69%; c. CrO_3–H_2SO_4, $Me_2C{=}O$, 69%; d, i. Me_3CCOCl, Et_3N, THF, 0 °C, ii. Aux*-Li, THF, 77%; e, i. NaHMDS, THF, −78 °C, ii. 1-chloro-1-nitrosocyclohexane, THF, iii. HCl (aq), iv. $NaHCO_3$ (aq); f, i. $TiCl_4$, *i*-Pr_2EtN, CH_2Cl_2, 0 °C, ii. 1-chloro-1-nitrosocyclohexane, THF, iii. HCl (aq), iv. $NaHCO_3$ (aq).

Contrary to observations of Yamamoto, we were unable to improve the (*Z*)-selectivity by the addition of HMPA to the reaction mixture immediately after the addition of the aldehyde, and therefore this highly toxic reagent was omitted (the use of DMPU led to a reversal of the selectivity in poor yield). The *N*-acylsultam **39** was prepared, but the sodium enolate decomposed rapidly to an intractable gum even at −78 °C, and all attempts at hydroxylamination were unsuccessful. It is thought that this instability may have been due to the acidity of the γ-allylic protons adjacent to the enenitrile functionality. In order to avoid this, hydroxylamination using the milder Evans procedure for the direct formation of titanium enolates was attempted.[54] Precomplexation with titanium(IV) chloride, followed by addition of Hünig's base, resulted in the clean and rapid formation of a deep red solution of the titanium enolate. In this case the co-ordination of titanium was presumably directed to the required site by the additional co-ordinating power of the nearby sultam group. However, it was probably less reactive, and failed to react with 1-chloro-1-nitrosocyclohexane even at 25 °C, leading to the recovery of starting material.

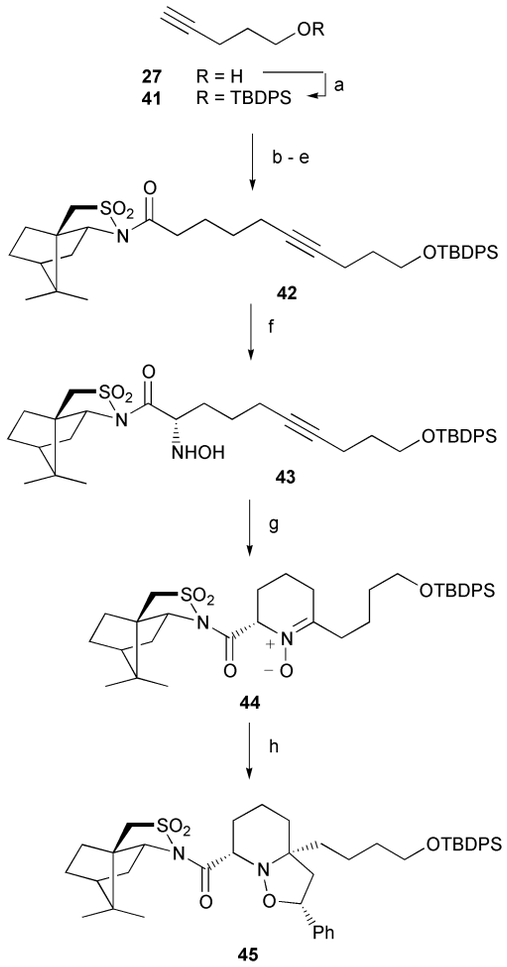
Protection of the cyclic nitrone as a styrene adduct

The conclusion drawn from the above experiment is that the hydroxylamination would have to be carried out before the introduction of the enenitrile. However, hydroxylamines are not convenient reaction intermediates, and the subsequent nitrone also possesses acidic hydrogen atoms adjacent to the C=N. These would also be incompatible with the Yamamoto enenitrile synthesis. The results of the above work led us to develop a novel nitrone protection strategy. The key was to form the nitrone before the Yamamoto enenitrile synthesis, and then to mask the highly reactive and awkwardly polar nitrone functional group as the intermolecular 1,3-dipolar cycloadduct with a suitable dipolarophile. The choice of dipolarophile was governed by a number of factors; firstly, the cycloaddition must proceed in high yield and with a high degree of regio- and diastereoselectivity, and secondly the resulting isoxazolidine adduct must be inert to the Yamamoto reaction. A third consideration is that the cycloreversion of the isoxazolidine must cleanly yield the nitrone with easy separation of the released dipolarophile, clearing the way for the required intramolecular dipolar cycloaddition. Styrene was selected for the protection of the intermediate nitrone, and seemed to fit all the above design criteria. We were aware of the earlier use by Tufariello of the strategy of regenerating nitrones from their isoxazolidine cycloadducts in the synthesis of natural products. He reported the use of nitrone-methyl acrylate adducts in the synthesis of (±)-cocaine.[55,56] We chose to avoid these acrylate and acrylonitrile adducts in the expectation that they would introduce further unwanted enolisable functionality into the molecule. Once the required enenitrile side chain had been elaborated we wished to release the required nitrone by a thermal dipolar cycloreversion of styrene (deprotection)[57] followed by the planned intramolecular dipolar cycloaddition. Since the publication of our preliminary communication on this work,[5] Brandi has reported a cycloreversion of a styrene cycloadduct in a synthesis of hydroxyindolizidines.[58]

In order to attempt the above strategy, the original route (Scheme 5) was modified in a number of ways. We exchanged the THP protecting group for a TBDPS ether, as it was envisaged that the presence of a chiral centre in the THP group would lead to the formation of diastereomers on introduction of the sultam auxiliary. This led to improved yields in the acetylide coupling step (Scheme 8), presumably due to enhanced solubility of the lithium acetylide. Following this, the order of deprotection and functionalisation was reversed from the original route. The side chain TBDPS ether was left intact, and the chiral auxiliary was introduced by a method similar to that used in the original synthetic route; benzyl ether cleavage (boron trichloride–methyl sulfide) was followed by Jones oxidation and auxiliary attachment, to give the *N*-acyl sultam **42**. Electrophilic hydroxylamination afforded the hydroxylamine **43**. This was heated in toluene (80 °C, 6 h) to give very cleanly the intermediate highly polar nitrone **44**, which could be fully characterised without purification. The nitrone **44** was then simply dissolved in neat styrene in the presence of 2–3 crystals of quinol** to inhibit polymerisation, and was heated at 80 °C for 7 hours. Gratifyingly, this led to the formation of the desired isoxazolidine **45** as a single regio- and diastereoisomer (as shown by ^{1}H NMR spectroscopy) in high overall yield (85% over the two steps). The stereochemistry was assigned by NOE analysis as shown in Fig. 3.

Deprotection of the silyl ether **45** followed by Swern oxidation gave the aldehyde **46** (Scheme 9), which could not be

** The IUPAC name for quinol is 4-hydroxycyclohexa-2,5-dien-1-one.



Scheme 8 *Reagents and conditions:* a, TBDPSCl, imidazole, CH_2Cl_2, 0 °C, 90%; b, i. **41**, *n*-BuLi, THF, −30 °C, ii. **26**, THF, 50 °C, 90%; c, BCl_3·SMe_2, CH_2Cl_2, 0 °C, 97%; d, CrO_3–H_2SO_4, Me_2C=O, 98%; e, i. Me_3CCOCl, Et_3N, THF, 0 °C, ii. Aux*-Li, THF, 84%; f, i. NaHMDS, THF, −78 °C, ii. 1-chloro-1-nitrosocyclohexane, iii. HCl (aq), iv. $NaHCO_3$ (aq), 70%; g, PhMe, 80 °C; h, styrene, quinol (2–3 mg), 80 °C, 85% (2 steps).

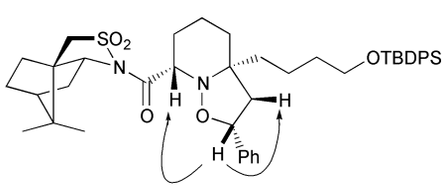
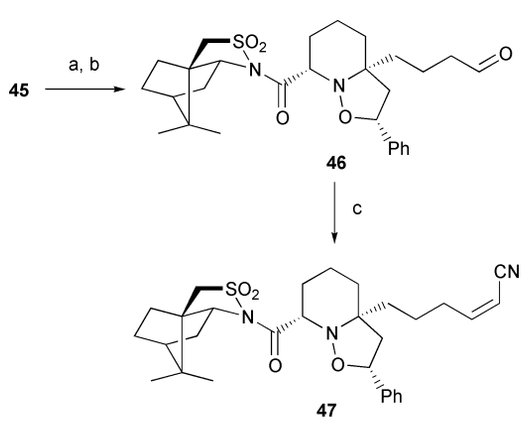


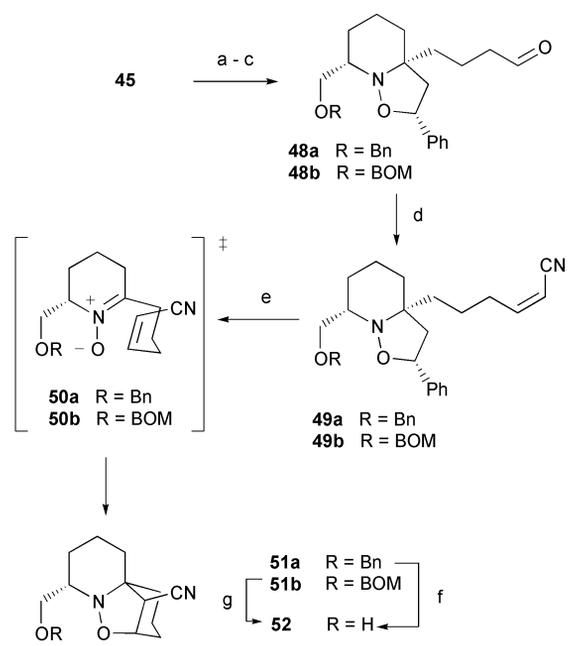
Fig. 3 NOE enhancements observed for the cycloadduct **45**.



Scheme 9 *Reagents and conditions:* a, HF–MeCN, 97%; b, DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C then Et_3N, 90%; c, i. $TMSCH_2CN$, *n*-BuLi, THF, −78 °C; ii. $B(O^iPr)_3$; iii. **46**, THF, <20%.

elaborated to the ene-nitrile **47** by the Yamamoto–Peterson reaction in good yield. Attempts to introduce alternative olefins by Wittig reaction or Petasis reaction[59] of **46** also failed, presumably owing to the presence of the *N*-acyl sultam functionality. This was therefore removed at this stage.

Reductive cleavage of the sultam auxiliary using lithium aluminium hydride[60] resulted in an inseparable mixture of the product alcohol and camphorsultam auxiliary. Benzylation of this crude mixture (sodium hydride, 24 h then benzyl bromide, THF, 60 °C, 48 h) afforded a separable mixture of the benzyl ether, and the presumed *N*-benzylated sultam (Scheme 10). The



Scheme 10 *Reagents and conditions:* a, i. $LiAlH_4$, THF, 0 °C, ii. NaH, THF, 65 °C, 24 h then BnBr, 65 °C, 48 h, 94% or $^iPr_2EtN$, BOMCl, nBu_4NI, toluene, 65 °C, 90%; b, HF–MeCN, 91% (R = Bn), 89% (R = BOM); c, IBX, DMSO, 100% (**48a** and **48b**); d, i. $TMSCH_2CN$, *n*-BuLi, THF, −78 °C, ii. $B(O^iPr)_3$, iii. **48**, THF, 84% (**49a**), 80% (**49b**); e, PhMe, sealed tube, 190 °C, 82% (**51a**) 83% (**51b**); f, BCl_3·SMe_2, CH_2Cl_2, 0 °C, 99%; g, Amberlyst-15™, MeOH, 95%.

formation of the alkoxide anion and subsequent reaction with benzyl bromide were both remarkably sluggish, requiring prolonged heating in order to drive the reaction to completion. Later studies showed that benzyloxymethylation (BOM protection) could be accomplished more readily (Hünigs base, BOMCl, toluene, 65 °C, 4.5 h). Desilylation of the TBDPS ether using HF–acetonitrile (TBAF–THF resulted in a faster reaction but reduced yields) followed by IBX (2-iodoxybenzoic acid)[61] (100%) or Swern (93%) oxidation gave the aldehyde **48**, which was observed to decompose slowly on standing. Exposure of **48** to the Yamamoto enenitrile formation conditions led to a 9 : 1 (*Z*–*E*) mixture of isomers of the required dipolarophile **49** in high yield ready for the attempted deprotective cycloreversion–cycloaddition. The (*Z*)–(*E*)-enenitrile isomers could not be separated, and the mixture was carried right through the synthesis to the stage of the isoxazolidine dipolar cycloaddition adducts which were separable.

After much experimentation, it was found that the optimum conditions for the cycloreversion–cycloaddition reaction were heating a solution of the precursor **49** in toluene at 190 °C in a sealed tube for 3.5 hours. Lower temperatures and alternative solvents resulted in slow decomposition, and longer reaction times resulted in small decreases in yield (Table 1). Under these conditions, the product of the reaction was found to be the required *exo*-adduct **51**, as shown by extensive 1- and 2-dimensional ^1H NMR work (Fig. 4). Final proof of this was

Table 1 Cycloreversion–cycloaddition reactions of **49a** showing effect of solvent, temperature (T) and reaction time (t) on yield of the adduct **51a**

Solvent	T/°C	t/h	Yield(%)
PhMe	110	16	–[a]
m-Xylene	140	16	–[a]
$scCO_2$[b]	90	16	–[c]
PhMe	190[d]	3.5	80

[a] Decomposition of **49**. No product formed. [b] Reaction performed in $scCO_2$ at 90 °C and 3550 psi in a stainless steel cell with sapphire windows. [c] Only **49** recovered. [d] Reaction performed in a sealed glass tube.

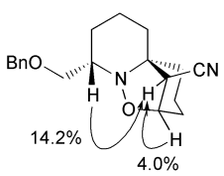


Fig. 4 NOE enhancements observed for the cycloadduct **51a**.

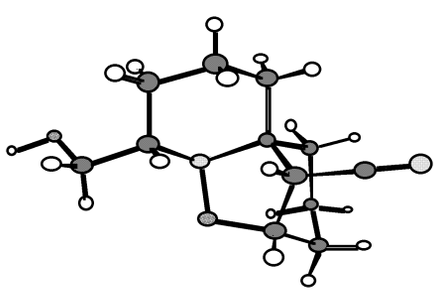


Fig. 5 Chem-3D® representation of the X-ray structure of the cycloadduct **52** showing the required bridged 1-azaspiro[5.5]undecane ring system and correct relative stereochemistry. ††

obtained in the form of an X-ray crystal structure of the crystalline debenzylated material **52** (see Fig. 5). †† In this single step, the relative (and hence the absolute) stereochemistry of three of the four stereocentres of the histrionicotoxin core has been controlled with outstanding selectivity, governed by the steric approach of the dipolarophile to the less hindered face of the intermediate nitrone determined by the benzyloxymethyl side chain, the stereochemistry of which had been controlled by the hydroxylamination of the sultam auxiliary. A minor by-product from the cycloaddition is the equatorial nitrile arising from intramolecular dipolar cycloaddition of the minor (*E*)-enenitrile isomer. The conclusion is that the cycloreversion reaction affords the intermediate nitrone **50** which undergoes an *in situ* stereospecific (concerted) dipolar cycloaddition reaction. At this stage it is not clear what factors determine the regioselectivity of the intramolecular dipolar cycloaddition. Our initial hypothesis was that the regiocontrol arose from a different reaction pathway for the enenitrile **49** from that followed by the enyne **35**. We have performed some basic molecular modelling of the transition states and the adducts to attempt to distinguish kinetic and thermodynamic factors which determine the outcome of the regiochemistry of the cycloaddition step. We have also performed the cycloreversion–cycloaddition protocol with intramolecular dipolarophiles having hydrogen, trialkylsilylethynyl, methoxycarbonyl and cyano substituents, and we have attempted equilibration of a number of the resulting adducts. These studies remain incomplete and will be reported in detail elsewhere. The simplest conclusion is that the presence of the enenitrile is the most important feature controlling the regiochemical outcome of the intramolecular dipolar cycloaddition reaction, and this is supported indirectly by the results of Stockman.[8]

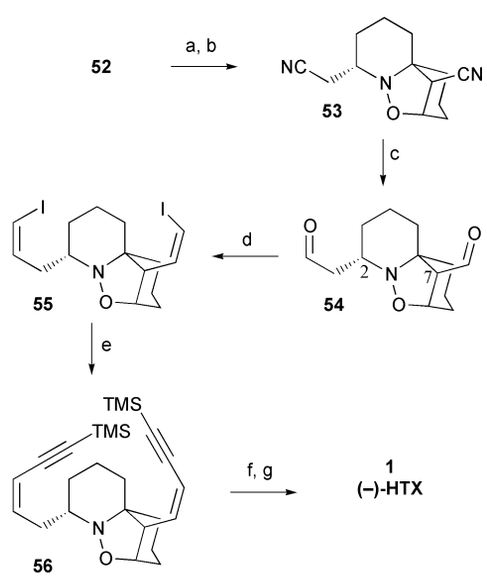
The nitrogen–oxygen bond of the isoxazolidine ring of the tricycle **51** can also serve as a useful and relatively inert protecting group of 'negative' mass – *i.e.* deprotection actually increases the mass of the molecule. It can be carried through the synthesis until the final stages when the more "reactive" amino and hydroxy groups can be released.

The potential versatility of compound **51** required its availability on a large scale, and with this in mind we have scaled up the early steps of the synthesis to the point that all the steps as far as the synthesis of the *N*-acyl sultam **42** could be carried out on scales up to 170 mmol with no loss in yield.

Elaboration of the core structure 51 to selected histrionicotoxins

We envisage that the core structure **51** will prove to be a versatile generic intermediate in the synthesis of all 16 naturally occurring HTX alkaloids. In this paper, we report its use in the synthesis of alkaloids, including histrionicotoxin itself, in which chain extension reactions are carried out with identical reagents, through a 'symmetrisation' process. Stepwise introduction of two different side chains using similar chemistry to that described below enables the synthesis of the side chain unsymmetrical alkaloids, in which the two side chains differ in length and/or degree of unsaturation.[62]

The first step in the synthesis of the side chain symmetrical alkaloids is to 'symmetrise' the two side chain positions, by the displacement of the benzyl or benzyloxymethyl ether moiety by a cyano group (Scheme 11). This was achieved readily by deprotection, mesylation and nucleophilic displacement of the mesylate (methanesulfonic acid) with sodium cyanide in DMSO in the presence of 4 Å molecular sieves. This latter

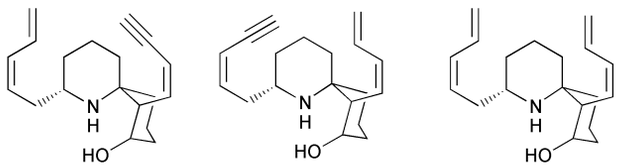


Scheme 11 *Reagents and conditions:* a, MsCl, Et_3N, CH_2Cl_2, 0 °C, 99%; b, NaCN (20 eq.), DMSO, 4 Å sieves, 50 °C, 96 h, 84% (rec. 90%); c, DIBAL, PhMe, −78 °C, then aq MeOH, HCl, 16 h, 25 °C, 100%; d. $[ICH_2PPh_3]^+I^-$, KHMDS, THF, −30 °C then stand at −78 °C, 30 min and add supernatant to **54** at −78 °C, 95%; e. TMS-C≡CH, $Pd(PPh_3)_4$, CuI, Et_2NH, 25 °C, 92%; f. Zn, AcOH, rt, 15 min, 98%; g. K_2CO_3, MeOH, 94%.

†† $C_{12}H_{18}N_2O_2$, M = 222.28, monoclinic, space group $P2_1$, a = 6.949(2), b = 14.011(4), c = 12.055(3) Å, β = 93.60(2)°, U = 1171.4(6) Å^3, T = 294(2) K, Z = 4, μ(Mo-Kα) = 0.087 mm^{-1}, 6718 reflections measured, 3371 unique (R_{int} = 0.065) which were used in all calculations. The final $R1$ ($F^2 > 2\sigma(F^2)$) was 0.065 and the final $wR(F^2)$ (all data) was 0.155. The absolute structure could not be determined reliably and was assigned according to the known stereochemistry. CCDC reference number 178859. See http://www.rsc.org/suppdata/p1/b2/b200328g/ for crystallographic files in .cif or other electronic format.

reaction was very slow, normally requiring the recycling of recovered starting material in order to achieve an acceptable degree of conversion with an acceptable reaction time, again highlighting the extremely hindered nature of this position. The resulting 'symmetrised' bisnitrile **53** is a white crystalline solid which represents a convenient stable precursor to the symmetrical histrionicotoxins. Simultaneous reduction of both nitrile groups with DIBAL was found to be sluggish and impossible to drive to completion in THF even with a large excess of the reagent, but proceeded cleanly and rapidly in toluene at −78 °C to give the dialdehyde **54** in quantitative yield. The *C*-7 stereocentre of **54** slowly epimerised on standing to the apparently more stable equatorial aldehyde, but this could be avoided by immediate use of the aldehyde after preparation. Care in working up the reduction was also required to avoid this; the preferred procedure was to quench the reaction mixture at low temperature with wet methanol, followed by the addition of ethyl acetate, and a 50% saturated aqueous solution of Rochelle's salt. The mixture was then neutralised by the dropwise addition of dilute hydrochloric acid, to avoid rapid epimerisation under the highly basic conditions. It is noted that the epimeric *C*-7 aldehyde is less reactive towards various nucleophilic reagents, and can be removed at a later stage after the more reactive diastereoisomer has reacted.

