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Abstract

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Diasteroselective Synthesis of the A-B-C Tricyclic Ring Structure of Stemocurtisine

Xuan Duc Dau[a], Anthony C. Willis[b], Stephen G. Pyne*[a]

Abstract: The diastereoselective synthesis of the A-B-C tricyclic ring structure of the *Stemona* alkaloid stemocurtisine is described. Attempts to prepare the C-3a−C-11 ether moiety of this alkaloid using a photochemically induced oxidative cyclization method were unsuccessful due to cleavage of the A-ring.

Introduction

The *Stemona* alkaloids represent a unique class of natural products exclusively isolated from the monocotyledonous family Stemonaceae, mainly distributed in East and South East Asia.[1] Structurally the alkaloids are characterized by the presence of either a pyrrolo[1,2-*a*]azepine (Figure 1, n = 1), the most common type, or a pyrido[1,2-*a*]azepine core A-B ring structure (Figure 1, n = 2).[2] In 2010, Pilli organized the Stemona alkaloids into eight different structural groups: stenine, stemoamide, tuberostemospironine, stemoamine, parvistemoline, stemofoline (all having the pyrrolo[1,2-*a*]azepine core structure), stemocurtisine (having the pyrido[1,2-*a*]azepine core structure) and a miscellaneous group, formed from those alkaloids which do not display the structural motifs mentioned above, or are the sole representative of a new group.[2]

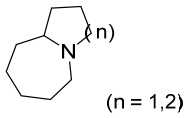
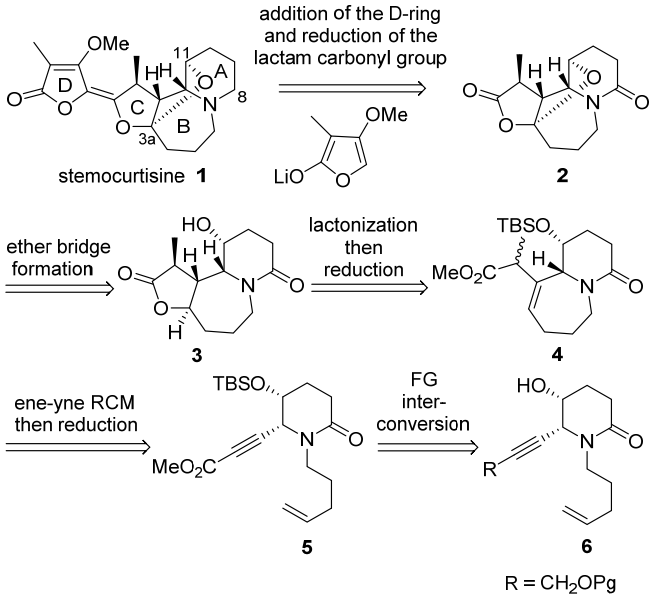


Figure 1. Core bicyclic A-B-ring structure of the *Stemona* alkaloids

Herbal extracts made from plants belonging to the Stemonaceae family have been used in folk medicine in East Asia for thousands of years, with three species of the *Stemona* genus (*S. tuberosa*, *S. japonica* and *S. sessilifolia*) being listed in the 2000 edition of the Chinese Pharmacopoeia as antitussive medicinal herbs.[3] The dried roots from these species, known as '*Bai Bu*' in Chinese traditional medicine, '*Bach Bo*' in Vietnam and '*Non Tai Yak*' or '*Pong Mot Ngam*' in Thailand, are used to suppress coughing, and are claimed to have antituberculosis, antibacterial, antifungal and antihelmintic properties.[4]

These interesting biological activities and the synthetically challenging polycyclic structures of the *Stemona* alkaloids have prompted numerous synthetic studies and the total synthesis of many *Stemona* alkaloids have been reported.[2a−c, 5] However no report has been made on the total synthesis of a stemocurtisine group *Stemona* alkaloid.[6] Here we report on our studies towards the total synthesis of stemocurtisine **1** by the preparation of the tricyclic compound **3**, having the A-B-C ring structure of alkaloid **1**. Our aim was to employ this compound in the synthesis of the tetracyclic compound **2** using a photochemical induced oxidative cyclization process to introduce the ether bridge between C-3a and C-11 in the target alkaloid.