Initial attempts to introduce the two (*Z*)-enyne side chains simultaneously in a single step using the titanium-allene methodology of Yamamoto that had been used successfully in the preparation of TMS-enyne **34** again gave a mixture of products and much decomposition to material which did not elute from the baseline of a TLC plate. There have been a number of reports that alkyl-titanium,[63] titanium-based Lewis acids[63,64] and Petasis reagents[65] react with nitrogen–oxygen bonds resulting in either decomposition or nitrogen–oxygen bond cleavage depending on the substrate, suggesting that the nitrogen–oxygen bond of the isoxazolidine moiety present in this substrate may interfere with this reaction. Furthermore, changing from the titanium allene to the boron allene led to no product being formed, although decomposition was greatly reduced. We decided to abandon this approach, and instead to build the side chains simultaneously in two steps in an approach similar to that used by Stork in his synthesis of histrionicotoxin.[7] Stork–Wittig olefination under the conditions described by Stork[66] led to the formation of the bis(vinyl iodide) **55** in poor yield (<35%) with much simultaneous decomposition of the dialdehyde **54** to polar baseline material on TLC analysis. A number of possible base-induced decomposition pathways can be envisaged for this substrate, and we feel that this is the most likely source of difficulty, both with this reaction and the Wittig methylenation described below. After much work, it was discovered that the yield of the Stork Wittig reaction could be improved to an impressive 95% by making a number of simple modifications: i) the ylide was formed at −30 °C instead of 0 °C; ii) the base was changed from NaHMDS to KHMDS; iii) the salts were allowed to settle at −78 °C, giving a supernatant solution of the 'salt-free' ylide, which was then added to a pre-cooled solution of the dialdehyde **54**. Under these conditions, aqueous workup gave the required, configurationally stable vinyl iodide **55**. The *E*–*Z* ratio could not be determined directly, but ^{1}H NMR spectroscopic analysis of the final natural product showed no evidence of the (*E*)-isomers, suggesting the olefination to proceed with >95% selectivity in favour of the required *Z,Z*-isomer. Sonogashira coupling[67] of **55** with TMS-acetylene led to the required bis(TMS-enyne) **56** in high yield. Initially, deprotection of the TMS groups (K_2CO_3–methanol) was followed by zinc–acetic acid reduction of the nitrogen–oxygen bond, but ^{1}H NMR spectroscopic analysis showed that some over-reduction of the terminal acetylenes to a statistical mixture of the dienes **57**, **58** and **59** had occurred, as a 20% contaminant, which could not be separated (a disappointing result, since these compounds themselves are all natural products in the histrionicotoxin family) (Fig. 6).



HTX **285E** **57** HTX **285B** **58** HTX **287B** **59**

Fig. 6 Over-reduction products **57**–**59**.

Reversing the order of the final two steps led to a pure sample of the alkaloid (−)-histrionicotoxin **1**. The silylated enyne evidently protects the alkyne against the unwanted reduction, which is reminiscent of our early model work on the (*Z*)-enynes by Lindlar partial hydrogenation of silylated diynes.[68] Attempts to crystallise the hydrochloride or hydrobromide salts of **1** failed to give crystals suitable for X-ray analysis, but to our surprise, the free base crystallised on standing and could be recrystallised from hexane, allowing us to obtain the first X-ray crystal structure of the free base (Fig. 7). ‡‡

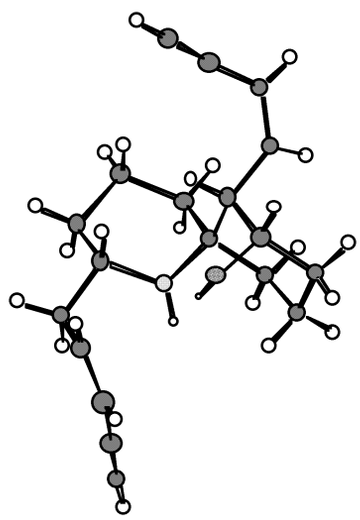
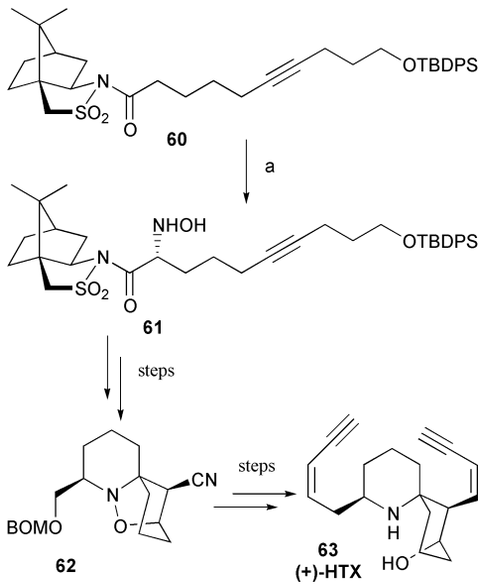


Fig. 7 Chem-3D® representation of the X-ray structure of synthetic (−)-histrionicotoxin **1**. Note the *trans* diaxial arrangement of substituents on the carbocyclic ring due to the intramolecular NH ··· OH hydrogen bond.

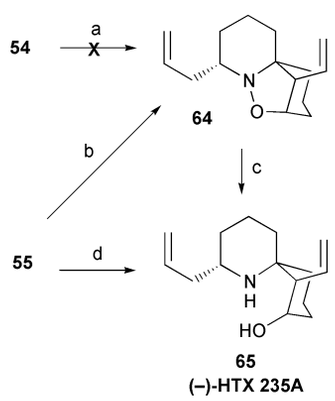
Biological studies on both enantiomers of the synthetic analogue, perhydrohistrionicotoxin PHTX,[69,70] suggest that the enantiomer of the naturally occurring histrionicotoxin may show similar biological activity to its natural antipode. We therefore synthesised (+)-HTX **63** using the same synthetic route as described above (Scheme 12). Starting from (2*S*)-*N*-[*tert*-butyldiphenylsilyloxy)dec-6′-ynoyl]bornane-10,2-sultam **60**, electrophilic hydroxylamination yielded hydroxylamine **61** containing all the stereochemical information required to introduce the three new stereocentres in the tricyclic core **62**. Functionalisation of the 6,6,5-core as described above, gave enantiomeric histrionicotoxin, (+)-HTX **63**, the optical rotation of which, satisfyingly, was found to be equal and opposite to that of the naturally occurring material {$[a]_D^{22}$ +113 (*c* 0.26 in EtOH); (−)-HTX $[a]_D^{22}$ −112 (*c* 0.34 in EtOH)}.

Following the synthesis of both enantiomers of the parent alkaloid, attention was then focused on the apparently simpler

‡‡ For the X-ray crystal structure of **1** see Ref. 5, Supporting Information, JA990138L.



Scheme 12 *Reagents and conditions*; a, i. NaHMDS, THF, −78 °C, ii. 1-chloro-1-nitrosocyclohexane, iii. HCl (aq), iv. $NaHCO_3$ (aq), 77%.



Scheme 13 *Reagents and conditions*: a, $[MePPh_3]^+I^-$, *n*-BuLi, THF, −78 °C or $[MePPh_3]^+I^-$, KHMDS, THF, −30 °C then stand at −78 °C, 0.5 h and add supernatant to **43**; b, Bu_3SnH, $Pd(PPh_3)_4$, PhH, 39%; c, Zn, AcOH, rt, 15 min, 95%; d, Zn, AcOH, rt, 15 min then 90 °C, 4 days, 90%.

alkaloid, (−)-HTX **235A 65** (Scheme 13). Initial attempts to introduce the two olefinic side chains in a single step using simple Wittig methylenation of bisaldehyde **54** failed, resulting in only decomposed polar material. We think that this was a result of the sensitivity of the dialdehyde **54** to the more basic unsubstituted ylide (see above). Furthermore, application of the optimised salt-free conditions described above for the Stork–Wittig procedure to this reaction also failed. It was decided instead to perform a triple reduction protocol on the bisvinyl iodide **55**, reducing both vinyl iodide groups and the nitrogen–oxygen bond. Our initial method was a two step procedure. Firstly, selective reduction of the vinyl iodide bonds using the procedure of Oshima and Utimoto[71] [$Pd(PPh_3)_4$, Bu_3SnH, PhH] gave the cyclic histrionicotoxin derivative **64** in an unoptimised yield of 39%. Reduction of the nitrogen–oxygen bond with zinc–acetic acid gave (−)-histrionicotoxin **235A 65** in near-quantitative yield {$[\alpha]_D^{22}$ −107 (*c* 0.07 in EtOH), lit.[7] $[\alpha]_D^{25}$ −102 (*c* 1.82 in EtOH)}. Alternatively, a one-pot procedure using zinc–acetic acid was tried and showed initial promise. The nitrogen–oxygen bond was rapidly cleaved at 25 °C in 0.25 h, but it was necessary to heat the mixture to 90 °C in order to reduce the less reactive vinyl iodide substituents. Optimisation of this procedure (rt, 0.25 h, 90 °C, 3.5 days) afforded the alkaloid **65** in 90% yield from the bis(vinyl iodide) **55**, an impressive yield for a triple reduction reaction.

Conclusion

In conclusion, we have achieved the total synthesis of the alkaloids (−)-histrionicotoxin **1**, (+)-histrionicotoxin **63** and (−)-histrionicotoxin **235A 65**, using a novel nitrone protection strategy as the key step in our synthesis. The crystalline bisnitrile **53** represents a key intermediate for the synthesis of the remaining side chain symmetric alkaloids, and the core structure **51** also allows synthesis of the non-symmetrical alkaloids by independent introduction of the two side chains in a stepwise fashion.

Experimental

^{1}H-NMR spectra were recorded on Bruker DPX-250 (250 MHz), Bruker DRX-400 (400 MHz) and Bruker DRX-500 (500 MHz) spectrometers. The chemical shift data for each signal are given in units of δ relative to tetramethylsilane (TMS) where δ(TMS) = 0.00 ppm and referenced to the residual solvent. The multiplicity of the signal is indicated as: s–singlet, d–doublet, t–triplet, q–quartet, qn–quintet, br–broad, m–multiplet, dd–doublet of doublets, dt–doublet of triplets *etc*. Coupling constants (J) are quoted in Hz and are recorded to the nearest 0.5 Hz. Where useful, the FID was zero filled (128 K) and sine-bell shifted (SSB = 30) prior to Fourier Transformation in order to provide baseline resolved multiplets and, as a result, easily identifiable and measurable coupling constants.

Two dimensional spectra (2D) spectra were recorded on Bruker DRX-500 (500 MHz) and DRX-400 (400 MHz) spectrometers, fitted with gradient coils. Double Quantum Filtered (DQF) and magnitude COSY spectra were typically acquired with 256 slices in F_1 and 2048 points in F_2 (acquisition time approximately 20 min). 1D gradient NOE spectra[72,73] were acquired using standard Gauss selective pulses and mixing times (τ_m) of the order of 1.2 s.

^{13}C-NMR spectra were recorded on Bruker DPX-250 (63 MHz), Bruker DRX-400 (100 MHz) and Bruker DRX-500 (125 MHz) instruments using an internal deuterium lock with proton decoupling. The chemical shift data for each signal are given in units of δ relative to tetramethylsilane (TMS) where δ(TMS) = 0.00 ppm. The multiplicity of the signal was determined by APT (Attached Proton Test) experiments and is indicated as C (s), CH (d), CH_2 (t) and CH_3 (q) groups where determined.

Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer. The sample was prepared as a thin liquid film or as a solution in the solvent indicated. Relative intensities are indicated as s, strong; m, medium; w, weak; br, broad.

Mass spectra were recorded by the Mass Spectrometry Services of the University of Swansea. In Swansea, Electron Impact (EI) and Chemical Ionisation (CI) low resolution spectra were carried out on a VG model 12–253 under ACE conditions and a Quattro II low resolution triple quadrupole MS. Accurate mass measurements for EI and CI were performed on a +VG ZAB-E instrument and Finnigan MAT 900 XLT instruments. All CI measurements were performed with NH_3 as the carrier gas.

Microanalyses were carried out by the staff of the Microanalytical Service at the University of Cambridge.

Melting Points were determined using a Köfler block melting point apparatus and are uncorrected.

Optical specific rotations were measured using a Perkin-Elmer 241 polarimeter in a cell of path length 1 dm^3. The concentration (c) is expressed in g 100 cm^{-3}. Specific rotations denoted as $[\alpha]_D^T$ imply units of deg dm^2 g^{-1} (T = temp °C).

Kugelrohr bulb-to-bulb distillations were carried out using a Büchi GKR-51 machine. Boiling points are the actual oven temperatures.

Flash chromatography[74] was carried out on silica gel [Merck 9385 Kieselgel 60 (230–400 ASTM)]. TLC was performed on 0.25 mm thick plates precoated with Merck Kieselgel 60 F_{254} silica gel.

Non-aqueous reactions were carried out under an atmosphere of dry nitrogen or argon unless indicated to the contrary.

Dry THF was distilled from potassium in a recycling still using benzophenone ketyl as indicator. Other solvents were purified by standard techniques.[75] Ether refers to diethyl ether. Dioxan refers to 1,4-dioxane. Brine refers to a saturated solution of sodium chloride in water.

Iodomethyltriphenylphosphonium iodide,[76] 3-(*tert*-butyl dimethylsilyl)-1-trimethylsilylprop-1-yne,[50] 2-(pent-4-ynyloxy)-tetrahydro-2*H*-pyran,[19] and 1-chloro-1-nitrosocyclohexane[77] were prepared according to the previously published procedures. 1-Chloro-1-nitrosocyclohexane was stored under argon at −18 °C and distilled in the Kugelrohr apparatus immediately prior to use [bp 100 °C, 20 mmHg (lit.,[77] 51 °C, 12 mmHg)].

Hept-5-ynal oxime 6

A solution of hept-5-yn-1-ol (429 mg, 3.83 mmol) in dry CH_2Cl_2 (5 cm^3) was added dropwise to a stirred suspension of PCC (1.24 g, 5.57 mmol, 1.45 eq.) and powdered, activated 3 Å molecular sieves (100 mg) in dry CH_2Cl_2 (5 cm^3). After 4 h, the suspension was filtered through a Florisil column, and the solvent was removed under reduced pressure. 1 : 1 Pyridine–ethanol (10 cm^3) and hydroxylamine hydrochloride (799 mg, 11.5 mmol, 3 eq.) were added, and the solution was stirred for 0.25 h at 25 °C. The solution was poured into hydrochloric acid (2 M; 20 cm^3), and the mixture extracted with CH_2Cl_2 (4 × 20 cm^3). The combined organics were dried ($MgSO_4$). After removal of the solvent under reduced pressure, the compound was purified by flash column chromatography (CH_2Cl_2) and recrystallised from hexane to give *hept-5-ynal oxime* **6**, a mixture of *E* and *Z* oximes, as white needles (300 mg, 63%); R_f 0.40 and 0.50 (9 : 1 CH_2Cl_2–ether); mp 65–67 °C (from hexane); Found: C, 67.2; H, 8.9; N, 11.2. $C_7H_{11}NO$ requires C, 67.2; H 8.9; N, 11.2%; ν_{max} (CCl_4)/cm^{-1} 3610s (O–H), 3300brs (O–H), 3080w (=C–H) and 3040w (C–H); δ_H(250 MHz; $CDCl_3$) 7.39 and 6.71 (1 H, t, *J* 6.0 and t, *J* 6.0, CH=N), 2.43 and 2.27 (2 H, td, *J* 7.5 and 6.0 and td, *J* 7.5 and 6.0, CH_2CH=N), 2.22–2.09 (2 H, m, CH_2C≡C), 1.72 (3 H, t, *J* 2.5, CH_3) and 1.63–1.62 (2 H, qu, *J* 7.5 and qu, *J* 7.5, $CH_2CH_2CH_2$); δ_C(100 MHz; $CDCl_3$) 152.0 (d), 151.5 (d), 78.1 (s), 78.0 (s), 76.4 (s), 76.3 (s), 28.6 (t), 25.8 (t), 25.5 (t), 24.3 (t), 18.6 (t), 18.2 (t) and 3.4 (q); *m*/*z* (CI) 126.0919 [$(M + H)^+ \cdot C_7H_{12}NO$ requires *M*, 126.0919], 126 ([M + H]$^+$, 71%), 108 (48), 95 (48), 84 (50), 81 (48), 79 (47), 67 (61), 55 (54), 53 (65), 50 (48) and 41 (100).

6-Ethyl-2,3,4,5-tetrahydropyridine 1-oxide 8

Hydrochloric acid (6 M in MeOH) was added dropwise to a stirred solution of the oxime **6** (100 mg, 0.80 mmol), sodium cyanoborohydride (151 mg, 2.40 mmol, 3 eq.) and methyl orange solution (1 drop) in methanol (5 cm^3) at −10 °C under nitrogen, so as just to keep the solution pink. After 0.5 h, the solution was basified with NaOH (20% aq), the suspension was poured into brine (20 cm^3) containing ice and extracted with CH_2Cl_2 (4 × 20 cm^3). The combined organic extracts were dried ($MgSO_4$). The solvent was removed under reduced pressure and toluene (20 cm^3) was added. The solution was refluxed under nitrogen for 2 h. After removal of the solvent under reduced pressure, the compound was purified by flash column chromatography on a short silica column (EtOAc ⟶ 17 : 3 EtOAc–MeOH) to give the nitrone **8** as a pale yellow oil (94 mg, 94%); R_f 0.10 (17 : 3 EtOAc–MeOH); ν_{max} (CCl_4)/cm^{-1} 1600m (C=N$^+$); δ_H(250 MHz; $CDCl_3$) 3.76 (2 H, t, *J* 6.0, CH_2N^+), 2.53 (2 H, q, *J* 7.5, CH_2CH_3), 2.38 (2 H, t, *J* 6.0, CH_2CH_2C=N$^+$), 1.93–1.83 (2 H, m, $CH_2CH_2N^+$), 1.74–1.64 (2 H, m, CH_2CH_2C=N$^+$) and 1.07 (3 H, t, *J* 7.5, CH_3); δ_C(100 MHz; $CDCl_3$) 150.2 (s), 57.9 (t), 27.8 (t), 24.7 (t), 22.9 (t), 18.6 (t) and 8.7 (q); *m*/*z* (EI) 127.0997 [$(M + H)^+ \cdot C_7H_{13}NO$ requires *M*, 127.0997], 127 (M$^+$, 67%), 110 (12), 82 (15) and 55 (100).

Hex-5-yn-1-yl toluene-4-sulfonate 10

Toluene-4-sulfonyl chloride (10.7 g, 56 mmol, 1.1 eq.) was added to a stirred solution of hex-5-yn-1-ol **9** (5.0 g, 51 mmol) in pyridine (100 cm^3) at 0 °C. The solution was stirred at 0 °C for 16 h, when satd. $NaHCO_3$(200 cm^3) was added. The mixture was stirred at 0 °C for 10 min. The mixture was poured into satd. $NaHCO_3$(200 cm^3), and extracted with ether (3 × 200 cm^3). The organic layers were washed with HCl (2 M; 3 × 200 cm^3) and water (200 cm^3). The combined organics were dried ($MgSO_4$), and the solvent removed under reduced pressure. The compound was purified by flash column chromatography (3 : 1 hexane–EtOAc) to give the tosylate **10** as a colourless oil (12.7 g, 99%); R_f 0.45 (7 : 3 hexane–EtOAc); ν_{max} (CCl_4)/cm^{-1} 3300s (≡C–H) and 2100w (C≡C); δ_H(250 MHz; $CDCl_3$) 7.77 (2 H, d, *J* 8.5, C*H*CSO$_2$), 7.3 (2 H, d, *J* 8.5, C*H*CHCSO$_2$), 4.04 (2 H, t, *J* 6.0, CH_2O), 2.44 (3 H, s, CH_3), 2.15 (2 H, td, *J* 7.0 and 2.5, CH_2C≡CH), 1.91 (1 H, t, *J* 2.5, C≡CH), 1.79–1.71 (2 H, m, CH_2CH_2O) and 1.60–1.48 (2 H, m, CH_2CH_2C≡C); *m*/*z* (EI) 252 (M$^+$, 1%), 188 (24), 162 (16), 155 (65), 97 (47), 91 (100), 80 (96), 77 (20), 69 (22) and 65 (58).

Hept-6-ynenitrile 11

A stirred solution of the tosylate **10** (12.7 g, 51 mmol) and sodium cyanide (3.47 g, 71 mmol, 1.4 eq.) in DMSO (60 cm^3) was heated at 90 °C under nitrogen for 2 h. The solution was cooled to 25 °C and poured into water (180 cm^3). The mixture was extracted with ether (3 × 180 cm^3), and the organic layers were washed with water (3 × 180 cm^3). The combined organic layers were dried ($MgSO_4$), and the solvent removed *in vacuo*. The compound was distilled using a Vigreux column to give the *nitrile* **11** as a colourless oil (4.95 g, 92%); R_f 0.40 (3 : 1 hexane–ether); bp 98–99 °C, 23 mmHg; ν_{max} (CCl_4)/cm^{-1} 3300s (≡C–H), 2220m (C≡N) and 2120w (C≡C); δ_H(250 MHz; $CDCl_3$) 2.38 (2 H, t, *J* 7.0, CH_2CN), 2.25 (2 H, td, *J* 6.5 and 2.5, CH_2C≡CH), 1.97 (1 H, t, *J* 2.5, C≡CH) and 1.86–1.56 (4 H, m, 2 × CH_2); *m*/*z* (CI) 108 ([M + H]$^+$, 52%), 103 (42), 91 (71), 78 (54), 61 (56) and 44 (27).

Hept-6-ynoic acid

Ethanol (7.5 cm^3), water (25 cm^3) and sodium hydroxide (3.70 g, 92.6 mmol, 2 eq.) were added to the nitrile **11** (4.95 g, 46.3 mmol). The stirred mixture was heated at reflux under nitrogen for 12 h. The solution was cooled to 20 °C and poured onto ice. The mixture was acidified with hydrochloric acid (6 M) and extracted with ether (8 × 50 cm^3). The combined organic layers were washed with brine (400 cm^3), and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the compound was purified by filtration through a silica column (ether) to give the *acid* as a pale yellow oil (5.67 g, 97%); R_f 0.15 (16 : 3 : 1 hexane–ether–acetic acid); ν_{max} (CCl_4)/cm^{-1} 3300s (≡C–H), 3400–2500s (carboxylic acid O–H), 2120w (C≡C) and 1710s (C=O); δ_H(250 MHz; $CDCl_3$) 2.38 (2 H, t, *J* 7.5, CH_2COOH), 2.20 (2 H, td, *J* 7.0 and 2.5, CH_2C≡CH), 1.95 (1 H, t, *J* 2.5, C≡CH), 1.79–1.72 (2H, m, CH_2CH_2COOH) and 1.62–1.54 (2 H, m, CH_2CH_2C≡CH); *m*/*z* (CI) 144 ([M + NH_4]$^+$, 70%), 81 (28), 74 (19), 58 (17), 52 (12), 46 (11) and 35 (100).

7-Trimethylsilyl-6-heptynoic acid 12

n-Butyllithium (1.6 M in hexane; 10.9 cm^3, 17.5 mmol) was added dropwise to a stirred solution of hept-6-ynoic acid (1.00 g, 7.94 mmol) in dry THF (50 cm^3) at −78 °C under nitrogen. Chlorotrimethylsilane (3.0 cm^3, 23.8 mmol) was added rapidly to the white suspension. The solution was

warmed to 20 °C and quenched with aqueous HCl (2 M; 50 cm^3). Dichloromethane (50 cm^3) was added, and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 50 cm^3), and the combined organic layers were dried ($MgSO_4$). The solvent was removed under reduced pressure and the compound was purified by recrystallisation from hexane at −40 °C to give the acid **12** as a white solid (1.23 g, 78%); R_f 0.15 (80 : 15 : 5 hexane–ether–acetic acid); mp 35–37 °C (from hexane); Found: C, 60.5; H, 9.3. $C_{10}H_{18}O_2Si$ requires C, 60.6; H, 9.2%; ν_{max} (CCl_4)/cm^{-1} 3400–2500s (O–H), 2180s (CC) and 1715s (C=O); δ_H(250 MHz; $CDCl_3$) 2.38 (2 H, t, *J* 7.5, CH_2COOH), 2.24 (2 H, t, *J* 7.5, CH_2C≡C), 1.79–1.67 (2 H, m, CH_2CH$_2$COOH), 1.62–1.51 (2 H, m, CH_2CH$_2$C≡C) and 0.13 [9 H, s, Si(CH_3)$_3$]; δ_C(100 MHz; $CDCl_3$) 179.9 (s), 106.6 (s), 84.9 (s), 33.5 (t), 27.8 (t), 23.7 (t), 19.5 (t) and 0.1 (q); *m*/*z* (CI) 216.142 [(M + NH_4)·$C_{10}H_{22}NO_2Si$ requires *M*, 216.142], 216 [(M + NH_4)$^+$, 85%], 199 [(M + H)$^+$, 100%] and 166 (99).

(*R*)-3-(7-Trimethylsilylhept-6-ynoyl)-4-phenylmethyl-1,3-oxazolidin-2-one 13

Triethylamine (1.67 cm^3, 10.9 mmol, 1 eq.) and pivaloyl chloride (1.34 cm^3, 10.9 mmol, 1 eq.) were added dropwise to a stirred solution of the acid **12** (2.15 g, 10.9 mmol) in dry ether (100 cm^3) at −78 °C under nitrogen. The white suspension was warmed to 0 °C and stirred at 0 °C for 50 min.

n-BuLi (1.6 M in hexane; 6.40 cm^3, 10.9 mmol, 1 eq.) was added dropwise to a stirred solution of (*R*)-4-phenylmethyl-1,3-oxazolidin-2-one (1.92 g, 10.9 mmol, 1 eq.) in dry THF (100 cm^3) containing diphenylacetic acid (5 mg) as an indicator. The yellow solution was stirred at −78 °C for 20 min. The anhydride mixture was cooled to −78 °C and the auxiliary anion solution added by cannula at −78 °C. The white suspension was allowed to warm to 25 °C before the suspension was poured into brine (200 cm^3) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 200 cm^3) and the combined organic layers dried ($MgSO_4$). The solvent was removed under reduced pressure and the compound purified by flash column chromatography (17 : 3 hexane–EtOAc) to give the *N-acyloxazolidinone* **13** as a very viscous colourless oil (2.84 g, 73%); R_f 0.20 (4 : 1 hexane–EtOAc); $[a]_D^{21}$ −67.8 (*c* 1.03 in EtOH); Found: C, 67.4; H, 7.6; N, 4.0. $C_{20}H_{27}NO_3Si$ requires C, 67.2; H, 7.7; N, 3.9%; ν_{max} (CCl_4)/cm^{-1} 2200m (C≡C), 1800s (C=O) and 1710s (C=O); δ_H(250 MHz; $CDCl_3$) 7.36–7.18 (5 H, m, aromatic), 4.70–4.61 (1 H, m, C*H*HO), 4.23–4.12 (2 H, m, C*H*HO and C*H*N), 3.29 (1 H, dd, *J* 13.5 and 3.5, C*H*HPh), 3.02–2.86 (2 H, m, CH_2CO), 2.75 (1 H, dd, *J* 13.5 and 9.5, C*H*HPh), 2.22 (2 H, t, *J* 7.0, CH_2C≡C), 1.85–1.73 (2 H, m, CH_2CH$_2$CO), 1.66–1.54 (2 H, m, CH_2CH$_2$C≡C) and 0.14 (9 H, s, Si(CH_3)$_3$); δ_C(100 MHz; $CDCl_3$) 172.9 (s), 153.4 (s), 135.2 (s), 129.4 (d), 128.9 (d), 127.3 (d), 106.8 (s), 84.7 (s), 66.2 (t), 55.1 (d), 37.9 (t), 35.0 (t), 28.0 (t), 23.3 (t), 19.7 (t) and 0.1 (q); *m*/*z* (EI) 358.1840 [(M$^+$)·$C_{20}H_{27}NO_3Si$ requires *M*, 358.1839], 357 (M$^+$, 8%), 342 (95), 250 (100), 181 (31), 165 (14), 117 (40), 91 (69) and 73 (60).

(4*R*,1′*R*)-3-Hydroxy-1-(1-phenylmethyl-2-hydroxyethyl)-4-(5-trimethylsilylpent-4-ynyl)-1,3-imidazolidine-2,5-dione 16 and (4*R*,2′*R*)-3-[(6-methyl-1-oxo-2,3,4,5-tetrahydro-2-pyridyl)methanoyl]-4-phenylmethyl-1,3-oxazolidin-2-one 15

NaHMDS (1.0 M in THF; 0.31 cm^3, 0.31 mmol, 1.1 eq.) was added dropwise to a stirred solution of the *N*-acyloxazolidinone **13** (100 mg, 0.28 mmol) in dry THF (5 cm^3) at −78 °C under nitrogen. After 0.5 h, 1-chloro-1-nitrosocyclohexane (42 μL, 0.32 mmol, 1.15 eq.) was added dropwise and stirring continued for 0.5 h. The reaction was quenched with HCl (2.0 M aq; 2 cm^3) and allowed to warm to 25 °C. After 0.25 h, the solution was basified with aq $NaHCO_3$ (satd.) and stirred for a further 0.5 h. The mixture was poured into aq $NaHCO_3$ (satd; 20 cm^3), and the mixture extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The compound was purified by flash column chromatography (19 : 1 CH_2Cl_2–MeOH) and HPLC (9 : 1 CH_2Cl_2–MeOH) to give *imidazolidinedione* **16** as a very viscous colourless oil (16 mg, 15%); R_f 0.30 (19 : 1 CH_2Cl_2–MeOH); +22.7 (*c* 1.34 in CCl_4); ν_{max} (CCl_4)/cm^{-1} 3250brm (O–H), 2180m (C(C)), 1775m (C=O) and 1715s (C=O); δ_H(250 MHz; $CDCl_3$) 7.29–7.14 (5 H, s, aromatics), 4.52–4.49 (1 H, m, NC*H*CON), 4.11–3.99 (2 H, m, NC*H*Bn and C*H*HOH), 3.83 (1 H, dd, *J* 11.5 and 4.0, CH*H*OH), 3.13 (1 H, dd, *J* 14.0 and 11.0, C*H*HPh), 2.99 (1 H, dd, *J* 14.0 and 6.0, C*H*HPh), 2.12 (2 H, t, *J* 7.0, CH_2C≡C), 1.89–1.65 (2 H, m, CH$_2$), 1.32–1.20 (1 H, m, CH), 1.04–0.94 (1 H, m, CH) and 0.15 (9 H, s, Si(CH$_3$)$_3$); δ_C(100 MHz; $CDCl_3$) 170.4 (s), 159.7 (s), 136.6 (s), 129.2 (d), 129.0 (d), 126.9 (d), 106.4 (s), 85.4 (s), 63.3 (d), 62.5 (t), 55.3 (d), 33.8 (t), 27.0 (t), 22.2 (t), 19.5 (t) and 0.1 (q); *m*/*z* (CI) 389.1897 [(M + H)$^+$·$C_{20}H_{28}N_2O_4Si$ requires *M*, 389.1897], 389 ([M + H]$^+$, 72%), 373 (100) and 357 (22); and the *nitrone* **15** as a white foam (18 mg, 20%); R_f 0.25 (19 : 1 CH_2Cl_2–MeOH); $[a]_D^{22}$ −74.6 (*c* 1.00 in CCl_4); ν_{max} (CCl_4)/cm^{-1} 1790s (C=O) and 1715s (C=O); δ_H(250 MHz; $CDCl_3$) 7.37–7.22 (5 H, m, aromatics), 5.90 (1 H, br s, C$_H$N$^+$), 4.77–4.67 (1 H, m, C*H*HO), 4.30–4.11 (2 H, m, CH*H*O and C*H*N), 3.35 (1 H, dd, *J* 13.5 and 3.0, CH*H*Ph), 2.92 (1 H, dd, *J* 13.5 and 9.0, C*H*HPh), 2.68–2.42 (2 H, m, CH_2), 2.35–1.99 (2 H, m, CH_2), 2.21 (3 H, br s, CH_2C=N$^+$) and 1.90–1.72 (2 H, m, CH_2); δ_C(63 MHz; $CDCl_3$) 168.4 (s), 152.8 (s), 148.5 (s), 134.7 (s), 129.6 (d), 128.9 (d), 127.3 (d), 68.1 (d), 66.3 (t), 55.2 (d), 37.2 (t), 30.4 (t), 26.2 (t), 18.6 (q) and 15.6 (t); *m*/*z* (CI) 317.150 [(M + H)$^+$·$C_{17}H_{21}N_2O_4$ requires *M*, 317.150], 317 ([M + H]$^+$, 100%), 301 (96), 195 (63) and 178 (90).

(2*R*)-*N*-(7-Trimethylsilylhept-6-ynoyl)bornane-10,2-sultam 17

Triethylamine (0.98 cm^3, 7.0 mmol, 1 eq.) and pivaloyl chloride (0.87 cm^3, 7.0 mmol, 1 eq.) were added dropwise to a stirred solution of the acid **12** (1.40 g, 7.0 mmol) in dry ether (50 cm^3) at −78 °C under nitrogen. The white suspension was warmed to 0 °C and stirred at 0 °C for 50 min.

n-BuLi (1.6 M in hexane; 4.4 cm^3, 7.0 mmol, 1 eq.) was added dropwise to a stirred solution of (1*S*)-(−)-camphor-10,2-sultam (1.52 g, 7.0 mmol, 1 eq.) in dry THF (50 cm^3) containing diphenylacetic acid (5 mg) as an indicator at −78 °C under nitrogen.

After 20 min, the anhydride mixture was cooled to −78 °C and the auxiliary anion solution added by cannula at −78 °C. The white suspension was allowed to warm to 25 °C before the suspension was poured into brine (200 cm^3) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 200 cm^3) and the combined organic layers dried ($MgSO_4$). The solvent was removed under reduced pressure and the compound purified by flash column chromatography (1 : 1 hexane–EtOAc) to give the *N-acylsultam* **17** as a white solid (1.93 g, 69%); R_f 0.55 (1 : 1 hexane–EtOAc); $[a]_D^{22}$ −72.2 (*c* 1.34 in CCl_4); mp 48–49 °C (from hexane at −40 °C); Found: C, 60.9; H, 8.6; N, 3.3; S, 8.1. $C_{20}H_{33}NO_3SiS$ requires C, 60.7; H, 8.4; N, 3.5; S, 8.1%; ν_{max} (CCl_4)/cm^{-1} 2200s (C≡C) and 1710s (C=O); δ_H(250 MHz; $CDCl_3$) 3.85 (1 H, dd, *J* 7.0 and 5.5, C*H*N), 3.48 (1 H, d, *J* 14.0, C*H*HSO$_2$), 3.40 (1 H, d, *J* 14.0, CH*H*SO$_2$), 2.72 (2 H, t, *J* 7.5, CH_2CO), 2.23 (2 H, t, *J* 7.0, CH_2C≡C), 2.09–2.05 (2 H, m, CH_2), 1.92–1.85 (2 H, m, CH_2), 1.78–1.69 (2 H, m, CH_2CH$_2$CO), 1.61–1.49 (2 H, m, CH_2CH$_2$C≡C), 1.43–1.32 (2 H, m, CH$_2$), 1.25–1.22 (1 H, m, CH), 1.14 (3 H, s, CH_3C), 0.95 (3 H, s, CH_3C) and 0.12 (9 H, s, Si(CH_3)$_3$); δ_C(100 MHz; $CDCl_3$) 171.6 (s), 106.8 (s), 84.7 (s), 65.2 (d), 52.9 (s), 48.4 (t), 47.7 (s), 44.6 (d), 38.5 (t), 34.9 (t), 32.8 (t), 27.9 (t), 26.4 (t), 23.5 (t), 20.8 (q), 19.9 (q), 19.6 (t) and 0.1 (q); *m*/*z* (CI) 396.203 [(M + H)$^+$·$C_{20}H_{34}NO_3SiS$ requires *M*, 396.203], 396 ([M + H]$^+$, 100%) and 90 (13).

(2*R*, 2′*R*)-*N*-[(6-Methyl-1-oxo-2,3,4,5-tetrahydro-2-pyridyl)-methanoyl]bornane-10,2-sultam 19

NaHMDS (1.0 M in THF; 0.28 cm^3, 0.28 mmol, 1.1 eq.) was added dropwise to a stirred solution of the *N*-acylsultam **17** (100 mg, 0.25 mmol) in dry THF (5 cm^3) at −78 °C under nitrogen. After 0.5 h, 1-chloro-1-nitrosocyclohexane (36 μL, 0.28 mmol, 1.15 eq.) was added dropwise and stirring continued for 0.5 h. The reaction was quenched with HCl (2.0 M aq; 2 cm^3) and allowed to warm to 25 °C. After 1 h, the solution was poured into aq $NaHCO_3$ (satd; 20 cm^3), and the mixture extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The compound was purified by flash column chromatography (19 : 1 CH_2Cl_2–MeOH) and HPLC (94 : 6 CH_2Cl_2–MeOH) to give the nitrone **19** as a white solid (76 mg, 85%); R_f 0.20 (19 : 1 CH_2Cl_2–MeOH); $[\alpha]_D^{23}$ −63.3 (*c* 1.06 in CCl_4); mp 162–164 °C (from 1 : 1 hexane–EtOAc); δ_H(400 MHz; $CDCl_3$) 5.18 (1 H, br s, CHN$^+$), 3.87 (1 H, dd, *J* 7.5 and 5.0, C*H*N), 3.5 (1 H, d, *J* 13.5, CH*H*SO_2), 3.41 (1 H, d, *J* 13.5, CH*H*SO_2), 2.56–2.12 (5 H, m, 2 × CH_2 and CH), 2.10 (3 H, s, CH_3C=N$^+$), 2.00 (1 H, dd, *J* 14.0 and 8.0, CH), 1.93–1.83 (4 H, m, 2 × CH_2), 1.69–1.59 (1 H, m, CH), 1.37 (1 H, t, *J* 10.0, CH), 1.34 (1 H, t, *J* 10.0, CH), 1.25 (3 H, s, CH_3) and 0.93 (3 H, s, CH_3).

5-Benzyloxypentan-1-yl toluene-4-sulfonate [78]

5-Benzyloxypentan-1-ol **25** (4.79 g, 26.9 mmol) was dissolved in CH_2Cl_2 (35 cm^3) and cooled to 0 °C under nitrogen. Triethylamine (5.6 cm^3, 40.3 mmol, 1.5 eq.) and DMAP (100 mg, cat.) were added followed by the portionwise addition of toluene-4-sulfonyl chloride (4.98 g, 26.1 mmol, 0.97 eq.) over 0.25 h. After stirring for 20 minutes at 0 °C, the reaction was stirred at 25 °C for 3 h. The reaction was poured into ether (250 cm^3) and washed with water (50 cm^3) then hydrochloric acid (2 M; 100 cm^3). The combined aqueous layers were extracted with ether (2 × 100 cm^3) and the organics combined, dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a yellow oil. Purification by flash column chromatography (2 : 1 hexane–EtOAc) furnished the tosylate as a colourless oil (8.03 g, 88%); R_f 0.37 (2 : 1 hexane–EtOAc); δ_H(200 MHz; $CDCl_3$) 7.78 (2 H, dd, *J* 8.5 and 2.0, aromatics), 7.40–7.21 (7 H, m, aromatics), 4.50 (2 H, s, PhCH_2O), 4.02 (2 H, t, *J* 6.0, C$H_2$$OSO_2$), 3.42 (2 H, t, *J* 6.0, CH_2OPh), 2.44 (3 H, s, CH_3) and 1.82–1.36 (6H, m, 3 × CH_2).

1-Benzyloxy-5-iodopentane 26 [48]

5-Benzyloxypentan-1-yl toluene-4-sulfonate (8.03 g, 23.0 mmol) was dissolved in dry acetone (55 cm^3). Sodium iodide (5.18 g, 34.6 mmol, 1.5 eq.) was added and the mixture stirred under nitrogen at 25 °C for 62 h. The resulting orange suspension was filtered and the white filtrate washed with acetone. The solvent was removed *in vacuo* to leave the crude product as a dark orange semi-solid. The product was purified by flash column chromatography (9 : 1 hexane–EtOAc) to yield the iodide **26** as a pale yellow oil (5.95 g, 85%); R_f 0.68 (2 : 1 hexane–EtOAc) and 0.53 (9 : 1 hexane–EtOAc); δ_H(200 MHz; $CDCl_3$) 7.5–7.2 (5 H, m, aromatics), 4.50 (2 H, s, PhCH_2O), 3.48 (2 H, t, *J* 6.0, CH_2O), 3.19 (2 H, t, *J* 7.0, CH_2I) and 1.92–1.40 (6 H, m, 3 × CH_2).

This compound could also be obtained in improved yield without isolation of the intermediate tosylate.

2-(10-Benzyloxydec-4-yn-1-yloxy)tetrahydropyran 29

2-(Pent-4-yn-1-yloxy)tetrahydropyran **28** (1.3 g, 7.7 mmol) was dissolved in dry THF (65 cm^3), and cooled under nitrogen to −65 °C. *n*-Butyllithium (1.6 M in hexane; 5.1 cm^3, 8.1 mmol, 1.05 eq.) was added slowly dropwise over 5 minutes, maintaining the temperature between −62 °C and −67 °C. The mixture was stirred for 1 h then a solution of 1-benzyloxy-5-iodopentane **26** (2.35 g, 7.73 mmol, 1 eq.) in dry THF (15 cm^3) was added slowly dropwise over 5 minutes. The mixture was allowed to warm to 25 °C, then heated at 55 °C for 48 hours. Water (2 cm^3) was added, and the mixture allowed to cool to 25 °C. The solvents were reduced *in vacuo* and the residue taken up in ether (15 cm^3). The solvents were again reduced *in vacuo* and the residue taken up in EtOAc (250 cm^3). The resulting orange solution was washed with water (50 cm^3) and brine (50 cm^3). The organic layer was dried ($MgSO_4$), and the solvent removed *in vacuo*. The mixture was purified by flash column chromatography (9 : 1 hexane–EtOAc) to yield the alkyne **29** as a colourless oil (2.18 g, 82%); R_f 0.21 (9 : 1 hexane–EtOAc); Found: C, 76.7; H, 9.3. $C_{22}H_{32}O_3$ requires C, 76.7; H, 9.3%; ν_{max} (thin film)/cm^{-1} no absorptions other than C–H stretches above 1500 cm^{-1}; δ_H(400 MHz; $CDCl_3$) 7.36–7.22 (5 H, m, aromatics), 4.57 (1 H, t, *J* 3.0, C*H*O_2), 4.48 (2 H, s, PhCH_2), 3.88–3.75 (2 H, m, CH_2O), 3.36–2.50 (2 H, m, CH_2OTHP), 3.46 (2 H, t, *J* 6.0, CH_2OBn), 2.26–2.24 (2 H, m, CH_2C≡C), 2.23–2.11 (2 H, m, C≡CCH_2) and 1.78–1.48 (14 H, m, 7 × CH_2); δ_C(100 MHz; $CDCl_3$) 136.6 (s), 136.3 (d), 127.7 (d), 127.6 (d), 80.4 (s), 79.8 (s), 72.7 (t), 70.2 (t), 62.4 (t), 31.8 (t), 29.2 (t), 26.7 (t), 25.4 (t), 25.3 (t) and 18.6 (t); *m*/*z* (CI) 362.2695 [(M + NH_4)$^+$·$C_{22}H_{36}NO_3$ requires *M*, 362.2694], 362 ([M + NH_4]$^+$, 47%), 261 (100), 169 (22), 102 (100) and 85 (100).