Scheme 1. Retrosynthetic analysis of stemocurtisine **2**

Our planned synthesis of stemocurtisine **1** was based on the retrosynthetic analysis shown in Scheme 1. In principle, this alkaloid could be obtained from the tricyclic compound **2** by addition of the D-ring, following the method described by Olivo,[7] followed by reduction of the lactam carbonyl group.[8] It was anticipated that the ether bridge in compound **2** could be prepared from the tricyclic compound **3** via a photochemically induced oxidative cyclization reaction.[9] The tricyclic compound **3** could be obtained from the ester **4** via a bromolactonization reaction of its corresponding carboxylic acid followed by base-

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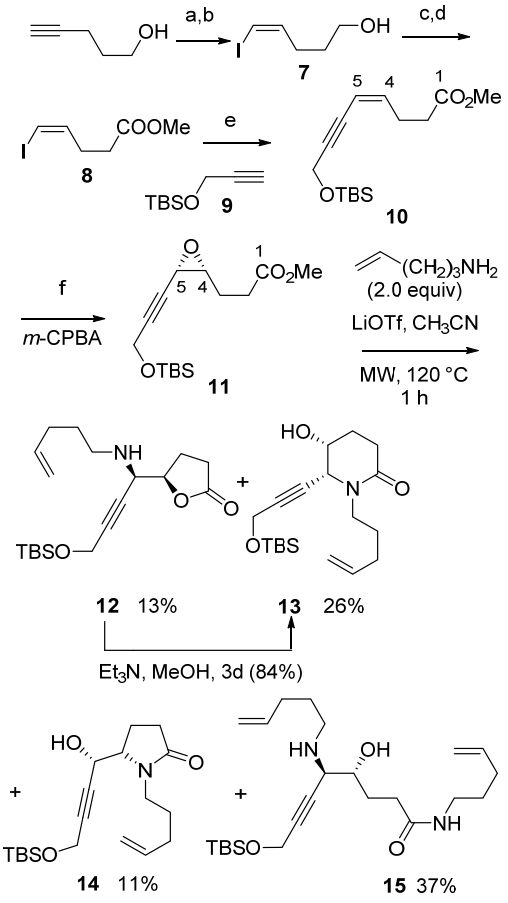
catalyzed elimination of HBr and then 1,4-hydride reduction of the corresponding α,β-unsaturated lactone. Compound **4** could be synthesized from the ene-yne **5** via a RCM reaction after reduction of the resulting α,β-unsaturated ester. Related chemistry has been developed by Mori for the stereoselective synthesis of the pyrrolo[1,2-*a*]azepine *Stemona* alkaloid, stemoamide[10] and by us for the preparation of 1-hydroxystemoamide.[11] The ene-yne ester **5** could be obtained from ene-yne lactam **6** via functional group interconversions.

Results and Discussion

The synthesis of the racemic 5,6-*cis*-lactam **13** (**6**, Pg = OTBS) started with commercially available 4-pentyne-1-ol which was converted to the known *Z*-iodo ester **8** via the known vinyl iodide **7** using the literature procedures.[12] A Sonogashira coupling reaction of this vinyl iodide with alkyne **9** afforded the novel *Z*-ene-yne **10** ($J_{4,5}$ = 10.7 Hz) in 71% yield which upon epoxidation with *m*-CPBA led to the racemic epoxide **11**. The coupling constant $J_{4,5}$ = 4.0 Hz in the ^{1}H NMR spectrum of **11** was consistent with the expected *cis*-epoxide (Scheme 2).[13]

Aminolysis of epoxide **11**[14] with 1-amino-4-pentene (2.0 equiv) using LiOTf (1.0 equiv) as a Lewis acid catalyst gave a separable mixture of the desired lactam **13**, in modest yield (26%), and the undesired lactone **12** (13%), lactam **14** (11%), and bisadduct **15** (37%) as the major product formed (Scheme 2). Lactam **14** most likely arises from reaction of 1-amino-4-pentene with the ester group of **11** followed by an intramolecular 5-*exo*-*tet* cyclization[16] of the resulting amide. An alternative mechanism involving the aminolysis of **11** with ring opening at C-4 followed by lactam formation seemed less likely since aminolysis reactions of vinyl and alkynyl epoxides are normally regioselective for attack at the more activated allylic or propargylic carbon, as observed in the regioselective ring opening of epoxide **19** in Scheme 3. Bisadduct **15** clearly arises from the reaction of the lactone **12** with the excess amount of 1-amino-4-pentene.