10-Benzyloxydec-4-yn-1-ol 30

2-(10-Benzyloxydec-4-yn-1-yloxy)tetrahydropyran **29** (1.30 g, 3.77 mol) was dissolved in methanol (30 cm^3), Amberlyst-15® acidic ion exchange resin (0.61 g) added and the mixture stirred at 25 °C for 42 h. The mixture was filtered through Celite, and the solvent removed *in vacuo* to give the crude product as a yellow oil which was purified by flash column chromatography (1 : 1 hexane–EtOAc) to give the alcohol **30** as a colourless oil (0.98 g, 100%); R_f 0.36 (1 : 1 hexane–EtOAc); Found: C, 78.3; H, 9.4. $C_{17}H_{24}O_2$ requires C, 78.4; H, 9.3%; ν_{max} (thin film)/cm^{-1} 3400brm (O–H); δ_H(250 MHz; $CDCl_3$) 7.43–7.17 (5 H, m, aromatics), 4.49 (2 H, s, PhCH_2O), 3.67 (2 H, t, *J* 7.0, CH_2OH), 3.48 (2 H, t, *J* 6.5, CH_2OBn), 2.20–2.11 (4 H, m, CH_2C≡CCH_2) and 1.75–1.37 (9 H, m, 4 × CH_2 and OH); δ_C(100 MHz; $CDCl_3$) 138.5 (s), 128.3 (d), 127.6 (d), 127.4 (d), 80.8 (s), 79.4 (s), 72.8 (t), 70.3 (t), 61.8 (t), 31.8 (t), 29.2 (t), 28.8 (t), 25.4 (t), 18.7 (t) and 15.3 (t); *m*/*z* (CI) 261.1854 [(M + H)$^+$·$C_{17}H_{25}O_2$ requires *M*, 261.1854], 261 ([M + H]$^+$, 100%), 169 (37), 108 (41) and 91 (61).

10-Benzyloxydec-4-ynal 31

To a stirred solution of oxalyl chloride (1.50 cm^3, 16.9 mmol, 2.2 eq.) in CH_2Cl_2 (140 cm^3) under argon at −65 °C was added slowly dropwise a solution of DMSO (2.42 cm^3, 33.8 mmol) in dry CH_2Cl_2 (10 cm^3) over 0.5 h. A white precipitate formed which was stirred at −65 °C for 0.5 h. A solution of 10-benzyloxydec-4-yn-1-ol **30** (2.03 g, 7.68 mmol) in CH_2Cl_2 (15 cm^3) was added slowly dropwise over 20 min. The mixture was stirred at −70 °C for a further 20 min, before the dropwise addition of a solution of triethylamine (5.87 cm^3, 42.3 mmol, 5.5 eq.) in CH_2Cl_2 (5 cm^3). After a further 10 minutes at −70 °C, the reaction was allowed to warm to 25 °C. Water (50 cm^3) was added, the aqueous layer separated and extracted with CH_2Cl_2 (2 × 100 cm^3). The combined organics were washed with brine (100 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the crude product as a pale yellow oil. Purification by flash column chromatography (4 : 1 hexane–EtOAc) furnished the aldehyde **31** as a colourless oil (1.86 g, 94%); R_f 0.33 (4 : 1 hexane–EtOAc); Found: C, 79.1; H, 8.7. $C_{17}H_{22}O_2$ requires C, 79.0; H, 8.7%; ν_{max} (thin film)/cm^{-1} 2920–2820s (CH), 2720w (CH-aldehyde) and 1720s (C=O); δ_H(250 MHz; $CDCl_3$) 9.77

(1 H, t, *J* 1.5, C*H*O), 7.37–7.23 (5 H, m, aromatics), 4.48 (2 H, s, PhCH_2O), 3.47 (2 H, t, *J* 6.5, CH_2OBn), 2.56 (2 H, td, *J* 7.0 and 3.5, CH_2CHO), 2.47–2.42 (2 H, m, CH_2C≡C), 2.15–2.10 (2 H, m, C≡CCH_2), 1.63–1.57 (2 H, m, CH_2CH$_2$O) and 1.49–1.40 (4 H, m, 2 × CH_2); δ_C(100 MHz; $CDCl_3$) 201.2 (d), 138.8 (s), 128.5 (t), 127.8 (d), 127.7 (d), 81.5 (s), 78.1 (s), 73.0 (t), 70.4 (t), 43.1 (t), 29.5 (t), 28.9 (t), 25.6 (t), 18.8 (t) and 12.3 (t); *m*/*z* (CI) 259.1698 [(M + H)$^+$·$C_{17}H_{23}O_2$ requires *M*, 259.1698], 276 ([M + OH]$^+$, 44%), 259 ([M + H]$^+$, 100%), 241 (31), 223 (20), 108 (36) and 91 (31).

(*Z*)-13-Benzyloxy-1-trimethylsilyltridec-1,7-diyn-3-ene 32

tert-Butyllithium (1.7 M in pentane; 5.5 cm^3, 9.36 mmol, 1.5 eq.) was added dropwise to a stirred solution of 3-(*tert*-butyldimethylsilyl)-1-trimethylsilylprop-1-yne (2.12 g, 9.36 mmol, 1.5 eq.) in dry THF (20 cm^3) at −78 °C under nitrogen. After 1 h a solution of titanium(IV) isopropoxide (2.81 cm^3, 9.36 mmol, 1.5 eq.) in THF under nitrogen (10 cm^3) was added dropwise at −78 °C. After 10 minutes a solution of the aldehyde **31** (1.65 g, 6.40 mmol) in dry THF (20 cm^3) was added and the resultant mixture stirred for a final 0.5 h at −78 °C then 25 °C for 1 h.

The solution was poured into aqueous hydrochloric acid (2 M, 150 cm^3) and the mixture extracted with hexane (3 × 150 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The compound was purified by flash column chromatography (97 : 3 hexane–ether) to yield enyne **32** as a pale yellow oil (1.93 g, 86%; *Z*–*E*, 1 : 20); R_f 0.15 (97 : 3 hexane–ether); Found: C, 78.1; H, 9.0. $C_{23}H_{32}OSi$ requires C, 78.3; H, 9.1%; ν_{max} (thin film)/cm^{-1} 2150s (C≡C); δ_H(250 MHz; $CDCl_3$) 7.34–7.25 (5 H, m, aromatics), 6.02 (1 H, dt, *J* 11.0 and 7.0, CH=C*H*CH$_2$), 5.54 (1 H, dt, *J* 11.0 and 1.5, C*H*=CHCH$_2$), 4.50 (2 H, s, PhCH_2O), 3.48 (2 H, t, *J* 7.0, CH_2OBn), 2.50 (2 H, q, *J* 7.0, CH=CHCH_2), 2.29–2.24 (2 H, m, CH_2C≡C), 2.19–2.13 (2 H, m, C≡CCH_2), 1.67–1.60 (2 H, m, CH_2), 1.51–1.42 (4 H, m, 2 × CH_2) and 0.20 (9 H, s, Si(CH_3)$_3$); *Trans*-isomer: 6.23 (dt, *J* 16.0 and 7.0, CH=C*H*CH$_2$), 5.60 (dt, *J* 16.0 and 1.5, C*H*=CHCH$_2$) and 0.17 (9 H, s, Si(CH_3)$_3$); δ_H(100 MHz; $CDCl_3$) 143.4 (d), 138.6 (s), 128.3 (d), 127.6 (d), 127.4 (d), 110.1 (d), 101.7 (s), 99.1 (s), 80.7 (s), 79.2 (s), 72.9 (t), 70.3 (t), 29.8 (t), 29.7 (t), 29.3 (t), 25.5 (t), 18.7 (t) and 18.4 (t); *m*/*z* (CI) 370.2566 [(M + NH_4)$^+$·$C_{23}H_{36}NOSi$ requires *M*, 370.2566], 370 ([M + NH_4]$^+$, 38%), 353 ([M + H]$^+$, 24), 259 (47), 108 (61), 91 (100) and 90 (93).

(*Z*)-13-Hydroxy-1-trimethylsilyltridec-1,7-diyn-3-ene

Boron trichloride–methyl sulfide complex (2.0 M in CH_2Cl_2; 2.56 cm^3, 1.8 eq.) was added to a stirred solution of (*Z*)-13-benzyloxy-1-trimethylsilyltridec-1,7-diyn-3-ene **32** (1.00 g, 2.84 mmol) in CH_2Cl_2 (25 cm^3) under nitrogen at 25 °C. After 2 h the purple–black solution was poured into saturated aqueous sodium hydrogen carbonate solution (80 cm^3) and extracted with ether (3 × 80 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (1 : 1 hexane–ether) to yield the alcohol as a colourless oil (0.67 g, 85%); R_f 0.22 (1 : 1 hexane–ether); Found: C, 73.1; H, 10.0. $C_{16}H_{26}OSi$ requires C, 73.2; H, 10.0%; ν_{max} ($CHCl_3$)/cm^{-1} 3640m (O–H), 3450brm (O–H) and 2160s (C≡C); δ_H(200 MHz; $CDCl_3$) 6.02 (1 H, dt, *J* 12.0 and 7.0, CH=CHCH_2), 5.57 (1 H, dt, *J* 12.0 and 6.0, CH=CHCH_2), 3.65 (2 H, t, *J* 6.5, CH_2OH), 2.48 (2 H, q, *J* 6.0, CH=CHCH_2), 2.30–2.13 (4 H, m, CH_2C≡CCH$_2$), 1.65–1.46 (6 H, m, 3 × CH_2) and 0.13 (9 H, s, Si(CH_3)$_3$); δ_c(63 MHz; $CDCl_3$) 143.4 (d), 110.1 (d), 101.7 (s), 99.1 (s), 80.6 (s), 79.3 (s), 63.0 (t), 32.3 (t), 29.8 (t), 28.8 (t), 25.0 (t), 18.7 (t), 18.2 (t) and 0.0 (q); *m*/*z* (CI) 263.1831 [(M + H)$^+$·$C_{16}H_{27}OSi$ requires *M*, 263.1831], 263 ([M + H]$^+$, 100%), 173 (21), 131 (12) and 90 (40).

(*Z*)-13-Trimethylsilyltridec-6,12-diyn-10-enoic acid 33

To a solution of 13-hydroxy-1-trimethylsilyltridec-1,7-diyn-3-ene (1.0 g, 3.8 mmol) in acetone (40 cm^3) at −5 °C, was added Jones reagent (2.0 M; 7.6 cm^3, 7.6 mmol, 2 eq.) dropwise over 10 min. This process was repeated at 15 min intervals until TLC analysis showed formation of product acid (R_f 0.45, 7 : 3 ether–hexane) and disappearance of starting alcohol (R_f 0.36, 7 : 3 ether–hexane).

The excess oxidant was quenched with excess propan-2-ol (50 cm^3) and the resulting green solution poured into water (100 cm^3). The aqueous solution was extracted with EtOAc (3 × 150 cm^3), the organic layers combined, dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was purified by flash column chromatography (7 : 3 ether–hexane) to yield the acid **33** as a colourless oil (950 mg, 90%); R_f 0.45 (7 : 3 ether–hexane); Found: C, 69.4; H, 8.6. $C_{16}H_{24}O_2Si$ requires C, 69.5; H, 8.7%; ν_{max} (thin film)/cm^{-1} 3400–2900brm (COO-H), 2170s (C≡C) and 1710s (C=O); δ_H(250 MHz; $CDCl_3$) 6.05 (1 H, dt, *J* 10.5 and 6.5, CH=CHCH_2), 5.55 (1 H, dt, *J* 10.5 and 1.5, C*H*≡CHCH$_2$), 2.50 (2 H, q, *J* 6.5, CH=CHCH_2), 2.35 (2 H, t, *J* 8.0, CH_2CO$_2$H), 2.35–2.20 (4 H, m, CH_2C≡CCH$_2$), 1.80–1.70 (2 H, m, –CH_2–), 1.60–1.50 (2 H, m, –CH_2–) and 0.20 (9 H, s, Si(CH_3)$_3$); δ_C(63 MHz; $CDCl_3$) 179.5 (s), 143.3 (d), 110.2 (d), 101.7 (s), 99.5 (s), 80.1 (s), 79.7 (s), 35.5 (t), 29.8 (t), 28.3 (t), 23.8 (t), 18.4 (t), 18.2 (t) and 0.0 (q); *m*/*z* (CI) 276.1551 [(M)$^+$·$C_{16}H_{24}O_2Si$ requires *M*, 276.1545], 276 (M$^+$, 34), 261 (33), 243 (26), 217 (40), 189 (96), 181 (75), 175 (37), 161 (65), 157 (44) and 73 (100).

(*Z*)-(2*S*)-*N*-(13′-Trimethylsilyltridec-6′,12′-diyn-10′-enoyl)-bornane-10,2-sultam 34

Triethylamine (0.47 cm^3, 3.4 mmol, 1 eq.) and pivaloyl chloride (0.42 cm^3, 3.4 mmol) were added dropwise to a solution of the acid **33** (930 mg, 3.4 mmol) in dry ether (30 cm^3) at −78 °C under nitrogen. The white suspension was allowed to warm to 0 °C and stirred for 50 min.

n-Butyllithium (1.6 M in hexane; 2.23 cm^3, 3.41 mmol, 1 eq.) was added dropwise to a solution of (1*R*)-(+)-camphor-10,2-sultam (725 mg, 3.41 mmol) in dry THF (30 cm^3) containing diphenylacetic acid (3 mg) as an indicator at −78 °C under nitrogen. After 20 min the anhydride mixture was cooled to −78 °C, and the auxiliary anion solution was added by cannula at −78 °C under nitrogen. The white suspension was allowed to warm to 25 °C. The suspension was poured into brine (100 cm^3) and the mixture extracted with CH_2Cl_2 (3 × 100 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (4 : 1 hexane–EtOAc) to yield pure sultam **34** as a colourless oil (1.36 g, 86%); R_f 0.3 (4 : 1 hexane–EtOAc); $[\alpha]_D^{20}$ +0.40 (*c* 0.75, $CHCl_3$); Found: C, 65.8; H, 8.2; N, 3.0. $C_{26}H_{39}NO_3SSi$ requires C, 65.9; H, 8.3; N 3.0%; ν_{max} (thin film)/cm^{-1} 2253m (C≡C), 2140m (C≡C) and 1697s (C=O); δ_H(250 MHz; $CDCl_3$) 6.01 (1 H, dt, *J* 11.0 and 7.0, CH=C*H*CH$_2$), 5.53 (1 H, d, *J* 11.0, C*H*=CHCH$_2$), 3.84 (2 H, dd, *J* 7.0 and 5.5, CHN), 3.49 (1 H, d, *J* 14.0, CH*H*SO$_2$), 3.40 (1 H, d, *J* 14.0, C*H*HSO$_2$), 2.71 (2 H, t, *J* 7.0, CH_2C≡C), 2.44 (2 H, q, *J* 7.0, CH=CHCH_2), 2.28–2.12 (4 H, m, 2 × CH$_2$), 2.12–2.00 (2 H, m, CH$_2$), 1.91–1.80 (2 H, m, CH$_2$), 1.80–1.68 (2 H, m, CH_2CH$_2$CO), 1.62–1.47 (2 H, m, CH_2CH$_2$C≡C), 1.40–1.33 (1 H, m, CH$_2$), 1.25–1.20 (1 H, m, CH), 1.14 (3 H, s, CH_3), 0.94 (3 H, s, CH_3) and 0.11 (9 H, s, Si(CH_3)$_3$); δ_C(63 MHz; $CDCl_3$) 171.1 (s), 143.5 (d), 109.9 (d), 101.7 (s), 99.0 (s), 80.0 (s), 79.5 (s), 65.3 (d), 53.9 (t), 48.4 (t), 47.7 (s), 44.6 (d), 38.5 (t), 34.9 (t), 32.8 (t), 29.8 (t), 28.3 (t), 26.4 (t), 23.6 (t), 20.8 (q), 19.9 (q), 18.5 (s), 18.2 (s) and 0.0 (q); *m*/*z* (CI) 474.2498 [(M + H)$^+$·$C_{26}H_{40}NO_3SSi$ requires *M*, 474.2498], 491 ([M + NH_4]$^+$, 6%), 474 ([M + H]$^+$, 21), 397 (16), 380 (15), 317 (50), 300 (28), 233 (100), 216 (19) and 90 (47).

(*Z*)-(2*S*,2′*S*)-*N*-(2′-Hydroxyamino-13′-trimethylsilyltridec-6′,12′-diyn-10′-enoyl)bornane-10,2-sultam 35

Sodium hexamethyldisilazide (1.0 M in THF; 0.46 cm^3, 0.46 mmol, 1.1 eq.) was added dropwise to a stirred solution of the *N*-acyl sultam **34** (200 mg, 0.42 mmol) in dry THF (10 cm^3) at −78 °C under nitrogen. After 1 h, 1-chloro-1-nitrosocyclohexane (60 μL, 0.46 mmol, 1.1 eq.) in THF (2 cm^3) was added dropwise at −78 °C under nitrogen. After a further 0.5 h the reaction was quenched with aqueous hydrochloric acid (2 M, 3 cm^3) and allowed to warm to 25 °C. The solution was stirred at 25 °C under argon for 1 h.

The solution was poured into sodium hydrogen carbonate (satd.; 30 cm^3) and extracted with CH_2Cl_2 (3 × 30 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The compound was purified by flash column chromatography (4 : 1 hexane–EtOAc) to give hydroxylamine **35** as a colourless gum (124 mg, 61%); R_f 0.42 (1 : 1 hexane–EtOAc); $[\alpha]_D^{20}$ +42.1 (*c* 1.97, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3472m (N–H), 3265m (O–H), 2144s (C≡C) and 1692s (C=O); δ_H(400 MHz; $CDCl_3$) 6.01 (1 H, dt, *J* 11.0 and 7.0, CH=C*H*CH$_2$), 5.53 (1 H, d, *J* 11.0, C*H*=CHCH$_2$), 5.39 (1 H, br s, NH or OH), 4.17–4.04 (2 H, m, C*H*NHOH and O*H* or N*H*), 3.84 (1 H, dd, *J* 7.0 and 5.5, C*H*N), 3.52 (1 H, d, *J* 14.0, CH*H*SO$_2$), 3.44 (1 H, d, *J* 14.0, C*H*HSO$_2$), 2.50–2.43 (2 H, m, CH=CHC*H*$_2$), 2.28–2.16 (4 H, m, C*H*$_2$C≡CC*H*$_2$), 2.12–2.00 (2 H, m, C*H*$_2$), 1.93–1.80 (5 H, m, 2 × C*H*$_2$ and C*H*), 1.70–1.55 (2 H, m, C*H*$_2$CHCO), 1.47–1.32 (2 H, m, C*H*$_2$CH$_2$C≡C), 1.17 (3 H, s, C*H*$_3$), 0.94 (3 H, s, C*H*$_3$) and 0.11 (9 H, s, Si(C*H*$_3$)$_3$); δ_C(100 MHz; $CDCl_3$) 173.1 (s), 143.5 (d), 109.9 (d), 101.7 (s), 99.0 (s), 80.0 (s), 79.5 (s), 65.3 (d), 64.3 (d), 53.0 (t), 48.7 (t), 47.8 (t), 44.5 (d), 38.2 (t), 32.7 (t), 29.7 (t), 27.7 (t), 26.4 (t), 25.4 (t), 20.6 (q), 19.9 (q), 18.7 (s), 18.2 (s) and 0.0 (q); *m*/*z* (EI) 504.2480 [(M)$^+$·$C_{26}H_{40}N_2O_4SSi$ requires *M*, 504.2478], 505 ([M + H$_4$]$^+$, 53%), 504 (M$^+$, 47), 489 (35), 461 (34), 432 (35), 304 (62), 289 (49), 262 (100), 91 (48) and 69 (89).

(2*S*,3′a*R*,4′*R*,7′*S*,10′a*R*)-*N*-[4′-(Trimethylsilylethynyl)-octahydro-1′*H*-cyclopenta[3,4]isoxazolo[2,3-*a*]pyridin-7′-ylmethanoyl]bornane-10,2-sultam 37

Hydroxylamine **35** (60 mg, 0.12 mmol) was dissolved in toluene (10 cm^3) and refluxed under argon for 18 h. On cooling the solvent was removed under reduced pressure and the product purified by flash column chromatography (1 : 1 hexane–ether) to give pure *tricycle* **37** as a white solid (50 mg, 83%); R_f 0.15 (1 : 1 hexane–ether); mp 72–74 °C (from 1 : 1 hexane–ether); $[\alpha]_D^{20}$ −25 (*c* 0.4 in $CHCl_3$); Found: C, 61.5; H, 8.2; N, 5.3. $C_{26}H_{40}N_2O_4SSi$ requires C, 61.8; H, 8.0; N, 5.6%; δ_H(500 MHz; $CDCl_3$) 5.31 (1 H, d, *J* 9.0, C*H*(O)C≡C), 3.91 (1 H, dd, *J* 7.5 and 5.0, C*H*N), 3.87 (1 H, dd, *J* 11.5 and 2.5, C*H*C=O), 3.52 (1 H, d, *J* 13.5, CH*H*SO$_2$), 3.42 (1 H, d, *J* 13.5, C*H*HSO$_2$), 2.68 (1 H, dd, *J* 9.0 and 6.5, C*H*C(O)C≡C), 2.25–2.23 (1 H, m, C*H*), 2.11–2.07 (4 H, m, 2 × C*H*$_2$), 1.95–1.82 (5 H, m, 2 × C*H*$_2$ and C*H*), 1.69–1.55 (5 H, m, 2 × C*H*$_2$ and C*H*), 1.42–1.23 (4 H, m, 2 × C*H*$_2$), 1.13 (3 H, s, C*H*$_3$), 0.94 (3 H, s, C*H*$_3$) and 0.17 (9 H, s, Si(C*H*$_3$)$_3$); δ_C(100 MHz; $CDCl_3$) 170.8 (s), 100.6 (s), 94.1 (d), 78.7 (s), 71.3 (d), 65.4 (d), 64.5 (t), 53.3 (d), 49.6 (t), 48.6 (t), 47.8 (s), 44.6 (d), 40.6 (t), 38.1 (t), 33.4 (t), 32.7 (t), 28.4 (t), 27.0 (t), 26.4 (t), 22.9 (q), 20.6 (q), 20.3 (s), 19.9 (s) and 0.0 (q); *m*/*z* (EI) 504.2482 [(M)$^+$·$C_{26}H_{40}N_2O_4SSi$ requires *M*, 504.2478], 504 (M$^+$, 12%), 489 (10), 461 (14), 311 (24), 304 (60), 262 (100), 112 (21), 73 (27) and 55 (16).

(*Z*)-12-Benzyloxydodec-2-en-6-ynenitrile

To a stirred solution of trimethylsilylacetonitrile (357 mg, 3.15 mmol, 1.05 eq.) in dry THF (7 cm^3) at −78 °C under argon was added *n*-butyllithium (1.6 M in hexanes; 2.1 cm^3, 3.15 mmol, 1.05 eq.) slowly dropwise. After 20 min triisopropyl borate (0.73 cm^3, 3.15 mmol, 1.05 eq.) was added and the mixture stirred at −78 °C for a further 10 min. A solution of 10-benzyloxydec-4-ynal **31** (774 mg, 3.00 mmol) in dry THF (2.5 cm^3) was added slowly dropwise. After 2 min HMPA (1.5 cm^3) was added and the mixture stirred at −78 °C for 1 h. Water (15 cm^3) was added, and the mixture allowed to warm to 25 °C. Water (5 cm^3) and ether (150 cm^3) were added and the aqueous layer separated and extracted with ether (2 × 100 cm^3). The organic extracts were combined, dried ($MgSO_4$) and the solvents were removed *in vacuo* to yield the crude product as a pale yellow oil. The crude product was purified by flash column chromatography (4 : 1 hexane–CH_2Cl_2) to yield the *nitrile* as a colourless/white semi-solid (738 mg, 87%; *E*–*Z*, 1 : 8.8); R_f 0.21 (4 : 1 hexane–CH_2Cl_2); ν_{max} (thin film)/cm^{-1} 2220s (C≡N), 1624w (C=C), 1496w, 738s and 699m (*cis*-CH=CH); δ_H(250 MHz; $CDCl_3$) 7.41–7.23 (5 H, m, aromatics), 6.57 (1 H, dt, *J* 11.0 and 7.0, C*H*=CHCN), 5.35 (1 H, dt, *J* 11.0 and 1.0, CH=C*H*CN), 4.50 (2 H, s, PhC*H*$_2$O), 3.48 (2 H, t, *J* 6.5, BnOC*H*$_2$), 2.58 (2 H, q, *J* 7.0, C*H*$_2$CH=CHCN), 2.33 (2 H, tt, *J* 7.0 and 2.5, C*H*$_2$C≡C), 2.15 (2 H, tt, *J* 7.5 and 2.5, C≡CC*H*$_2$) and 1.68–1.42 (6 H, m, 3 × –C*H*$_2$–); δ_H(63 MHz; $CDCl_3$) 153.2 (d), 138.7 (s), 128.3 (d), 127.6 (d), 127.5 (d), 115.8 (s), 100.5 (d), 82.0 (s), 77.7 (s), 72.9 (t), 70.3 (t), 31.2 (t), 29.3 (t), 28.7 (t), 25.5 (t), 18.6 (t) and 17.9 (t); *m*/*z* (CI) 282.1858 [(M + H)$^+$·$C_{19}H_{24}NO$ requires *M*, 282.1858], 299 ([M + NH$_4$]$^+$, 60%), 282 ([M + H]$^+$, 100), 264 (11), 108 (16) and 91 (11).

(*Z*)-12-Hydroxydodec-2-en-6-ynenitrile

To a stirred solution of (*Z*)-12-benzyloxydodec-2-en-6-ynenitrile (483 mg, 1.72 mmol) in dry CH_2Cl_2 (25 cm^3) under nitrogen was added boron trichloride–methyl sulfide complex (2.0 M solution in CH_2Cl_2; 1.6 cm^3, 3.27 mmol, 2.5 eq.). The mixture was stirred under nitrogen for 4 h at 25 °C, poured into sodium hydrogencarbonate solution (satd.; 50 cm^3) and extracted with ether (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (1 : 1 hexane–ether ⟶ ether) to yield the *alcohol* as a pale yellow oil (227 mg, 69%); R_f 0.1 (1 : 1 hexane–ether); ν_{max} (thin film)/cm^{-1} 3400brs (O–H), 2221s (C≡N) and 1624w (C=C); δ_H(250 MHz; $CDCl_3$) 6.59 (1 H, dt, *J* 11.0 and 7.5, C*H*=CHCN), 5.38 (1 H, dt, *J* 11.0 and 0.5, CH=C*H*CN), 3.48 (2 H, t, *J* 6.0, C*H*$_2$O), 2.59 (2 H, q, *J* 7.5, C*H*$_2$CH=CHCN), 2.39–2.30 (2 H, m, C*H*$_2$C≡C), 2.20–2.15 (2 H, m, C≡CC*H*$_2$) and 1.68–1.48 (7 H, m, 3 × C*H*$_2$ and OH); δ_C(63 MHz; $CDCl_3$) 153.2 (d), 115.8 (s), 100.6 (d), 81.9 (s), 77.8 (s), 62.8 (t), 32.3 (t), 31.2 (t), 28.6 (t), 25.0 (t), 18.6 (t) and 17.9 (t); *m*/*z* (CI) 192.1388 [(M + H)$^+$·$C_{12}H_{18}NO$ requires *M*, 192.1388], 209 ([M + NH$_4$]$^+$, 97%), 192 ([M + H]$^+$, 39%), 58 (63), 52 (50), 45 (36) and 44 (100).

(*Z*)-11-Cyanoundec-10-en-6-ynoic acid

(*Z*)-12-Hydroxydodec-2-en-6-ynenitrile (220 mg, 1.15 mmol) was dissolved in acetone (50 cm^3) and cooled to 0 °C before Jones′ reagent (2.5 M; 1.15 cm^3, 2.88 mmol, 2.5 eq.) was added dropwise. After 1.25 h propan-2-ol (2 cm^3) was added and the solvents were reduced *in vacuo*. Water (50 cm^3) was added and the mixture was extracted with EtOAc (3 × 75 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvents removed *in vacuo* to yield the crude product as a colourless oil. Flash column chromatography (1 : 1 hexane–EtOAc ⟶ EtOAc) afforded the *acid* as a colourless oil (163 mg, 69%); R_f 0.22 (1 : 1 hexane–EtOAc); ν_{max} (thin film)/cm^{-1} 3680–2340brm (COO–H), 2221s (C≡N), 1707s (C=O) and 1624w (C=C); δ_H(500 MHz; $CDCl_3$) 6.57 (1 H, dt, *J* 11.0 and 7.0, C*H*=CHCN), 5.39 (1 H, br d, *J* 11.0, CH=C*H*CN), 2.59 (2 H, q, *J* 7.0, C*H*$_2$CH=CHCN), 2.38 (2 H, t, *J* 7.5, C*H*$_2$COOH), 2.34 (2 H, tt, *J* 7.0 and 2.5, C*H*$_2$C≡C), 2.18 (2 H, tt, *J* 7.5 and 2.5, C≡CC*H*$_2$), 1.74 (2 H, qn, *J* 7.5, C*H*$_2$) and 1.54 (2 H, qn, *J* 7.5, C*H*$_2$); δ_C(63 MHz; $CDCl_3$) 178.9 (s), 153.1 (d), 117.0 (s), 100.6 (d), 81.3 (s), 78.2 (s), 33.4 (t), 31.1 (t), 28.1 (t), 23.8 (t), 18.4 (t) and 17.9 (t); *m*/*z* (CI) 206.1172

[(M + H)$^+$·$C_{12}H_{16}NO_2$ requires M, 206.1180], 228 ([M + NH_4]$^+$, 100%), 206 ([M + H]$^+$, 4) and 188 (58).

(*Z*)-(2*R*)-*N*-(11′-Cyanoundec-10′-en-6′-ynoyl)bornane-10,2-sultam 40

(*Z*)-11-Cyanoundec-10-en-6-ynoic acid (247 mg, 1.20 mmol) was dissolved in dry THF (10 cm^3) and cooled to −78 °C under nitrogen. Triethylamine (0.13 cm^3, 1.23 mmol, 1.03 eq.) was added followed by freshly distilled trimethylacetyl chloride (0.15 cm^3, 1.23 mmol, 1.03 eq.). The temperature was allowed to rise to 0 °C and stirred for 50 min during which time a white suspension formed.

(1*R*)-(+)-2,10-Camphorsultam (265 mg, 1.23 mmol, 1.03 eq.) was dissolved in dry THF (10 cm^3) with pyren-1-ylacetic acid (1 mg) as indicator. The solution was cooled to −78 °C under nitrogen. *n*-Butyllithium (1.6 M solution in hexane; 0.82 cm^3, 1.23 mmol, 1.03 eq.) was added slowly dropwise until the pink colour persisted. The solution was stirred at −78 °C for a further 20 min.

The solution of the anhydride was cooled to −78 °C and the solution of the auxiliary anion added by cannula. The mixture was stirred at −78 °C for 5 min then allowed to warm to 25 °C and stirred for 0.5 h. The mixture was poured into brine (50 cm^3) and extracted with CH_2Cl_2 (3 × 75 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvents removed *in vacuo* to yield the crude product as a pale yellow semi-solid. The product was purified by flash column chromatography (4 : 1 CH_2Cl_2–hexane), to yield the pure *sultam* **39** as a pale yellow oil (375 mg, 77%); R_f 0.42 (1 : 1 hexane–EtOAc); $[\alpha]_D^{22}$ +72.2 (*c* 0.85, CH_2Cl_2); ν_{max} (thin film)/cm^{-1} 2220s (C≡N), 1695s (C=O), 1624w (C=C), 1329m (SO_2N) and 1167m (SO_2N); δ_H(500 MHz; $CDCl_3$) 6.57 (1 H, dt, *J* 11.0 and 7.5, C*H*=CHCN), 5.37 (1 H, dt, *J* 11.0 and 1.5, CH=C*H*CN), 3.83 (1 H, dd, *J* 7.5 and 5.0, C*H*N), 3.47 (1 H, d, *J* 14.0, C*H*HSO$_2$), 3.40 (1 H, d, *J* 14.0 CH*H*SO$_2$), 2.70 (2 H, t, *J* 7.5, CH_2C(O)N), 2.56 (2 H, qd, *J* 7.5 and 1.5, CH_2CH=CHCN), 2.30 (2 H, tt, *J* 7.0 and 2.5, CH_2C≡C), 2.14 (2 H, tt, *J* 7.5 and 2.5, C≡CCH_2), 2.10–2.02 (2 H, m, CH_2), 1.94–1.83 (3 H, m, CH_2 and C*H*), 1.78–1.69 (2 H, m, –CH_2), 1.47–1.55 (2 H, m, CH_2), 1.40–1.28 (2 H, m, CH_2), 1.12 (3 H, s, CH_3) and 0.94 (3 H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 171.8 (s), 153.4 (d), 115.9 (s), 100.5 (d), 81.5 (s), 78.1 (s), 65.2 (d), 53.0 (t), 48.4 (s), 47.8 (s), 44.6 (d), 38.5 (t), 35.0 (t), 32.8 (t), 31.1 (t), 28.1 (t), 26.4 (t), 23.6 (t), 20.8 (q), 19.9 (q), 18.5 (t) and 17.9 (t); *m*/*z* (CI) 425.1881 [(M + Na)$^+$·$C_{22}H_{30}N_2O_3$SNa requires M, 425.1875], 425 ([M + Na]$^+$, 100%) and 403 ([M + H]$^+$, 3).

tert-Butyl(pent-4-ynyloxy)diphenylsilane 41[79]

Pent-4-yn-1-ol (30.0 g, 357 mmol) and chloro-*tert*-butyldiphenylsilane (102 cm^3, 392 mmol, 1.1 eq.) were dissolved in CH_2Cl_2 (250 cm^3) and stirred under nitrogen. A solution of imidazole (36.4 g, 535 mmol, 1.5 eq.) in CH_2Cl_2 (480 cm^3) was added dropwise over a period of approx. 0.5 h and the mixture left to stir at 25 °C overnight.

The residue was poured into aq HCl (1 M; 500 cm^3) and the layers separated. The organic layer was dried ($MgSO_4$) and the solvents removed *in vacuo* to yield a pale yellow oil. Purification by flash column chromatography (9 : 1 hexane–ether) furnished the silyl ether **41** as a colourless oil (115.1 g, 100%); R_f 0.55 (9 : 1 hexane–ether); δ_H(250 MHz; $CDCl_3$) 7.70–7.66 (4 H, m, aromatics), 7.43–7.35 (6 H, m, aromatics), 3.76 (2 H, t, *J* 6.5, CH_2O), 2.36 (2 H, td, *J* 6.5 and 2.5, CH_2C≡CH), 1.92 (1 H, t, *J* 2.5, ≡C*H*), 1.78 (2 H, tt, *J* 6.5 and 6.5, CH_2) and 1.06 (9 H, s, C(CH_2)$_3$).

10-Benzyloxy-1-(*tert*-butyldiphenylsilyloxy)dec-6-yne

tert-Butyl(pent-4-ynyloxy)diphenylsilane **32** (55.3 g, 171 mmol) was dissolved in dry THF (250 cm^3) under nitrogen and cooled to −50 °C with stirring. *n*-Butyllithium (1.6 M in hexanes; 107 cm^3, 171 mmol, 1 eq.) was added dropwise over 1 h and the mixture stirred at −50 °C for a further 1.25 h. A solution of 1-benzyloxy-5-iodopentane **26** (47.4 g, 159 mmol) in dry THF (100 cm^3) was added and the mixture heated to 50 °C for 96 h with the exclusion of light. NH_4Cl (satd.; 350 cm^3) was added and the mixture extracted with ether (3 × 350 cm^3). The combined organic extracts were dried ($MgSO_4$), and the product purified by dry powder chromatography (1 : 49 ether–hexane). The pure acetylene was isolated as a very pale yellow oil (69.5 g, 90%); R_f 0.25 (1 : 1 CH_2Cl_2–hexane); Found: C, 78.9; H, 8.6. $C_{33}H_{42}O_2Si$ requires C, 79.5; H, 8.5%; ν_{max} (thin film)/cm^{-1} 3069w (Ar–H), 2931s (C–H), 2857s (C–H), 1427m and 1111s (C–Si); δ_H(250 MHz; $CDCl_3$) 7.69–7.65 (4 H, m, aromatics), 7.40–7.26 (11 H, m, aromatics), 4.50 (2 H, s, PhCH_2O), 3.74 (2 H, t, *J* 6.0, CH_2OSi), 3.46 (2 H, t, *J* 6.5, CH_2OBn), 2.30 (2 H, tt, *J* 6.5 and 2.5, CH_2C≡), 2.14 (2 H, m, ≡CCH_2), 1.79–1.44 (8 H, m, 4 × CH_2) and 1.06 (9 H, s, C(CH_3)$_3$); δ_C(63 MHz; $CDCl_3$) 138.6 (s), 135.6 (d), 134.0 (s), 129.5 (d), 128.4 (d), 127.6 (d), 127.5 (d), 80.2 (s), 79.8 (s), 72.9 (t), 70.3 (t), 62.5 (t), 32.0 (t), 29.3 (t), 28.9 (t), 26.8 (q), 25.5 (t), 19.2 (s), 18.7 (t) and 15.3 (t).

10-(*tert*-Butyldiphenylsilyloxy)dec-6-yn-1-ol

10-Benzyloxy-1-(*tert*-butyldiphenylsilyloxy)dec-6-yne (20.4 g, 40.9 mmol) was dissolved in CH_2Cl_2 (195 cm^3) and cooled to 0 °C under nitrogen. Boron trichloride–methyl sulfide complex (2.0 M in CH_2Cl_2; 30.7 cm^3, 61.5 mmol, 1.5 eq.) was added slowly dropwise over 0.5 h. The ice bath was allowed to thaw and the mixture stirred overnight. The mixture was cooled back down to 0 °C and stirred vigorously during the addition of $NaHCO_3$ (satd.; 210 cm^3) portionwise. The residue was stirred for a further 10 min before the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 200 cm^3), washed with brine (3 × 100 cm^3) and the combined organics evacuated *in vacuo* before drying by azeotroping with toluene (2 × 50 cm^3). The crude product was purified *via* flash column chromatography (1 : 1 hexane–ether) to yield the *alcohol* as an orange viscous oil (16.7 g, 100%); R_f 0.57 (1 : 19 MeOH–CH_2Cl_2); Found: C, 76.3; H, 9.0. $C_{26}H_{36}O_2Si$ requires C, 76.4; H, 8.9%; ν_{max} (thin film)/cm^{-1} 3630–3134brs (O–H), 3070w (Ar–H), 2931s (C–H), 2857s (C–H), 1427m and 1111s (C–Si); δ_H(250 MHz; $CDCl_3$) 7.68–7.67 (4 H, m, aromatics), 7.44–7.36 (6 H, m, aromatics), 3.74 (2 H, t, *J* 6.0, CH_2OSi), 3.62 (2 H, t, *J* 6.5, CH_2OH), 2.30 (2 H, tt, *J* 7.0 and 2.0, CH_2C≡), 2.14 (2 H, tt, *J* 7.0 and 2.0, ≡CCH_2), 1.74 (2 H, tt, *J* 6.5 and 6.5, CH_2), 1.64–1.40 (7 H, m, 3 × CH_2 and O*H*) and 1.05 (9 H, s, C(CH_3)$_3$); δ_C(63 MHz; $CDCl_3$) 135.5 (d), 133.9 (s), 129.5 (d), 127.5 (d), 80.1 (s), 79.8 (s), 62.8 (t), 62.5 (t), 32.2 (t), 32.0 (t), 28.8 (t), 26.8 (q), 24.9 (t), 19.2 (s), 18.7 (t) and 15.2 (t); *m*/*z* (CI) 409.2593 [(M + H)$^+$·$C_{26}H_{37}O_2Si$ requires M, 409.2563], 409 ([M + H]$^+$, 21%) 351 (20), 331 (65), 273 (38), 253 (40), 216 (36), 199 (100), 151 (50) and 135 (61).

10-(*tert*-Butyldiphenylsilyloxy)dec-6-ynoic acid

10-(*tert*-Butyldiphenylsilyloxy)dec-6-yn-1-ol (19.4 g, 47.6 mmol) was dissolved in acetone (760 cm^3) and cooled to 0 °C. Jones′ reagent (2.59 M; 25 cm^3, 64.2 mmol; 1.3 eq.) was added dropwise and the mixture stirred for 3 h. The reaction was quenched by the addition of propan-2-ol (50 cm^3) and stirred for 10 min. The dark green suspension was filtered through silica and the solvents removed *in vacuo*. The crude product was dried by azeotroping with toluene (3 × 50 cm^3) and purified by flash column chromatography (1 : 1 hexane–ether) to afford the *acid* as a pale yellow oil (19.7 g, 98%); R_f 0.41 (1 : 1 hexane–EtOAc); Found: C, 73.4; H, 8.1. $C_{26}H_{34}O_3Si$ requires C, 73.9; H, 8.1%; ν_{max} (thin film)/cm^{-1} 3500–2600brs (COO–H), 2930s (C–H), 2858s (C–H), 1709s (C=O), 1427m and 1111s (C–Si); δ_H(250 MHz; $CDCl_3$) 11.90–10.60 (1 H, br s, OH), 7.69–7.67 (4 H, m, aromatics), 7.44–7.37 (6 H, m, aromatics), 3.74 (2 H, t, *J* 6.0,

CH_2OSi), 2.36 (2 H, t, *J* 7.5, CH_2COOH), 2.30 (2 H, tt, *J* 7.0 and 2.0, CH_2≡), 2.16 (2 H, tt, *J* 7.0 and 2.0, ≡CH_2), 1.77–1.69 (4 H, m, 2 × CH_2), 1.51 (2 H, tt, *J* 7.5, CH_2) and 1.06 (9 H, s, C(CH_3)$_3$); δ_C(63 MHz; $CDCl_3$) 179.7 (s), 135.6 (d), 134.0 (s), 129.5 (d), 127.6 (d), 80.2 (s), 79.6 (s), 62.6 (t), 33.5 (t), 32.0 (t), 28.4 (t), 26.9 (q), 23.8 (t), 19.3 (s), 18.5 (t) and 15.3 (t); *m*/*z* (CI) 423.2373 [(M + H)$^+$·$C_{26}H_{35}O_3Si$ requires *M*, 423.2355], 423 ([M + H]$^+$, 38%), 365 (20), 345 (37), 287 (100), 216 (42), 199 (78) and 78 (79).

(2*R*)-*N*-[10′-(*tert*-Butyldiphenylsilyloxy)dec-6′-ynoyl]bornane-10,2-sultam 42

To a stirred solution of 10-(*tert*-butyldiphenylsilyloxy)dec-6-ynoic acid (2.84 g, 6.7 mmol) and NEt_3 (0.94 cm^3, 6.7 mmol, 1 eq.) in dry THF (60 cm^3) cooled to −78 °C under nitrogen was added trimethylacetyl chloride (0.82 cm^3, 6.7 mmol, 1 eq.). The resulting white suspension was warmed to 25 °C and stirred for 1 h.

In a separate flask (1*R*)-(+)-10-camphor-10,2-sultam (1.57 g, 6.7 mmol, 1 eq.) was dissolved in dry THF (60 cm^3) under nitrogen and cooled to −78 °C. *n*-BuLi (1.58 M in hexane; 4.27 cm^3, 1 eq.) was added dropwise, pyren-1-ylacetic acid (2 mg) was added as an indicator and the mixture stirred for a further 20 min.