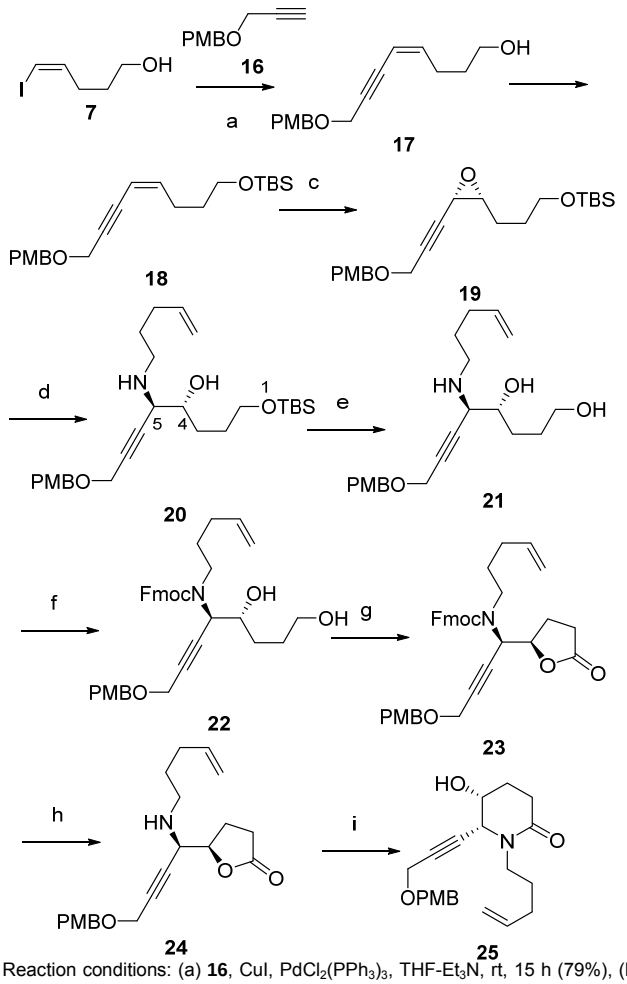
In model studies of this aminolysis reaction using epoxide **11** and allylamine, instead of 1-amino-4-pentene, we found that related products were also formed. When less equivalents (1.0 to 1.2 equiv) of allylamine were used then less amount of the bisadduct corresponding to **15** was formed however significant amounts of the starting epoxide **11** were also present. Lactone **12** was converted to lactam **13** in 84% yield by heating a solution of **12** in MeOH/Et_3N at reflux for 3 d. The vicinal coupling constant $J_{5,6}$ = 4.5 Hz in the ^{1}H NMR spectrum of **13** was consistent with the desired 5,6-*cis*-stereochemistry of the lactam **13**.[17] However, because of the problem associated with the ester group in the ring opening reaction of the epoxide **11** with amines we developed an alternative synthesis based on the epoxide **19** (Scheme 3) in which the problematic ester group was replaced with a less reactive CH_2OTBS group.



Reaction conditions: (a) I_2, MeOH, KOH, rt, 4 h (75%); (b) KOOCN=NCOOK, AcOH, pyridine, rt, 10 h (56%); (c) Jones' reagent, acetone, 0 °C, 30 min; (d) TMSCl, MeOH, rt, 14 h (60%); (e) **9**, CuI, $PdCl_2(PPh_3)_2$, THF-Et_3N, rt, 14 h (71%); (f) *m*-CPBA, CH_2Cl_2, rt, 18 h (56%).

Scheme 2. Synthesis of lactam **13**.

The vinyl iodide **7** was transformed to the racemic epoxide **19** via Sonogashira coupling with the alkene **16**, *O*-TBS protection with TBSCl/imidazole, and then epoxidation with *m*-CPBA (Scheme 3). Aminolysis of this epoxide with 1-amino-4-pentene in a microwave reactor afforded the amino alcohol **20** in 64% yield as a single diastereomer. The relative *syn*-sterochemistry of **20** was consistent with coupling constant $J_{4,5}$ = 8.5 Hz.[18] The diol **21** was then formed in 91% yield after TBS-deprotection of **20**. Our attempts to oxidize the diol **21** to the corresponding lactone using BAIB/TEMPO[19] or NMO/TPAP[20] were unsuccessful and resulted in complex mixtures of products. However, protection of the amino group of compound **21** as its Fmoc-derivative[21] **22** before oxidation with BAIB/TEMPO resulted in the lactone **23** in 84% yield. Base promoted Fmoc-deprotection of **23** with Et_3N/MeCN at rt gave the amino lactone **24** which upon heating with Et_3N in MeOH at reflux temperature provided the desired 5,6-*cis*-lactam **25** in 84% yield (Scheme 3).

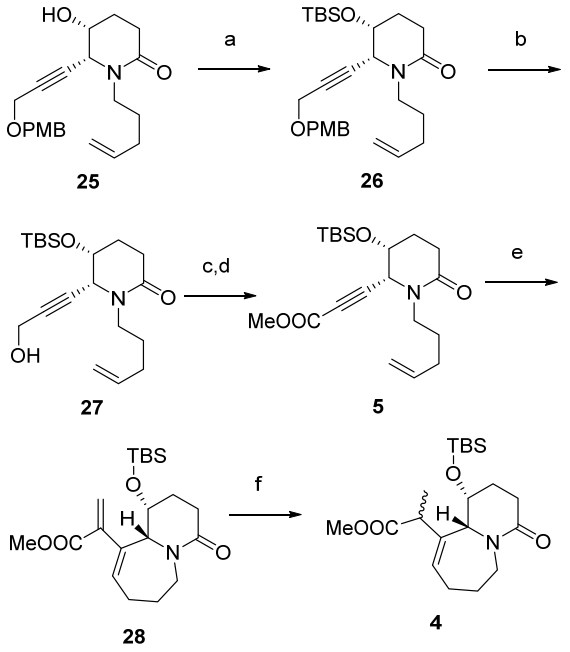


Reaction conditions: (a) **16**, CuI, $PdCl_2(PPh_3)_3$, THF-Et_3N, rt, 15 h (79%), (b) TBSCl, imidazole, DMF, rt, 8 h (93%); (c) *m*-CPBA, CH_2Cl_2, rt, 15 h (63%); (d) MW, 1-amino-4-pentene, LiOTf, CH_3CN, 120 °C, 60 W, 1.5 h (64%); (e) TBAF, THF, 0 °C to rt, 4 h (91%); (f) FmocCl, sat. Na_2CO_3-THF, 0 °C, 4 h (96%); (g) BAIB, TEMPO, CH_2Cl_2, rt, 16 h (84%); (h) Et_3N, CH_3CN, rt, 14 h (86%); (i) Et_3N, MeOH, reflux, 3 d,(84%).

Scheme 3. Synthesis of the 5,6-*cis*-lactam **25** (compounds **19-25** are racemic).

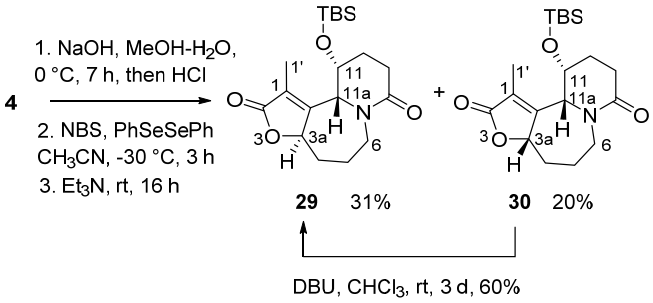
For the synthesis of the A-B ring system of stemocurtisine, lactam **25** was converted to the ene-yne ester **5** via a sequence of functional group interconversions (Scheme 4). This included the protection of the secondary alcohol as a TBS ether (TBSOTf, 2,6-lutidine, 81%),[22] oxidative removal of the PMB group under aqueous conditions (DDQ/CH_2Cl_2/H_2O, 79%), oxidation of the resulting primary propargyl alcohol to the corresponding acid with Jones' reagent and finally *O*-methylation (MeI, K_2CO_3, DMF, 67% for two steps) to the methyl ester **5**. Treatment of **5** with Grubbs' 1st generation Ru catalyst (10% mol, CH_2Cl_2, rt, 8 h) resulted in the bicyclic compound **28** in 78% isolated yield.[10] 1,4-Hydride reduction of the enoate group of **28** with $NaBH_4$/MeOH gave the ester **4** (78%) as a 3:1 mixture of diastereomers (Scheme 4).[10]

Surprisingly, compound **4** was unreactive under our previously described dihydroxylation (K_2OsO_4/NMO)[11] or Mori's bromolactonization reaction conditions ($CuBr_2$ on alumina on the corresponding carboxylic acid).[10] However, treatment of the corresponding carboxylic acid of this compound with NBS and PhSeSePh[23] in CH_3CN led to a mixture of desired product **29** and its 3a-epimer **30**. The minor isomer **30** could be converted to **29** by treatment with DBU in $CHCl_3$ (Scheme 5).