The THF solution of mixed anhydride was recooled to −78 °C and the preformed solution of auxiliary anion added dropwise over 0.75 h. The resulting mixture was allowed to warm to 25 °C and stirred for a further 1.5 h. The residue was filtered through a plug of silica (EtOAc) and concentrated *in vacuo*. The crude material was purified by flash column chromatography (1 : 1 hexane–ether) and thoroughly dried (50 °C, 2 mmHg with vigorous stirring) to yield the coupled product **42** as a viscous oil–glass (3.54 g, 85%); R_f 0.50 (2 : 1 hexane–EtOAc); $[\alpha]_D^{20}$ +47.8 (*c* 0.82 in $CHCl_3$); Found: C, 69.7; H, 7.9; N, 2.1. $C_{36}H_{49}O_4NSSi$ requires C, 69.75; H, 8.0; N, 2.3%; ν_{max} (thin film)/cm^{-1} 3070w (Ar–H), 2956s (C–H), 2857s (C–H), 1959w (C≡C), 1889w (C≡C), 1823w (C≡C), 1697s (C=O), 1427s (^{t}Bu) and 1331s (SO_2N); δ_H(250 MHz; $CDCl_3$) 7.69–7.66 (4 H, m, aromatics), 7.42–7.35 (6 H, m, aromatics), 3.84 (1 H, dd, *J* 7.0 and 6.0, C*H*N), 3.73 (2 H, t, *J* 6.0, CH_2OSi), 3.50 (1 H, d, *J* 14.0, C*H*HSO_2), 3.41 (1 H, d, *J* 14.0, CH*H*SO_2), 2.72 (1 H, t, *J* 7.5, C*H*HC=O), 2.71 (1 H, t, *J* 7.5, C*H*HC=O), 2.28 (2 H, tt, *J* 7.0 and 2.0, ≡CCH_2), 2.19–2.07 (4 H, m, CH_2C≡ and ≡CH_2), 1.92–1.83 (3 H, m, CH_2 and C*H*), 1.78–1.68 (4 H, m, 2 × CH_2), 1.51 (2 H, m, CH_2), 1.43–1.30 (2 H, m, CH_2), 1.15 (3 H, s, CH_3), 1.05 (9 H, s, C(CH_3)$_3$) and 0.95 (3 H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 171.7 (s), 135.6 (d), 134.0 (s), 129.6 (d), 127.6 (d), 80.1 (s), 79.7 (s), 65.2 (d), 62.6 (t), 53.0 (s), 48.4 (t), 47.8 (s), 44.7 (d), 38.6 (t), 35.0 (t), 32.9 (t), 32.0 (t), 28.4 (t), 26.9 (q), 26.5 (t), 23.6 (t), 20.9 (q), 19.9 (s), 18.6 (t) and 15.3 (t); *m*/*z* (CI) 620.3207 [(M + H)$^+$·$C_{36}H_{50}O_4NSSi$ requires *M*, 620.3230], 620 ([M + H]$^+$, 3%), 562 (88), 542 (45), 404 (80), 346 (63), 328 (72), 233 (33), 216 (100), 199 (20), 94 (35) and 78 (40).

(2*R*,2′*S*)-*N*-[10′-(*tert*-Butyldiphenylsilyloxy-2′-hydroxy aminodec-6′-ynoyl]bornane-10,2-sultam 43

The acyl sultam **42** (5.18 g, 8.34 mmol) was dissolved in dry THF (100 cm^3) and cooled to −78 °C under nitrogen. NaHMDS (1.0 M in THF; 10.4 cm^3, 10.4 mmol, 1.25 eq.) was added slowly dropwise and the mixture stirred at −78 °C for 1.25 h. A solution of freshly distilled 1-chloro-1-nitrosocyclohexane (1.35 g, 9.17 mmol, 1.1 eq.) in THF (3.5 cm^3) was added slowly dropwise until the blue colour just persisted and the mixture stirred at −78 °C for a further 0.5 h. Hydrochloric acid (2 M; 53 cm^3) was added in one portion and the mixture brought to 25 °C and stirred for a further 1 h. The mixture was neutralised by the addition of sodium acetate (4.35 g, 0.053 mol) to create a neutral buffer *in situ*. The layers were separated and the aqueous layer extracted with ether (3 × 20 cm^3). The combined organics were washed with brine (3 × 15 cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to yield a green oil. The crude hydroxylamine was purified by short path flash column chromatography (2 : 1 hexane–EtOAc, 1% NEt_3) furnishing the *hydroxylamine* **43** as a cream foam (4.20 g, 77%); R_f 0.24 (2 : 1 hexane–EtOAc); $[\alpha]_D^{16}$ +35.5 (*c* 1.67 in $CHCl_3$); Found: C, 66.4; H, 7.9; N 4.3; $C_{36}H_{50}N_2O_5SSi$ requires C, 66.4; H, 7.7; N, 4.3%; ν_{max} ($CHCl_3$)/cm^{-1} 3583s and 3338s (N–H or O–H), 3072w (Ar–H), 2960s (C–H), 2859s (C–H), 1700s (C=O), 1334m (SO_2N), 1270s and 1111s (C–Si); δ_H(250 MHz; $CDCl_3$) 7.69–7.65 (4 H, m, aromatics), 7.43–7.35 (6 H, m, aromatics), 5.85 (1 H, br s, N*H* or O*H*), 4.64 (1 H, br s, N*H* or O*H*), 4.14 (1 H, t, *J* 7.0, C*H*NHOH), 3.91 (1 H, dd, *J* 7.5 and 5.0, C*H*N), 3.73 (2 H, t, *J* 6.0, CH_2OSi), 3.52 (1 H, d, *J* 13.5, C*H*HSO_2), 3.42 (1 H, d, *J* 13.5, CH*H*SO_2), 2.28 (2 H, tt, *J* 7.0 and 2.5, CH_2C≡C), 2.20–1.30 (15 H, m, 7 × CH_2), 1.19 (3 H, s, CH_3), 1.05 (9 H, s, C(CH_3)$_3$) and 0.97 (3 H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 173.2 (s), 135.6 (d), 134.0 (s), 129.5 (d), 127.6 (d), 80.2 (s), 79.6 (s), 65.4 (d), 64.4 (d), 62.6 (t), 53.1 (s), 48.8 (t), 47.8 (s), 44.6 (d), 38.3 (t), 32.8 (t), 32.1 (t), 27.9 (t), 26.9 (q), 26.5 (t), 25.6 (t), 20.7 (q), 19.9 (q), 19.2 (s), 18.8 (t) and 15.3 (t); *m*/*z* (CI) 651.3276 [(M + H)$^+$. $C_{36}H_{51}N_2O_5SSi$ requires *M*, 651.3288], 651 [(*M* + H)$^+$, 19%], 635 (36), 573 (28), 407 (95), 390 (100), 312 (54), 283 (58) and 256 (59).

(2*R*,2′*S*,6′*R*,8′*R*)-*N*-{6′-[4″-(*tert*-Butyldiphenylsilyloxy)-1″-butyl]-8′-phenyl-1′-aza-9′-oxabicyclo[4.3.0]nonan-2′-ylcarbonyl}bornane-10,2-sultam 45

A stirred solution of (2*R*,2′*R*)-*N*-[10′-(*tert*-butyldiphenylsilyloxy)-2′-hydroxyaminodec-6′-ynoyl]bornane-10,2-sultam **43** (2.74 g, 4.2 mmol) in dry distilled toluene (40 cm^3) under an atmosphere of nitrogen was heated at 75 °C for 7 h. Cyclisation was deemed complete by this time and the solvent was removed *in vacuo* to afford the polar *nitrone* **44** as a glassy residue; R_f 0.04 (2 : 1 hexane–EtOAc); $[\alpha]_D^{20}$ +38.2 (*c* 0.17, $CDCl_3$); ν_{max} (KBr)/cm^{-1} 3071w (Ar–H), 2957s (C–H), 2935s (C–H), 2858m (C–H), 1703s (C=O), 1699s (C–N$^+$), 1332s, 1136s, 1112s (C–Si), 913s, 742s and 704s (Ph–); δ_H(400 MHz; $CDCl_3$) 7.66–7.64 (4 H, m, aromatics), 7.43–7.35 (6 H, m, aromatics), 5.23 (1 H, br t, *J* 6.5, C *H*N$^+$), 3.90 (1 H, dd, *J* 7.5 and 5.0, C*H*N), 3.67 (2 H, m, CH_2OSi), 3.55 (1 H, d, *J* 13.5, C*H*HSO_2), 3.42 (1 H, d, *J* 13.5, CH*H*SO_2), 2.70–2.64 (1 H, m, $^+$N=CC*H*H), 2.55–2.32 (3 H, m, $^+$N=CC*H**H* and N=CCH_2), 2.29–2.12 (1 H, m, C*H*), 2.04 (1 H, dd, *J* 14.0 and 7.5, C*H*), 1.93–1.87 (4 H, m, 2 × CH_2), 1.75–1.55 (5 H, m, 2 × CH_2 and C*H*), 1.45–1.18 (4 H, m, 2 × CH_2), 1.28 (3 H, s, CH_3), 1.04 (9 H, s, SiC(CH_3)$_3$) and 0.96 (3 H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 167.3 (s), 151.1 (s), 135.5 (d), 133.9 (s), 129.5 (d), 127.6 (d), 68.2 (d), 65.3 (d), 63.4 (t), 53.0 (s), 48.9 (t), 47.9 (s), 44.5 (d), 37.9 (t), 32.6 (t), 32.5 (t), 31.1 (t), 28.2 (t), 26.8 (q), 26.5 (t), 26.1 (t), 20.8 (q), 19.8 (q), 19.2 (s) and 16.4 (t); *m*/*z* (ES) 651.3314 [(M + H)$^+$·$C_{36}H_{51}O_5N_2SSi$ requires *M*, 651.3288]; *m*/*z* (Therm) 651 ([M + H]$^+$, 4%), 572 (2), 490 (2), 464 (100), 390 (65), 277 (6), 233 (44) and 152 (2). This intermediate was not purified but directly dissolved in styrene (20 cm^3), quinol (40 mg) was added and the solution heated at 80 °C for 6 h. The excess styrene was then removed *in vacuo* and the residue purified by flash chromatography (4 : 1 hexane–EtOAc) to afford the *isoxazolidine* **45** as a colourless oil (2.7 g, 85%); R_f 0.50 (2 : 1 hexane–EtOAc); $[\alpha]_D^{18}$ −12.5 (*c* 1.19, $CHCl_3$); Found; C, 70.2; H, 7.7; N, 3.7. $C_{44}H_{58}O_5N_2SSi$ requires C, 70.0; H, 7.7; N, 3.7%; ν_{max} (thin film)/cm^{-1} 3074w (Ar–H), 2956s (C–H), 2856s (C–H), 1707s (C=O), 1326s (SO_2N), 1111s (Si–C) and 703s (Ph–); δ_H(500 MHz; $CDCl_3$) 7.64–7.47 (4 H, m, aromatics), 7.42–7.18 (11 H, m, aromatics), 5.69 (1 H, dd, *J* 10.5 and 5.0, C*H*(O)Ph), 4.21 (1 H, dd, *J* 11.5 and 2.5, C*H*C=O), 3.94 (1 H, dd, *J* 7.5 and 4.5, C*H*N), 3.59 (2 H, t, *J* 6.5, CH_2OSi), 3.52 (1 H, d, *J* 13.5, C*H*HSO_2), 3.44 (1 H, d, *J* 13.5, CH*H*SO_2), 2.60 (1 H, dd, *J* 12.5 and 10.5, C*H*HCH(O)Ph), 2.25–1.13 (20 H, m, 9 × CH_2 and 2 × C*H*), 1.12 (3 H, s, CH_3), 1.02 (9 H, s,

C(CH_3)$_3$) and 0.93 (3 H, s, CH_3); δ_C(63 MHz; $CDCl_3$) 171.3 (s), 141.1 (s), 135.6 (d), 134.1 (s), 129.5 (d), 128.2 (d), 127.6 (d), 127.2 (d), 126.5 (d), 78.3 (d), 68.5 (s), 65.5 (d), 63.8 (d), 63.4 (d), 53.4 (s), 48.6 (t), 47.8 (s), 44.7 (d), 41.5 (t), 39.9 (t), 38.4 (t), 33.0 (t), 32.8 (t), 30.7 (t), 27.1 (t), 26.9 (q), 26.4 (t), 20.8 (q), 20.0 (t), 19.9 (q), 19.2 (s) and 19.1 (t); *m*/*z* (CI) 755.3851 [(M + H)$^+$·$C_{44}H_{59}O_5N_2SSi$ requires *M*, 755.3914], 755 ([M + H]$^+$, 50%), 697 (4) and 512 (100).

(2*S*,6*R*,8*R*)-2-(Benzyloxymethyl)-6-(4′-*tert*-butyldiphenylsilyloxy-1′-butyl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane

The *N*-acylsultam **45** (657 mg, 0.870 mmol) was dissolved in dry THF (20 cm^3) and cooled to 0 °C under nitrogen with stirring. Lithium aluminium(IV) hydride (40 mg, 1.05 mmol, 1.2 eq.) was added in one portion and stirring continued for 3 h. TLC analysis (2 : 1 hexane–EtOAc) showed the reaction to be near completion. Further lithium aluminium(IV) hydride (15 mg, 0.39 mmol, 0.45 eq.) was added and the reaction quenched after a further 0.5 h stirring at 0 °C by the careful addition of water (0.5 cm^3). The mixture was filtered through a plug of silica (EtOAc) and the solvent removed *in vacuo* giving the crude alcohol and auxiliary as an inseparable mixture, which was dissolved in dry THF (20 cm^3) without further purification and sodium hydride (60% dispersion in mineral oil; 77 mg, 1.9 mmol, 2.2 eq.) added. The mixture was stirred under nitrogen at 40 °C for 19 h. Benzyl bromide (0.31 cm^3, 2.61 mmol, 3 eq.) was added and the reaction stirred at 40 °C for a further 4 days. The reaction was quenched by the addition of NH_4Cl (satd.; 40 cm^3) and extracted with EtOAc (3 × 40 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. Flash column chromatography (4 : 1 hexane–EtOAc) afforded the *benzyl ether* as a colourless oil (517 mg, 94% over two steps); R_f 0.79 (2 : 1 hexane–EtOAc); $[\alpha]_D^{20}$ −17.9 (*c* 1.65, $CHCl_3$); Found: C, 78.1; H, 8.0; N, 2.2. $C_{41}H_{51}NO_3Si$ requires C, 77.7; H, 8.1; N, 2.2%; ν_{max} (thin film)/cm^{-1} 3068m (Ar–H), 2930s (C–H), 2857s (C–H), 1495m (Ar–H), 1111s (C–Si) and 702s (Ph); δ_H(250 MHz, $CDCl_3$) 7.73–7.65 (4 H, m, aromatics), 7.47–7.22 (16 H, m, aromatics), 5.46 (1 H, dd, *J* 10.0 and 5.0, C*H*(O)Ph), 4.38 (2 H, s, PhCH_2O), 3.99 (1 H, dd, *J* 8.5 and 3.20 C*H*HOBn), 3.64 (2 H, t, *J* 6.5, CH_2OSi), 3.46 (1 H, t, *J* 8.5, CH*H*OBn), 3.06 (1 H, dddd, *J* 11.5, 8.5, 3.0 and 3.0, C*H*N), 2.64 (1 H, dd, *J* 12.5 and 10.0, C*H*HC(O)Ph), 2.15 (1 H, m, CH), 2.04 (1 H, dd, *J* 12.5 and 5.0, CH*H*CH(O)Ph), 1.86 (1 H, m, CH), 1.72–1.15 (10 H, 5 × CH_2) and 1.06 (9 H, s, C(CH_3)$_3$); δ_C(63 MHz, $CDCl_3$) 141.5 (s), 138.5 (s), 135.3 (d), 133.9 (s), 129.3 (d), 128.1 (d), 128.1 (d), 127.5 (d), 127.4 (d), 127.3 (d), 126.9 (d), 125.8 (d), 77.1 (d), 73.3 (t), 73.3 (t), 67.7 (s), 63.6 (t), 59.0 (d), 41.7 (t), 41.6 (t), 32.9 (t), 31.0 (t), 28.2 (t), 26.7 (q), 19.9 (t), 19.1 (s) and 19.0 (t); *m*/*z* (CI) 634.3771 [(M + H)$^+$·$C_{41}H_{52}NO_3Si$ requires *M*, 634.3716], 634 [(M + H)$^+$, 100%], 512 (80), 322 (40), 307 (45) and 199 (40).

(2*S*,6*R*,8*R*)-2-(Benzyloxymethyloxymethyl)-6-(4′-*tert*-butyldiphenylsilyloxy-1′-butyl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]-nonane

N-Acylsultam **45** (1.33 g, 1.76 mmol) was dissolved in THF (45 cm^3) and cooled to 0 °C under nitrogen with stirring. Lithium aluminium hydride (120.3 mg, 3.17 mmol, 1.8 eq.) was added in one portion and stirring continued for 1 h. The reaction was quenched by the addition of the minimal quantity of satd. NH_4Cl and filtered through a plug of silica (EtOAc). The solvent was removed *in vacuo* yielding the crude alcohol as an inseparable mixture with the recovered auxiliary.

The crude mixture was dissolved in dry toluene (19 cm^3) under nitrogen and Bu_4NI (cat.) added. Hünig's base (3.05 cm^3, 17.6 mmol, 10 eq.) was added followed by BOMCl (0.98 cm^3, 7.04 mmol, 4 eq.) and the mixture stirred at 60 °C for 4.5 h. The residue was filtered, diluted with ether and concentrated *in vacuo* to leave an orange oil. Purification by flash column chromatography (9 : 1 hexane–EtOAc; 1% NEt_3) furnished the *benzyloxymethyl ether* as a clear oil (1.06 g, 90%, two steps) R_f 0.08 (9 : 1 hexane–EtOAc); $[\alpha]_D^{18}$ −15.7 (*c* 0.42 in $CHCl_3$); Found: C, 76.0; H, 8.0; N, 2.2. $C_{42}H_{53}NO_4Si$ requires C, 76.0; H, 8.1; N, 2.1%; ν_{max} ($CHCl_3$)/cm^{-1} 3070m (Ar–H), 3031m (Ar–H), 2942s (C–H), 2861s (C–H), 1604m (Ar), 1496m (Ar), 1245m, 1166m, 1111s (C–Si) and 1045s; δ_H(500 MHz; $CDCl_3$) 7.65–7.63 (4 H, m, aromatics), 7.41–7.26 (16 H, m, aromatics), 5.42 (1 H, dd, *J* 10.5 and 5.0, C*H*(O)Ph), 4.81 (1 H, d, *J* 6.5, OC*H*HO), 4.79 (1 H, d, *J* 6.5, OCH*H*O), 4.62 (2 H, s, PhCH_2O), 4.01 (1 H, dd, *J* 9.5 and 3.0, C*H*HOBOM), 3.61 (3 H, m, CH_2OSi and CH*H*OBOM), 3.00 (1 H, dddd, *J* 11.5, 8.0, 3.0 and 3.0, C*H*N), 2.61 (1 H, dd, *J* 12.5 and 10.5, C*H*HCHPh), 2.05–2.00 (2 H, m, CH_2), 1.84 (1 H, m, C*H*), 1.68–1.15 (10 H, m, 4 × CH_2 and 2 × C*H*) and 1.03 (9 H, s, C(CH_3)$_3$); δ_C(63 MHz; $CDCl_3$) 141.7, 138.1, 135.6, 134.2, 129.5, 128.4, 127.9, 127.6, 127.2, 126.1, 95.2, 77.3, 71.0, 69.4, 68.0, 63.9, 59.3, 42.0, 41.6, 33.1, 31.2, 28.3, 26.9, 20.1, 19.5 and 19.2; *m*/*z* (CI) 664.3818 [(M + H)$^+$·$C_{42}H_{54}NO_4Si$ requires *M*, 664.3822], 664 [M$^+$, 40%], 544 (100), 256 (26) and 154 (42).

(2*S*,6*R*,8*R*)-2-(Benzyloxymethyloxymethyl)-6-(4′-hydroxy-1′-butyl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane

To a solution of the above silyl ether (943 mg, 1.42 mmol) in acetonitrile (60 cm^3) under nitrogen was added HF (40% aq; 2.25 cm^3, 1.5% solution) and the mixture stirred at 25 °C overnight under nitrogen.

The reaction mixture was neutralised by the addition of NEt_3 (excess) and diluted with water (40 cm^3). The aqueous residue was extracted into EtOAc (3 × 100 cm^3) and washed with water (3 × 50 cm^3) and brine (2 × 50 cm^3). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to leave a viscous oil which was purified by flash column chromatography (2 : 1 hexane–EtOAc, 1% NEt_3) furnishing the *alcohol* as a colourless oil (539 mg, 89%); R_f 0.52 (EtOAc); $[\alpha]_D^{17}$ −23.1 (*c* 0.65 in $CHCl_3$); Found: C, 73.3; H, 8.3; N, 3.3. $C_{26}H_{35}NO_4$ requires C, 73.4; H, 8.3; N, 3.3%; ν_{max} ($CHCl_3$)/cm^{-1} 3418brs (O–H), 3062w (Ar–H), 3029w (Ar–H), 2937s (C–H), 2866s (C–H), 1604w (Ar), 1495w (Ar), 1453m, 1166w and 1049s; δ_H(250 MHz; $CDCl_3$) 7.40–7.25 (10 H, m, aromatics), 5.43 (1 H, dd, *J* 10.0 and 5.0, C*H*(O)Ph), 4.82 (1 H, d, *J* 7.0, OC*H*HO), 4.78 (1 H, d, *J* 7.0, OC*H*HO), 4.61 (2 H, s, PhCH_2O), 3.98 (1 H, dd, *J* 9.5 and 3.0, C*H*HOBOM), 3.64 (1 H, dd, *J* 9.5 and 7.5, C*H*HOBOM), 3.64–3.48 (2 H, br m, CH_2OH), 3.00 (1 H, dddd, *J* 11.0, 7.5, 3.0 and 3.0, C*H*N), 2.67 (1 H, dd, *J* 12.5 and 10.0, C*H*HCHPh), 2.02 (2 H, dd, *J* 12.5 and 5.0, CH_2) and 1.90–1.15 (11 H, m, 5 × CH_2 and C*H*); δ_C(63 MHz; $CDCl_3$) 141.8 (s), 138.0 (s), 128.4 (d), 127.9 (d), 127.6 (d), 127.2 (d), 126.0 (d), 95.1 (t), 77.1 (d), 70.7 (t), 69.4 (t), 68.1 (t), 62.0 (s), 59.3 (d), 42.1 (t), 41.0 (t), 32.7 (t), 31.1 (t), 28.2 (t), 19.6 (t) and 19.4 (t); *m*/*z* (CI) 426.2642 [(M + H)$^+$·$C_{26}H_{36}NO_4$ requires *M*, 426.2644], 426 [(M + H)$^+$, 28%], 306 (16), 138 (100), 106 (38) and 52 (65).