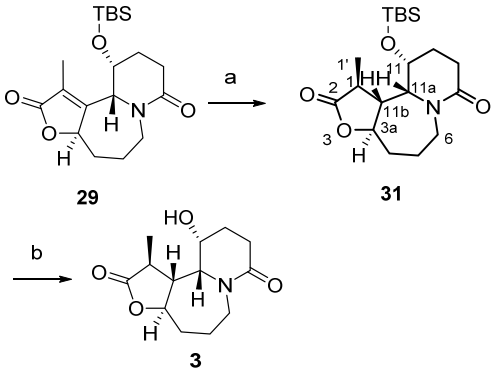
Reaction conditions: (a) TBSTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 14 h (81%); (b) DDQ, H_2O-CH_2Cl_2 (1:10), rt, 18 h (79%); (c) Jones' reagent, acetone, 0 °C, 30 min; (d) K_2CO_3, MeI, DMF, rt (67%, 2 steps); (e) Grubbs' 1st Ru catalyst (10% mol), CH_2Cl_2, rt, 8 h (78%); (f) $NaBH_4$/MeOH, 0 °C, 3.5 h (78% dr = 3:1).

Scheme 4. Synthesis of the bicyclic compound **4**



Scheme 5. Synthesis of the tricyclic compound **29**

The major product of the bromolactonization of **4** (compound **29**) and the conversion of compound **30** to compound **29** under basic conditions suggest that compound **29** is thermodynamically more stable than compound **30**. Semi-empirical calculations (SPARTAN, AM1) on **29** and **30** indicated that the heats of formation for compounds **29** and **30** were -863.2 kJ/mol and -851.5 kJ/mol, respectively, indicating that **29** was thermodynamically more stable than **30** in the gas phase by about 12 kJ/mol. The difference in energy between **29** and **30** could be attributed to the sterically unfavourable pseudo-1,3-diaxial interactions between H-3a and H-7β and H-3a and H-11a in **30** and the significantly closer calculated distance between Me-1' and the oxygen atom of the OTBS group in **30** (2.30 Å) compared to that in **29** (2.73 Å).



Reaction conditions: (a) Mg, MeOH, 0 °C to rt, 1 d (71%); (b) TBAF, AcOH, THF, 0 °C to rt, 16 h (80%).

Scheme 6. Synthesis of the tricyclic lactone **3**

Our attempts to reduce the C=C bond of the α,β-unsaturated lactone **29** by treatment with $NaBH_4/NiCl_2$ or $NaBH_4$/CuCl in MeOH were unsuccessful and only unreacted starting material was recovered. The less hindered *O*-TBS deprotected version of **29** also failed to undergo reduction under these conditions. In contrast, the pyrrolo[1,2-*a*]azepine analogues of these compounds were readily reduced under the aforementioned conditions.[10,11] However, treatment of **29** with Mg/MeOH[24] afforded the saturated derivative **31** as a single isomer in 71% yield (Scheme 6). The structure of **31** was confirmed by 2D NMR and single crystal X-ray crystallographic analyses. Evidence for the configuration of **31** was obtained from NOESY NMR experiments (Figure 2). Strong NOESY correlations were observed between H-11 and H-11a; H-11a and H-11b; H-11b and H-6β; H-11a and H-6β; H-1 and H-3a; and H-1' and H-11, H-11a and H-11b (Figure 2). No correlations were observed between H3a and H11b or between H1 and H11b, which further confirmed the relative configurations at C-1 and C-11b. Finally, the relative configuration of **31** was confirmed by its single crystal X-ray crystallography structure (Figure 3) which further indicated that **31** had the same A-B-C ring relative configuration as stemocurtisine **1**. Treatment of **31** with TBAF/HOAc in THF gave the target compound **3** 80% yield (Scheme 6).

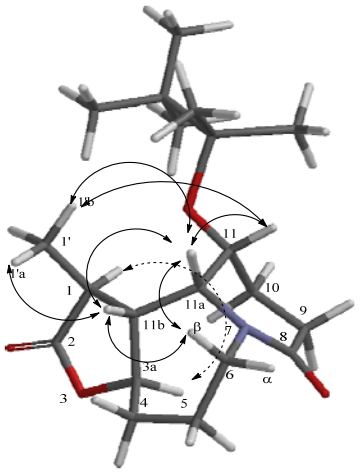


Figure 2. Spartan model (AM1) of **31** with atomic labeling and NOESY correlations shown by double-headed arrows

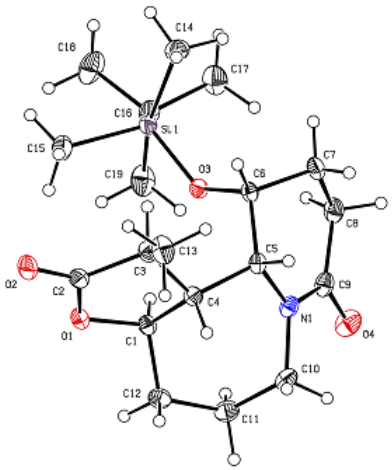
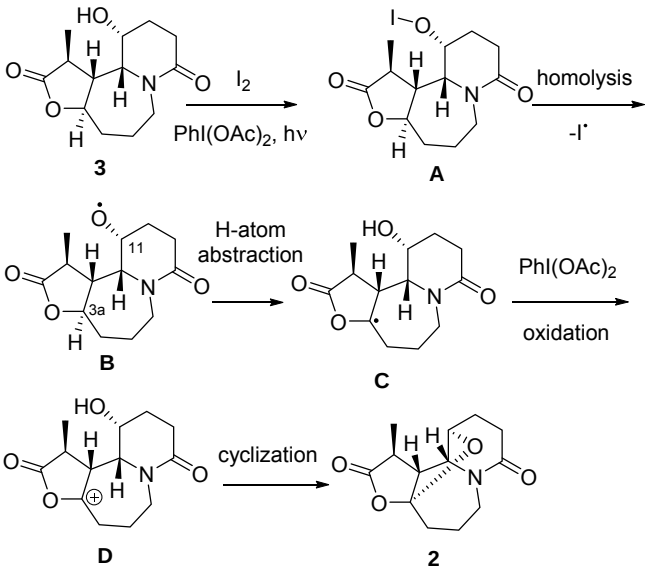


Figure 3. ORTEP X-ray crystal structure **31** with atomic labeling

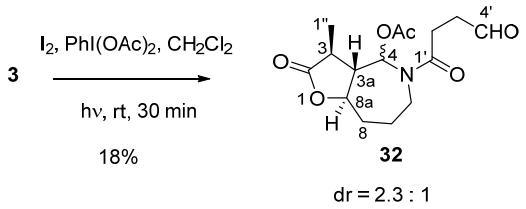
We next planned to prepare the tetracyclic compound **2** employing a photochemical oxidative cyclization process[9] using I_2 and $PhI(OAc)_2$. We anticipated that compound **3** would react with I_2 to form the hypoiodite **A**, which could then undergo homolytic cleavage (in the presence of light) to form the free radical **B** (Scheme 7). The radical **B** could then be transformed to the radical **C** by intramolecular H-atom abstraction at C-3a. The distance between the oxygen at C-11 and H-3a is 2.43 Å in the X-ray structure of **31**. Thus this oxygen would seem to be sufficiently close enough to abstract H-3a to give the resonance stabilized radical **C**. This radical then could then be oxidized to the resonance stabilized cation **D** by $PhI(OAc)_2$. Finally, intramolecular attack of the hydroxyl group to the electrophilic carbon in **D** could furnish the desired product **2**.