(2*S*,6*R*,8*R*)-2-(Benzyloxymethyloxymethyl)-6-(3′-formyl-1′-propyl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane 48b

IBX[80,81] (229.2 mg, 0.82 mmol, 1.4 eq.) was added to a solution of the alcohol (248.8 mg, 0.58 mmol) in dry DMSO (55 cm^3) under nitrogen and the mixture stirred at 25 °C overnight. The reaction was quenched by the addition of water (50 cm^3) and the aqueous extracted extensively with ether (6 × 50 cm^3). The organics were washed with water (6 × 50 cm^3) then brine (6 × 50 cm^3) and dried ($MgSO_4$). Purification of the crude material by flash column chromatography through a short plug of silica (1 : 1 hexane–EtOAc) yielded pure *aldehyde* **48b** as a colourless oil (246.9 mg, 100%); R_f 0.52 (1 : 1 hexane–EtOAc); $[\alpha]_D^{20}$ −16.5 (*c* 1.01 in $CHCl_3$); Found: C, 73.6; H, 8.0; N, 3.3. $C_{26}H_{33}NO_4$ requires C, 73.7; H, 7.9; N, 3.3%; ν_{max} ($CHCl_3$)/cm^{-1} 3061w (Ar–H), 3029w (Ar–H), 2939s (C–H), 2870s (C–H), 2720w (aldehyde C–H), 1722s (C=O), 1604w (Ar), 1495m (Ar), 1452m,

1108m and 1048s; δ_H(250 MHz; $CDCl_3$) 9.68 (1 H, t, *J* 1.5, C*H*O), 7.37–7.24 (10 H, m, aromatics), 5.44 (1 H, dd, *J* 10.5 and 5.0, C*H*(O)Ph), 4.80 (2 H, s, OCH_2O), 4.62 (2 H, s, PhCH_2O), 3.99 (1 H, dd, *J* 9.5 and 3.0, CH*H*OBOM), 3.61 (1 H, dd, *J* 9.5 and 8.0, C*H*HOBOM), 2.99 (1 H, dddd, *J* 11.0, 8.0, 3.0 and 3.0, C*H*N), 2.68 (1 H, dd, *J* 12.5 and 10.5, C*H*HCHAr), 2.49–2.24 (2 H, m, CH_2), 2.08–1.96 (2 H, m, CH_2) and 1.90–1.20 (9 H, m, 4 × CH_2 and C*H*); δ_C(63 MHz; $CDCl_3$) 202.6 (d), 141.6 (s), 138.0 (s), 128.4 (d), 128.4 (d), 127.9 (d), 127.6 (d), 127.2 (d), 125.9 (d), 95.1 (t), 77.1 (d), 70.8 (t), 69.4 (t), 67.7 (t), 59.2 (d), 44.2 (t), 42.2 (t), 41.4 (t), 30.9 (t), 28.2 (t), 19.4 (t) and 16.6 (t); *m*/*z* (CI) 424.2488 [(*M* + H)$^+$·$C_{26}H_{34}NO_4$ requires *M*, 424.2488], 424 [(M + H)$^+$, 33%], 138 (100), 106 (32) and 52 (62).

(2*S*,6*R*,8*R*)-2-(Benzyloxymethyloxymethyl)-6-(5′-cyanopent-4′-en-1′-yl)-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane 49b

TMS acetonitrile (97 μL, 0.71 mmol, 1.7 eq.) was dissolved in THF (3.0 cm^3) and cooled to −78 °C under nitrogen. *n*-BuLi (1.58 M in hexane; 0.42 cm^3, 0.67 mmol, 1.6 eq.) was added dropwise and the solution stirred for 20 min. B(O^{i}Pr)$_3$ (0.15 cm^3, 0.67 mmol, 1.6 eq.) was added dropwise and the solution stirred for a further 20 min. After this time a solution of aldehyde **48b** (176.6 mg, 0.42 mmol) in THF (1.0 cm^3, 1.0 cm^3 wash) was added and the mixture stirred for a further 20 min at −78 °C.

The reaction was quenched by the addition of a 1 : 1 water–THF mix (3.0 cm^3) and the solution warmed to 25 °C. The residue was diluted with water and ether, the organic layer separated and the aqueous further extracted with ether (3 × 2 cm^3). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to leave a yellow oil. This was purified by flash column chromatography (3 : 1 hexane–EtOAc; 1% NEt_3) to yield a 9 : 1 inseparable mixture of (*Z*–*E*) *nitrile* **39b** as a colourless oil (148.9 mg, 80%); R_f 0.32 (2 : 1 hexane–EtOAc; $[\alpha]_D^{22}$ −16.8 (*c* 0.72 in $CHCl_3$); Found: C, 75.2; H, 7.8; N, 6.2. $C_{28}H_{34}N_2O_3$ requires C, 75.3; H, 7.7; N, 6.3%; ν_{max} ($CHCl_3$)/cm^{-1} 3029s (Ar–H), 2944s (C–H), 2870s (C–H), 2222w (C≡N), 1604w (Ar), 1496w (Ar), 1453m, 1220m, 1207w, 1165m and 1109s; δ_H(500 MHz; $CDCl_3$) 7.37–7.24 (10 H, m, aromatics), 6.50 (0.08 H, dt, *J* 16.5 and 7.0, C*H*CHCN *trans*), 6.29 (0.92 H, dt, *J* 11.0 and 7.5, C*H*CHCN *cis*), 5.43 (1 H, dd, *J* 10.5 and 5.0, C*H*(O)Ph), 5.23 (0.08 H, d, *J* 16.5, C*H*CN *trans*), 5.19 (0.92 H, d, *J* 11.0, C*H*CN *cis*), 4.81 (1 H, d, *J* 6.5, OCH*H*O), 4.78 (1 H, d, *J* 6.5, OC*H*HO), 4.64 (1 H, d, *J* 12.0, PhCH_2O), 4.60 (1 H, d, *J* 12.0, Ph*C*H$_2$O), 3.99 (1 H, dd, *J* 9.5 and 3.0, C*H*HOBOM), 3.62 (1 H, dd, *J* 9.5 and 8.0, CH*H*OBOM), 2.99 (1 H, dddd, *J* 11.5, 8.0, 3.0 and 3.0, C*H*N), 2.68 (1 H, dd, *J* 12.0 and 10.5, C*H*HCHPh), 2.34 (2 H, dt, *J* 7.0 and 7.0, CH_2CH=CHCN), 2.03 (1 H, dm, *J* 14.0, CH), 1.99 (1 H, dd, *J* 12.0 and 5.0, CH*H*CHPh), 1.85–1.81 (1 H, m, C*H*), 1.72–1.61 (4 H, m, 2 × CH_2), 1.55–1.41 (2 H, m, CH_2) and 1.34–1.24 (2 H, m, CH_2); δ_C(63 MHz; $CDCl_3$) 154.9 (d), 141.7 (s), 138.0 (s), 128.4 (d), 127.9 (d), 127.6 (d), 127.2 (d), 125.9 (d), 125.7 (d), 115.9 (s), 99.5 (d), 95.1 (t), 76.5 (d), 70.8 (t), 69.3 (t), 67.6 (s), 59.3 (d), 42.0 (t), 41.0 (t), 31.9 (t), 30.9 (t), 28.2 (t), 22.6 (t) and 19.3 (t); *m*/*z* (CI) 447.2651 [(*M* + H)$^+$·$C_{28}H_{35}N_2O_3$ requires *M*, 447.2647], 447 [(M + H)$^+$, 28%], 191 (25), 138 (100), 121 (22) and 106 (45).

(1*R*,5*S*,8*S*,12*R*)-5-(Benzyloxymethyloxymethyl)-12-cyano-6-aza-7-oxatricyclo[6.3.1.0^{1,6}]dodecane 51b and (1*R*,5*S*,8*S*,12*S*)-5-(benzyloxymethyloxymethyl)-12-cyano-6-aza-7-oxatricyclo-[6.3.1.0^{1,6}]dodecane *epi*-51b

Nitrile **49b** (85.0 mg; 9 : 1 *cis*–*trans*, 0.19 mmol) was dissolved in dry ether and added to a high pressure reaction tube. The ether was removed under a nitrogen flow and the flask evacuated and refilled three times. Toluene (23 cm^3) was added and the suba seal exchanged quickly for the screw cap. The reaction vessel was then heated at 190 °C for 3.5 h.

The sealed tube was allowed to cool to 25 °C. The toluene was removed *in vacuo* and the residue purified by flash column chromatography (4 : 1 hexane–EtOAc; 1% NEt_3) to yield the *tricyclic* **51b** as a clear oil (53.9 mg, 83%); R_f 0.23 (3 : 1 hexane–EtOAc); $[\alpha]_D^{18}$ +120.7 (*c* 0.21 in $CHCl_3$); Found: C, 70.0; H, 7.7; N, 8.2. $C_{20}H_{26}N_2O_3$ requires C, 70.2; H, 7.7; N, 8.2%; ν_{max} ($CHCl_3$)/cm^{-1} 2941s (C–H), 2867s (C–H), 2238w (C≡N), 1452m (Ar), 1379w, 1108m (C–O), 1050s and 929m; δ_H(250 MHz; $CDCl_3$) 7.36–7.22 (5 H, m, aromatics), 4.79 (2 H, s, OCH_2O), 4.72 (1 H, m, C*H*O ring), 4.61 (2 H, s, PhCH_2O), 3.85 (1 H, dd, *J* 9.5 and 3.0, CH*H*OBOM), 3.59 (1 H, dd, *J* 9.5 and 7.0, C*H*HOBOM), 3.40 (1 H, dd, *J* 6.5 and 1.5, C*H*CN), 2.64 (1 H, dddd, *J* 11.0, 7.0, 3.0 and 3.0, C*H*N), 2.20 (1 H, dm, *J* 14.0, C*H*), 2.02–1.51 (9 H, m, 4 × CH_2 and CH) and 1.41–1.22 (2 H, m, CH_2); δ_C(63 MHz; $CDCl_3$) 138.0 (s), 128.4 (d), 127.8 (d), 127.7 (d), 117.7 (s), 95.1 (t), 75.8 (d), 69.9 (t), 69.4 (t), 65.5 (s), 65.0 (d), 38.1 (d), 35.9 (t), 32.2 (t), 28.3 (t), 27.1 (t), 18.8 (t) and 17.5 (t); *m*/*z* (CI) 343.2021 [(*M* + H)$^+$·$C_{20}H_{27}N_2O_3$ requires *M*, 343.2021], 343 [(M + H)$^+$, 100%], 191 (36) and 106 (72). On eluting the column further the *C*-7 *epimer epi*-**51b** was obtained as a clear oil (5.4 mg, 8%); R_f 0.13 (3 : 1 hexane–EtOAc); $[\alpha]_D^{17}$ +93.2 (*c* 2.68 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3018w (Ar–H), 2943s (C–H), 2880s (C–H), 2236w (C≡N), 1454m, 1168m, 1121m and 1052s; δ_H(500 MHz; $CDCl_3$) 7.38–7.26 (5 H, m, aromatics), 4.81 (3 H, s, OCH_2O and C*H*O), 4.63 (2 H, dd, *J* 12.0 and 4.0, PhCH_2O), 3.85 (1 H, dd, *J* 10.0 and 3.0, CH*H*OBOM), 3.67 (1 H, dd, *J* 10.0 and 6.5, CH*H*OBOM), 3.44 (1 H, m, C*H*N), 2.82 (1 H, s, C*H*CN), 2.38 (1 H, dm, *J* 14.5, C*H*), 2.10–1.93 (3 H, m, CH_2 and CH), 1.86–1.74 (2 H, m, CH_2), 1.62 (2 H, m, CH_2), 1.52 (1 H, m, CH), 1.40 (2 H, m, CH_2) and 1.29 (1 H, ddd, *J* 13.0, 13.0 and 6.0, CH); δ_C(125 MHz; $CDCl_3$) 138.1 (s), 128.4 (d), 127.9 (d), 127.6 (d), 120.2 (s), 94.9 (t), 78.7 (d), 69.9 (t), 69.2 (t), 65.0 (s), 63.7 (d), 44.6 (d), 41.9 (t), 33.2 (t), 31.4 (t), 27.1 (t), 18.9 (t) and 18.0 (t); *m*/*z* (ES) 343.2023 [(*M* + H)$^+$·$C_{20}H_{27}N_2O_3$ requires *M*, 343.2021]; *m*/*z* (CI) 343 [(M + H)$^+$, 100%], 191 (34), 106 (42) and 98 (41).

(1*R*,5*S*,8*S*,12*R*)-5-(Hydroxymethyl)-12-cyano-6-aza-7-oxatricyclo[6.3.1.0^{1,6}]dodecane 52

From 51a. The benzyl ether **51a** (225 mg, 0.72 mmol), prepared from **45** according to the analogous procedure reported below for **51b**, was dissolved in dry dichloromethane (10 cm^3) under an atmosphere of nitrogen and cooled to 0 °C with stirring. Boron trichloride–methyl sulfide complex (2 M in CH_2Cl_2; 0.54 cm^3, 1.08 mmol, 1.5 eq.) was then added in a dropwise fashion and the blackish solution stirred for 0.5 h at 0 °C then at 25 °C for a further 2 h. By this time the reaction was complete by TLC and was quenched by the careful, dropwise addition of aq $NaHCO_3$ (satd.; 5 cm^3; CAUTION: Vigorous delayed effervescence). After settling, the aqueous component was separated and extracted with EtOAc (2 × 25 cm^3). The combined organics were dried ($MgSO_4$), the solvent removed and the brown residue purified by flash chromatography (1 : 1 hexane–EtOAc) to afford the *alcohol* **52** as a colourless crystalline solid which was recrystallised from ether (159 mg, 99%).

From 51b. Benzyloxymethyl ether **51b** (53.9 mg, 0.15 mmol) was dissolved in methanol (20 cm^3) and Amberlyst-15™ resin (10 mg) added followed by stirring at 25 °C overnight. NEt_3 (4 cm^3) was added and the reaction stirred for a further hour. The solution was filtered to remove the resin and the filtrate concentrated *in vacuo*. The crude alcohol was purified by flash column chromatography (EtOAc) to yield the pure *alcohol* **41** as a white crystalline solid which was recrystallised from a hexane–ether mix (53.9 mg, 95%); R_f 0.32 (EtOAc); mp 93.5–94.5 °C (from hexane–ether); $[\alpha]_D^{19}$ −121.2 (*c* 0.61 in $CHCl_3$); Found: C, 65.2; H, 8.2; N, 12.4. $C_{12}H_{18}N_2O_2$ requires C, 64.8; H, 8.2; N, 12.6%; ν_{max} ($CHCl_3$)/cm^{-1} 3386brs (O–H), 2942s (C–H), 2868s (C–H), 2239m (C≡N), 1449m, 1084m, 1053m and 928m; δ_H(250 MHz; $CDCl_3$) 4.74 (1 H, ddd, *J* 3.0, 3.0 and 0.0, CHO

ring), 3.77 (1 H, ddd, *J* 11.0, 5.0 and 3.5, C*H*HOH), 3.63–3.54 (1 H, m, CH*H*OH), 3.42 (1 H, dd, *J* 5.0 and 2.0, C*H*CN), 2.65 (1 H, dddd, *J* 11.5, 3.5, 3.5 and 3.5, C*H*N), 2.49 (1 H, dd, *J* 5.0 and 5.0, O*H*), 2.20 (1 H, dm, *J* 11.0, C*H*) and 2.03–1.25 (11 H, m, 5 × CH_2 and C*H*); δ_C(63 MHz; $CDCl_3$) 117.4 (s), 76.0 (d), 65.7 (d), 65.5 (s), 65.3 (t), 38.5 (d), 35.9 (t), 32.0 (t), 27.2 (t), 27.1 (t), 18.7 (t) and 17.5 (t); *m*/*z* (CI) 223.1447 [(M + H)$^+$·$C_{12}H_{19}N_2O_2$ requires *M*, 223.1446], 223 [(M + H)$^+$, 100%], 193 (58), 191 (41), 177 (27), 106 (21) and 61 (22).

(1*R*,5*S*,8*S*,12*R*)-5-(Methanesulfonyloxymethyl)-12-cyano-6-aza-7-oxatricyclo[6.3.1.0^{1,6}]dodecane

Alcohol **52** (6.0 mg, 0.027 mmol), DMAP (2 mg, cat.) and NEt_3 (7.5 μL, 0.054 mmol, 2 eq.) were dissolved in dry CH_2Cl_2 (1.5 cm^3) and a solution of methanesulfonyl chloride (2.3 μL, 0.029 mmol, 1.1 eq.) in dry CH_2Cl_2 (0.3 cm^3) added dropwise followed by stirring for 1 h. The CH_2Cl_2 was removed *in vacuo* and the residue taken up in EtOAc (2 cm^3) and washed with brine (2 × 1 cm^3). The organic layer was separated and the aqueous further extracted with EtOAc (2 × 2 cm^3). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to leave a pale yellow oil. Purification by flash column chromatography (3 : 1 EtOAc–hexane) yielded the *mesylate* as a viscous, clear oil (8.1 mg, 100%); R_f 0.59 (EtOAc); $[\alpha]_D^{18}$ −177.5 (*c* 1.12, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2945s (C–H), 2869s (C–H), 2241m (C≡N), 1352s (SO_2O) and 1174s (SO_2O); δ_H(250 MHz; $CDCl_3$) 4.73 (1 H, m, C*H*(O)CHCN), 4.31 (1 H, dd, *J* 10.5 and 3.0, C*H*HOMs), 4.24 (1 H, dd, *J* 10.5 and 5.5, CH*H*OMs), 3.38 (1 H, dd, *J* 6.5 and 2.0, C*H*CN), 3.04 (3 H, s, OSO_2CH_3), 2.74 (1 H, dddd, *J* 12.0, 5.5, 3.0 and 3.0, C*H*N), 2.20 (1 H, m, CH) and 1.90–1.27 (11 H, m, 5 × CH_2 and CH); δ_H(63 MHz; $CDCl_3$) 117.3 (s), 76.0 (d), 71.0 (t), 65.4 (s), 63.9 (d), 38.2 (d), 37.2 (q), 35.7 (t), 32.0 (t), 27.3 (t), 27.0 (t), 18.3 (t) and 17.4 (t); *m*/*z* (CI) 301.1222 [(M + H)$^+$·$C_{13}H_{21}N_2O_4S$ requires *M*, 301.1222], 301 [(M + H)$^+$, 52%], 207 (100) and 191 (37).

(1*R*,5*S*,8*S*,12*R*)-5-(Cyanomethyl)-12-cyano-6-aza-7-oxatricyclo-[6.3.1.0^{1,6}]dodecane 53

To a mixture of the mesylate (210 mg, 0.69 mmol) and powdered molecular sieves (4 Å) was added dry DMSO (3 cm^3) followed by NaCN (888 mg, 18 mmol, 26 eq.) and the mixture stirred at 50 °C for 4 days. The reaction vessel was allowed to cool to 25 °C before the addition of a 1 : 1 mixture of ether and water (6 cm^3). The organic layer was separated and the aqueous further extracted with ether (5 × 6 cm^3). The combined organics were washed with water (5 × 5 cm^3) and brine (5 × 5 cm^3), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude residue by flash column chromatography (1 : 1 hexane–EtOAc) yielded the *bis nitrile* **53** as a white crystalline solid (162 mg, 85%); R_f 0.46 (1 : 1 hexane–EtOAc); mp 126–128 °C (from EtOAc); $[\alpha]_D^{16}$ −237.2 (*c* 0.96 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2946s (C–H), 2867s (C–H), 2242s (C≡N), 1450s, 1084s and 926s; δ_H(250 MHz; $CDCl_3$) 4.73 (1 H, ddd, *J* 6.0, 3.0 and 3.0, C*H*O ring), 3.36 (1 H, d, *J* 6.0, C*H*CN), 2.76 (1 H, dd, *J* 17.0 and 3.0, C*H*HCN), 2.80–2.71 (1 H, m, C*H*N), 2.55 (1 H, dd, *J* 17.0 and 8.0, C*H*HCN), 2.22 (1 H, dm, *J* 13.0, C*H*) and 2.05–1.35 (11 H, m, 5 × CH_2 and C*H*); δ_C(63 MHz; $CDCl_3$) 117.7 (s), 117.2 (s), 76.0 (d), 65.6 (s), 61.8 (d), 38.3 (d), 35.8 (t), 31.9 (t), 29.6 (t), 27.0 (t), 23.1 (t), 18.7 (t) and 17.4 (t); *m*/*z* (CI) 232.1450 [(M + H)$^+$·$C_{13}H_{18}N_3O$ requires *M*, 232.1450], 232 [(M + H)$^+$, 100%], 216 (21), 200 (28), 175 (33), 132 (40) and 94 (29). Further elution of the column gave unreacted mesylate (19 mg).

(1*R*,5*S*,8*S*,12*S*)-5-(Oxo-1′-ethyl)-12-formyl-6-aza-7-oxatricyclo[6.3.1.0^{1,6}]dodecane 54

Bisnitrile **53** (17.1 mg, 0.074 mmol) was dissolved in dry toluene (2 cm^3) and cooled to −78 °C under nitrogen. DIBAL-H (1.5 M in toluene; 123 μL, 0.185 mmol, 2.5 eq.) was added dropwise and the reaction stirred for 0.5 h.