Scheme 7. Anticipated synthesis of the cyclic ether **2**

However, irradiation of a CH_2Cl_2 solution of **3**, I_2 and $PhI(OAc)_2$ gave a mixture of products from which the major product was isolated as a 2.5:1 mixture of diastereomers (Scheme 8). This compound was tentively assigned as the structure **32** and was relatively unstable. The ^1H NMR spectrum of this compound indicated the presence of two isomeric compounds (A: major isomer, B: minor isomer) in a ratio of 2.5:1. Both products had

an aldehyde resonance (δ 9.81 (s, H4'B); δ 9.79 (s, H4'A)), an acetoxy resonance (δ 2.11 (s, CH_3COA); δ 2.03 (s, CH_3COB)), a resonance for a hemiaminal proton (δ 7.06 (d, *J* = 9.0 Hz, H4B); δ 6.66 (d, *J* = 8.0 Hz, H4A)), and a resonance for a methyl group attached to a methine (δ 1.25 (d, *J* = 6.5 Hz, H1"A); δ 1.21 (d, *J* = 6.5 Hz, H1"B)). The hemiaminal proton H-4 correlated to H-3a in the COSY spectrum (observed in both isomers). COSY correlations were also observed between H-3 and H-1" and H-3 and H3a (weak) (Figure 4 (I)). Similarly, the ^{13}C NMR spectrum showed resonances for an aldehyde group (δ 200.9 C4'A; 200.6 C4'B), a hemiaminal carbon (δ 82.6 C4A; 78.2 C4B), a methyl (δ 21.0, C1'A; 20.8, C1' B) and an acetyl methyl group (δ 15.0 COMeB; 14.7 COMeA). HMBC correlations were observed between H-3 and C-2; H-1" and C-2; H-4' and C-2' and C-3'; and H-4 and the acetoxy carbonyl group (Figure 4 (II)). While the ^{1}H and ^{13}C and 2D NMR spectroscopic data were consistent with the proposed structure **32** the high resolution mass spectrum (HRESIMS calcd. for $C_{15}H_{21}O_8NNa$, $(M+Na)^+$ 366.1165, found: 366.1158) indicated a molecular formula of $C_{15}H_{21}O_8N$ which has two more oxygen atoms than structure **32**. Clearly the NMR and MS data are not consistent and the structure of the main product from this reaction is not conclusive. However it is clear that the A-ring of compound **3** had undergone oxidative cleavage to a relatively unstable aldehyde product.



Scheme 8. Attempted photochemical oxidative cyclization of **3**

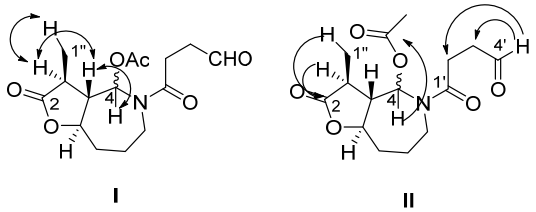
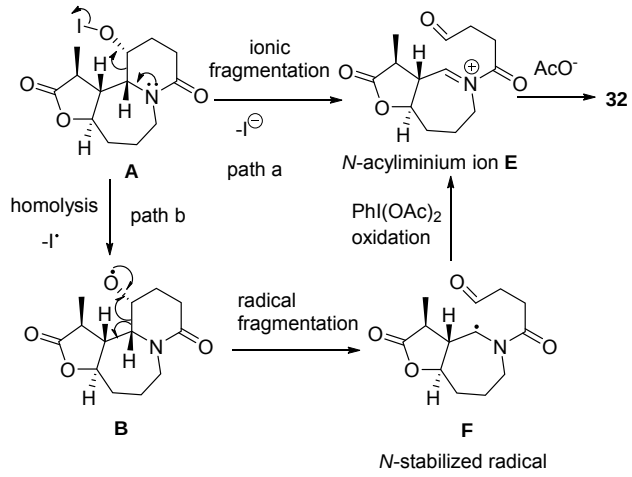


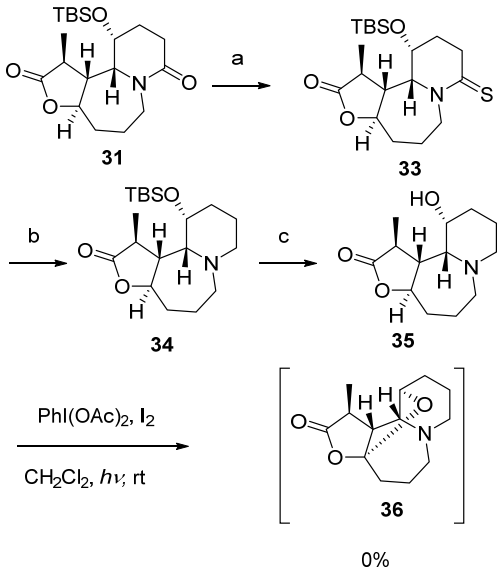
Figure 4. Observed COSY correlations (**I**) and HMBC correlations (**II**) of **32**