The reaction was quenched by the addition of wet MeOH (1 cm^3) and warmed to 25 °C. The mixture was diluted with EtOAc (5 cm^3) and Rochelles' salt added (2 cm^3) together with a few drops of HCl (2 M aq) in order to lower the pH to 5, followed by stirring at 25 °C overnight. The aqueous layer was separated, neutralised by the addition of $NaHCO_3$ (aq) and extracted with EtOAc (2 × 5 cm^3). The organics were washed with brine (2 × 2 cm^3), combined, dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude aldehyde. Purification by flash column chromatography (1 : 1 hexane–EtOAc) through a short plug yielded the *bisaldehyde* **54** as a clear oil (17.5 mg, 100%); R_f 0.19 (1 : 1 hexane–EtOAc); $[\alpha]_D^{14}$ −130.7 (*c* 0.17 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2942s (C–H), 2860s (C–H), 1713s (C=O) and 923m; δ_H(250 MHz; $CDCl_3$) 10.01 (1 H, d, *J* 2.5, CHO), 9.83 (1 H, dd, *J* 2.0 and 2.0, CH_2CHO), 4.78 (1 H, ddd, *J* 5.5, 5.5 and 0.0, C*H*O ring), 3.32 (1 H, m, C*H*CHO), 3.15 (1 H, dddd, *J* 9.0, 6.5, 5.0 and 3.0, C*H*N), 2.86 (1 H, ddd, *J* 16.5, 5.0 and 2.0, C*H*HCHO), 2.51 (1 H, ddd, *J* 16.5, 6.5 and 2.0, CH*H*CHO), 2.18–1.96 (2 H, m, CH_2) and 1.80–1.22 (10 H, m, 5 × CH_2); δ_C(63 MHz; $CDCl_3$) 202.1 (d), 200.7 (d), 76.0 (d), 65.5 (s), 60.7 (d), 56.4 (d), 49.3 (t), 35.9 (t), 32.3 (t), 30.9 (t), 26.6 (t), 19.1 (t) and 18.1 (t); *m*/*z* (ES) 238.1450 [(M + H)$^+$·$C_{13}H_{20}NO_3$ requires *M*, 238.1443], 238 [(M + H)$^+$, 100%].

(1*R*,5*S*,8*S*,12*S*)-(1″*Z*,2′*Z*)-5-(3′-Iodoprop-2′-enyl)-12-(2″-iodoethenyl)-6-aza-7-oxatricyclo[6.3.1.0^{1,6}]dodecane 55

A suspension of the iodomethyltriphenylphosphonium iodide (62.0 mg, 116.8 μmol) in dry, degassed THF (1.0 cm^3) under argon was cooled to −30 °C with stirring and potassium bis-(trimethylsilyl)amide (0.5 M in toluene; 234 μL, 117 μmol) added dropwise. The resulting yellow solution was stirred for 0.25 h at −30 °C then cooled to −78 °C and stirring stopped. The salts were allowed to settle over 0.5 h, leaving a pale yellow supernatant solution of the 'salt-free' ylide standing over a white precipitate.

The supernatant (1 cm^3, 94.6 μmol, 3.4 eq.) was added rapidly to a solution of the bisaldehyde 54 (6.6 mg, 27.8 μmol) in dry, degassed THF (1 cm^3) at −78 °C under argon. TLC (1 : 1 hexane–EtOAc) showed no starting material left after 5 min. The reaction was quenched after 0.75 h by the addition of wet THF (1 : 1 THF–water; 0.5 cm^3) and warmed to 25 °C. Satd. NH_4Cl (aq; 2 cm^3) and ether (2 cm^3) were added. The layers were separated, and the aqueous further extracted with ether (4 × 3 cm^3). The organic extracts were combined and dried ($MgSO_4$) for 0.5 h. The solvent was removed *in vacuo* and the crude product purified by flash column chromatography (3 : 1 hexane–EtOAc) to yield the pure *bis(vinyl iodide)* **55** as a colourless oil (12.9 mg, 95%); R_f 0.66 (1 : 1 hexane–EtOAc); $[\alpha]_D^{18}$ −39.8 (*c* 1.3, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3061w (=C–H), 2933s (C–H), 2863s (C–H), 1606w (C=C) and 923m; δ_H(250 MHz; $CDCl_3$) 6.53 (1 H, d, *J* 7.5, =C*H*I), 6.33 (1 H, d, *J* 8.5, =C*H*I), 6.40–6.27 (2 H, m, =C*H*CH_2 and =C*H*CH), 4.55 (1 H, t, *J* 6.5, C*H*O), 3.52 (1 H, br dd, *J* 8.5 and 6.5, =CHC*H*), 2.93 (1 H, dddd, *J* 12.0, 8.5, 3.5 and 3.5, C*H*N), 2.71–2.61 (1 H, m, =CHC*H*H), 2.33–2.45 (1 H, m, =CHCH*H*) and 2.09–1.16 (12 H, m, 6 × CH_2); δ_C(100 MHz; $CDCl_3$) 138.8 (d), 136.3 (d), 86.3 (d), 83.8 (d), 76.8 (d), 65.3 (s), 63.6 (d), 50.8 (d), 39.6 (t), 32.3 (t), 29.8 (t), 25.7 (t), 20.0 (t) and 17.6 (t); *m*/*z* (EI) 485.9785 [(M + H)$^+$·$C_{15}H_{22}I_2NO$ requires *M*, 485.9741], 485 [(M + H)$^+$, 1%], 358 (2) and 318 (100).

17,21-Bis(trimethylsilyl)-*N*,*O*-cyclohistrionicotoxin 56

Copper iodide (1 mg, cat.) was dissolved in $HNEt_2$ (0.1 cm^3) under nitrogen and TMS–acetylene (4.5 μL, 0.031 mmol, 3 eq.) added followed by stirring in the dark for 0.25 h. Meanwhile, the (bisvinyl)iodide **55** (5.1 mg, 0.010 mmol) was dissolved in $HNEt_2$ (0.25 cm^3) under nitrogen and $Pd(PPh_3)_4$ (1 mg, cat) added. After stirring for 5 min, the CuI–TMS acetylene mix was added rapidly and the reaction stirred for 1.5 h.

The reaction mixture was diluted by the addition of EtOAc (2 cm^3) and reduced to virtual dryness under vacuum. This process was repeated twice. The crude residue resulting was purified by flash column chromatography (9 : 1 hexane–EtOAc) to yield the *bis acetylene* **56** as a colourless oil (4.6 mg, 97%); R_f 0.31 (9 : 1 hexane–EtOAc); $[\alpha]_D^{20}$ +50.9 (*c* 0.57, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3029w (≡C–H), 2940s (C–H), 2935s (C–H), 2856s (C–H), 2149m (C≡C), 1940 (w), 1910 (w), 1250s ($SiMe_3$), 842s ($SiMe_3$) and 759m (*cis*-HC=CH); δ_H(250 MHz; $CDCl_3$) 6.11–5.98 (2 H, m, =C*H*CH_2 and =C*H*CH), 5.71 (1 H, d, *J* 10.5, C*H*=CHCH), 5.57 (1 H, d, *J* 11.0, C*H*=$CHCH_2$), 4.51 (1 H, br t, *J* 6.0, C*H*O), 3.91 (1H, dd, *J* 10.5 and 6.0, =CHC*H*), 2.87–2.77 (2 H, m, =CC*H*H and C*H*N), 2.57 (1 H, m, =CCH*H*), 2.06–1.14 (12 H, m, 6 × CH_2), 0.19 (9 H, s, $Si(CH_3)_3$) and 0.18 (9 H, s, $Si(CH_3)_3$); δ_C(63 MHz; $CDCl_3$) 142.6 (d), 139.4 (d), 113.1 (d), 110.7 (d), 102.3 (s), 101.9 (s), 99.9 (s), 98.4 (s), 77.6 (d), 66.1 (s), 64.6 (d), 46.3 (d), 35.4 (t), 34.6 (t), 32.5 (t), 30.1 (t), 25.3 (t), 19.9 (t), 18.0 (t), 0.0 (q) and −0.2 (q); *m*/*z* (ES) 426.2646 [(M + H)$^+$·$C_{25}H_{40}NOSi_2$ requires *M*, 426.2648], 426 [(M + H)$^+$, 100%].

16,20-Bis(trimethylsilyl)histrionicotoxin

The cyclohistrionicotoxin derivative **56** (34 mg, 79.8 μmol) was dissolved in glacial acetic acid (2 cm^3) and activated zinc dust (65 mg, 1 mmol) added in one portion. The mixture was stirred vigorously and after 0.5 h no starting material was evident by TLC analysis. The reaction was quenched by the addition of satd. NaOAc (aq; 2 cm^3) and EtOAc (2 cm^3) followed by stirring for 0.5 h. The aqueous layer was separated, neutralised by the addition of $KHCO_3$ and extracted further with EtOAc (2 × 15 cm^3). The organics were washed with water (3 × 15 cm^3), then brine (3 × 15 cm^3), combined and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue purified by flash chromatography (EtOAc ⟶ 1 : 24 MeOH–EtOAc) to afford the *title compound* as a pale yellow oil (33.6 mg, 98%); R_f 0.28 (1 : 24 MeOH–EtOAc); $[\alpha]_D^{24}$ −50.8 (*c* 0.59, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3500–2500brs (N–H and O–H), 2940s (C–H), 2934s (C–H), 2149m (C≡C), 1454m, 1250s ($SiMe_3$), 843s ($SiMe_3$) and 759, (*cis*-HC=CH); δ_H(250 MHz; $CDCl_3$) 6.01 (1 H, ddd, *J* 11.0, 8.0 and 8.0, =C*H*CH_2), 5.80 (1 H, t, *J* 11.0, CHC*H*=CH), 5.63 (1 H, ddd, *J* 11.0, 1.0 and 1.0, C*H*=$CHCH_2$), 5.56 (1 H, d, *J* 11.0, C*H*=CHCH), 3.78 (1 H, q, *J* 2.5, C*H*O), 3.72 (1 H, br d, *J* 11.0, =CCH), 3.13 (1 H, m, CHN), 2.46 (1 H, m, =CHCH*H*), 2.38 (1 H, ddd, *J* 14.0, 8.0 and 1.0, =CC*H*H), 2.16 (1 H, m, CH), 1.40–1.95 (9 H, m, 9 × C*H*), 1.27 (1 H, m, C*H*), 0.96 (1 H, dddd, *J* 12.0, 12.0, 12.0 and 4.0, C*H*), 0.81 (1 H, ddd, *J* 13.0, 13.0 and 4.0, C*H*), 0.21 (9 H, s, $Si(CH_3)_3$) and 0.20 (9 H, s, $Si(CH_3)_3$); δ_C(63 MHz; $CDCl_3$) 140.7 (d), 140.1 (d), 112.3 (d), 112.3 (d), 101.9 (s), 101.5 (s), 100.5 (s), 99.3 (s), 71.2 (d), 57.0 (s), 51.4 (d), 46.1 (d), 36.7 (t), 36.5 (t), 35.4 (t), 31.1 (t), 28.4 (t), 19.2 (t), 15.1 (t), 0.0 (q) and −0.1 (q); *m*/*z* (CI) 427.2723 [(M + H)$^+$·$C_{25}H_{42}NOSi_2$ requires *M*, 427.2727], 427 [(M + H)$^+$, 100%], 410 (1), 356 (20) and 290 (19).

(−)-Histrionicotoxin 1[1]

16,20-Bis(trimethylsilyl)histrionicotoxin (30 mg, 71 μmol) was dissolved in dry methanol (3 cm^3) under nitrogen and solid potassium carbonate (15 mg) added quickly in one portion and the resulting mixture stirred at rt for 2 h. EtOAc (10 cm^3) was added and the solvent volume reduced to approximately 1–2 cm^3. This process was repeated and the resulting solution was filtered through a small plug of silica gel (1 : 24 MeOH–EtOAc) affording the alkaloid **1** as a colourless oil which crystallised on standing (18.6 mg, 94%); R_f 0.4 (1 : 9 MeOH–EtOAc); mp 74.5–76.0 °C (from hexane); $[\alpha]_D^{20}$ −112 (*c* 0.34, EtOH) and $[\alpha]_D^{24}$ −116 (*c* 0.35, $CHCl_3$) {lit.,[7] $[\alpha]_D^{25}$ −114 (*c* 1.06, EtOH)}; ν_{max} (thin film)/cm^{-1} 3289m (≡C–H), 3215m (O–H), 3026w (=C–H), 2931s (C–H), 2093m (C≡C), 1456m, 1095w, 974m and 744w (*cis*-HC=CH); δ_H(250 MHz; $CDCl_3$) 6.08 (1 H, dddd, *J* 11.0, 7.5, 7.5 and 1.0, =C*H*CH_2), 5.86 (1 H, ddd, *J* 10.5, 10.5 and 1.0, CHC*H*=CH), 5.59 (1 H, dddd, *J* 11.0, 2.5, 1.5 and 1.5, C*H*=$CHCH_2$), 5.54 (1 H, ddd, *J* 10.5, 2.5 and 0.5, C*H*=CHCH), 3.79 (1 H, q, *J* 2.5, CHO), 3.67 (1 H, br d, *J* 10.5, =CCH), 3.16 (1 H, dd, *J* 2.5 and 1.0, CH_2CH=CHC≡C*H*), 3.12 (1 H, m, C*H*N), 3.09 (1 H, dd, *J* 2.5 and 1.0, CHCH=CHC≡C*H*), 2.45 (1 H, m, =CCH*H*), 2.34 (1 H, ddd, *J* 14.0, 7.5 and 1.5, =CC*H*H), 2.09 (1 H, m, C*H*), 1.80–1.36 (8 H, m, 8 × C*H*), 1.21 (1 H, m, C*H*), 0.90 (1 H, dddd, *J* 12.0, 12.0, 12.0 and 4.0, H-3) and 0.78 (1 H, ddd, *J* 13.0, 13.0 and 4.0, H-5); δ_C(63 MHz; $CDCl_3$) 143.1 (d), 141.8 (d), 110.5 (d), 110.2 (d), 82.6 (s), 81.8 (s), 80.6 (d), 79.9 (d), 71.6 (d), 54.3 (s), 49.9 (d), 41.6 (d), 38.1 (t), 38.0 (t), 37.1 (t), 32.9 (t), 29.1 (t), 19.6 (t) and 15.2 (t); *m*/*z* (ES) 284.2007 [(M + H)$^+$·$C_{19}H_{26}NO$ requires *M*, 284.2014], 284 [(M + H)$^+$, 100%].

(+)-Histrionicotoxin 63

All intermediates were synthesised as described for the (−) series. R_f, ^{1}H NMR, ^{13}C NMR and *m*/*z* were found to be identical to their antipodes and in all cases optical rotations were found to be equal and opposite.

R_f 0.10 (1 : 4 MeOH–CCl_4); $[\alpha]_D^{22}$ +113 (*c* 0.26 in EtOH); ν_{max} (thin film)/cm^{-1} 3200brs (O–H), 3020w (=C–H), 2955s (C–H), 2098m (C≡C), 1449m, 1087w and 742w; δ_H(500 MHz; $CDCl_3$) 6.09 (1 H, ddd, *J* 10.5, 7.5 and 7.5, *H*-13), 5.87 (1 H, dd, *J* 10.5 and 10.5, *H*-17), 5.61 (1 H, dd, *J* 10.5 and 1.5, *H*-14), 5.54 (1 H, dd, *J* 10.5 and 2.0, *H*-18), 3.79 (1 H, br dm, *J* 2.5, C*H*OH), 3.67 (1 H, br d, *J* 10.5, C*H*CH=), 3.16 (1 H, d, *J* 2.0, *H*-21), 3.13 (1 H, m, C*H*NH), 3.09 (1 H, d, *J* 1.5, *H*-16), 2.44–2.33 (2 H, m, C*HH*CH=), 2.10 (1 H, tddd, *J* 14.0, 14.0, 14.0 and 4.0, C*H*), 1.77–1.41 (7 H, m, 3 × CH_2 and C*H*), 1.23 (2 H, m, CH_2), 0.91 (1 H, dddd, *J* 13.0, 13.0, 13.0 and 4.0, C*H*) and 0.78 (1 H, ddd, *J* 13.5, 13.5 and 4.0, C*H*); δ_C(125 MHz; $CDCl_3$) 143.1 (d), 141.8 (d), 110.5 (d), 110.1 (d), 82.6 (s), 81.7 (s), 80.5 (s), 79.9 (s), 71.5 (d), 54.3 (s), 49.9 (d), 41.6 (d), 38.0 (t), 37.9 (t), 37.0 (t), 32.9 (t), 29.1 (t), 19.5 (t) and 15.1 (t); *m*/*z* (ES) 284.2019 [(M + H)$^+$·$C_{19}H_{26}NO$ requires *M*, 284.2014]; *m*/*z* (CI) 284 [(M + H)$^+$, 100%], 279 (19), 234 (16), 152 (13) and 123 (16).

N,O-Cyclohistrionicotoxin 235A 64

To a stirred solution of the bis(vinyl iodide) **55** (10.0 mg, 20.6 μmol) and tetrakis(triphenylphosphine)palladium(0) (0.6 mg) in dry benzene (1 cm^3) under argon was added dropwise tri-*n*-butyltin hydride (8.7 μL, 32.2 μmol, 1.6 eq.) and the flask wrapped in aluminium foil. Stirring was continued for 20 h with LCMS monitoring. Water (1 cm^3) was added and the mixture extracted with EtOAc (4 × 2 cm^3). The combined organic extracts were then washed with saturated brine (1 cm^3) and dried by stirring over Na_2SO_4 for 2 h. The mixture was filtered and the solvent removed under a stream of nitrogen. The crude brown oil was preabsorbed onto silica (CH_2Cl_2) and purified *via* flash column chromatography (hexane ⟶ 9 : 1 hexane–EtOAc) to afford the pure *bisalkene* **64** as a colourless oil (1.8 mg, 37%); R_f 0.43 (4 : 1 hexane–EtOAc) and 0.21 (9 : 1 hexane–EtOAc); $[\alpha]_D^{23.5}$ −110.5 (*c* 0.18, $CDCl_3$); ν_{max} (KBr)/cm^{-1} 3077w (=C–H), 2954m (C–H), 2927s (C–H), 2850m, 1638m (C=C), 1451w, 1260w, 1219w, 1093w, 1021w, 914.5w and 768s; δ_H(250 MHz; $CDCl_3$) 6.00–5.74 (2 H, m, 2 × C*H*=), 5.28–5.23 (1 H, m, =C*H*H), 5.19 (1 H, dd, *J* 9.0 and 2.0, =C*H*H), 5.11–4.99 (2 H, m, 2 × =CH*H*), 4.47–4.41 (1 H, m, C*H*O), 3.16 (1 H, br t, *J* 8.0, C*H*CH=), 2.80–2.65 (2 H, m, C*H*N and C*H*HCH=) and 2.13–1.05 (13 H, m, CH*H*CH= and 6 × CH_2); δ_C(63 MHz; $CDCl_3$) 136.1 (d), 133.6 (d), 119.3 (t), 116.6 (t), 78.2 (d), 64.8 (s), 64.2 (d), 49.8 (d), 39.3 (t), 34.4 (t), 32.1 (t), 29.7 (t), 25.2 (t), 19.1 (t) and 18.0 (t); *m*/*z* (ES) 234.1852 [(M + H)$^+$·$C_{15}H_{24}NO$ requires *M*, 234.1858], 234 [(M + H)$^+$, 100%].

(−)-Histrionicotoxin 235A 65[7,82]

The bis(vinyl iodide) **55** (0.8 mg, 35 μmol) was dissolved in glacial acetic acid (2 cm^3) and activated zinc dust (65 mg, 1 mmol) was added. The mixture was stirred for 0.25 h, whereupon TLC (9 : 1 $CHCl_3$–MeOH) showed all the starting material to have been consumed. The mixture was heated at 90 °C for 3 days with LCMS monitoring. The reaction was poured into water (20 cm^3) and neutralised by the addition of solid $NaHCO_3$. The mixture was extracted exhaustively with EtOAc (6 × 50 cm^3) and the combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by passing through a short plug of silica (hexane ⟶ 9 : 1 $CHCl_3$–MeOH) to afford (−)-*histrionicotoxin 235A* **65** (0.7 mg, 90%) as a colourless oil; R_f 0.14 (9 : 1 $CHCl_3$–MeOH); $[\alpha]_D^{20}$ −107 (*c* 0.07, EtOH) [lit., $[\alpha]_D^{25}$ −102 (*c* 1.82, EtOH);[7] $[\alpha]_D^{25}$ −38.6 (*c* 1.75, $CHCl_3$)[82]]; ν_{max} (KBr)/cm^{-1} 3240brw (O–H and N–H), 3076w (=C–H), 2931s (C–H), 2855s (C–H), 1650w (C=C), 1570w (C=C), 1557w, 1454w, 1384m, 1239m, 1220m, 1097w, 1073m, 966w, 916w and 771s; δ_H(500 MHz; $CDCl_3$) 5.78 (1 H, dddd, *J* 14.5, 10.0, 10.0 and 7.5, =C*H*CH_2), 5.65 (1 H, ddd, *J* 17.0, 10.0 and 10.0, =C*H*CH), 5.25–5.10 (4 H, m, 2 × =CH_2), 3.89 (1 H, br s, C*H*OH), 3.14–3.22 (1 H, m, C*H*N), 3.01 (1 H, d, *J* 10.0, C*H*CH=), 2.35–2.25 (2 H, m, CH_2CH=), 2.10–2.05 (2 H, m, CH_2) and 1.70–1.00 (12 H, m, 5 × CH_2, O*H* and N*H*); δ_C(100 MHz; $CDCl_3$) 134.9 (d), 133.5 (d), 118.7 (t), 118.6 (t), 72.7 (d), 56.1 (q), 50.6 (d), 45.0 (d), 40.1 (t), 35.6 (t), 35.0 (t), 29.7 (t), 27.9 (t), 18.3 (t) and 15.0 (t); *m*/*z* (ES) 236.2025 [$(M + H)^+ \cdot C_{15}H_{26}NO$ requires *M*, 236.2014], 236 [$(M + H)^+$, 100%], 218 (23), 159 (5).

Acknowledgements

We acknowledge the EPSRC for financial support and provision of the Swansea Mass Spectrometry Service. We also thank GlaxoWellcome (SDR), Novartis (CJS) and SmithKline Beecham (ECD and MEF) for financial support and Professor G. Stork for kindly supplying the spectra for synthetic HTX 235A **65**.

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