A proposed mechanism for the formation of the tentative structure **32** is shown in Scheme 9. The hypoiodite **A**, which could from the reaction of **3** with I_2, could undergo an ionic-fragmentation to form the *N*-acyliminium ion **E** (Scheme 9, path a). Alternatively, the intermediate **A** could undergo homolytic cleavage of the hypoiodite to form the free radical **B** (Scheme 9, path b), which could undergo radical fragmentation to form the radical intermediate **F**. This intermediate could then be oxidized to the *N*-acyliminium ion **E** by $PhI(OAc)_2$. Addition of acetate to this acyliminium ion (from both faces of the iminium ion) would provide hemiaminal **32** as a mixture of diastereomers.



Scheme 9. Proposed mechanism for the formation of **32**

Because of the aforementioned fragmentation process, which was possibly related to the formation of a *N*-acyliminium ion, we decided to reduce the lactam carbonyl group of **3** to avoid the formation of such an intermediate in these reactions. Lactam **31** was converted to the amine **35** by first following the procedure described by Zhang[8] by treatment with Lawesson's reagent to give the thioamide **33** (80% yield) and then reduction to the piperidine **34** with Raney-Ni (75%). Finally *O*-TBS deprotection of **34** gave the alcohol **35** (78%). Compound **35** was then subjected to the abovementioned photochemical oxidative cyclization reaction conditions. Unfortunately, this reaction led to a complex mixture of products (Scheme 10) and we were unable to isolate any pure product, including the desired product **26**, due to the small amount of starting material used and the close R_f values of the products on TLC.



Reaction conditions: (a) Lawesson' reagent, THF, reflux, 3 h (80%); (b) Raney-Ni, EtOH, reflux, 4 h (75%); (c) TBAF, AcOH, THF, 0 °C to rt, 14 h (78%).

Scheme 10. Synthesis of piperidine **35** and an attempt to make the ether compound **36**.

Conclusions

In conclusion, a diastereoselective synthesis of the A-B-C tricylic ring structure of the *Stemona* alkaloid stemocurtisine has been developed. The tricyclic compound **3** was obtained in 19 steps from the known vinyl iodide **7** in an overall yield of 1.2%. Attempts to prepare the C-3a−C-11 ether moiety of this alkaloid from compound **3** using a photochemically induced oxidative cyclization method were unsuccessful due to cleavage of the A-ring. Alternative procedures to make this ether moiety are now in progress.

Experimental Section

General Information: All reactions were performed in oven dried glassware under an atmosphere of dry nitrogen, unless otherwise stated. Anhydrous solvents were purchased or obtained from an anhydrous solvent dispenser. ^{1}H and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively. $CDCl_3$ was used at the NMR solvent unless otherwise stated. NMR assignments were based on COSY, HSQC, HMBC, NOESY and DEPT experiments. ^{1}H NMR chemical shifts are quoted in δ values in ppm and are referenced relative to the chemical shift of $CDCl_3$ (7.26 ppm) unless otherwise noted. Coupling constants (*J*) are reported in Hz, with signal multiplicities designated at singlet (s), doublet (d), doublet of doublet (dd), doublet of doublet of doublet (ddd), triplet (t), quartet (q), doublet of triplets (dt), triplet of doublets (td), doublet of doublet of triplets (ddt), multiplet (m), broad singlet (bs), broad multiplet (bm), quintet (quin), doublet of quartets (dq). ^{13}C NMR chemical shifts are quoted in δ values in ppm and are referenced relative to the chemical shift of $CDCl_3$ (77.36 ppm) unless otherwise noted. Melting points are uncorrected. Infrared spectra were obtained as neat samples. TLC analyses were performed using aluminium backed silica gel TLC plates. Column chromatography was performed using silica gel (40-63 µm) packed by the slurry method. Known compounds, **7**, **8**, **9** and **16** were prepared according to the literature methods.[12]

(*Z*)-Methyl 8-(*tert*-butyldimethylsilyloxy)oct-4-en-6-ynoate (10): To a solution of the vinyl iodide **8** (1.182 g, 4.93 mmol) in Et_3N (12 mL) under an argon atmosphere were added $PdCl_2(PPh_3)_2$ (69 mg, 0.098 mmol, 0.02 equiv) and CuI (189 mg, 0.098 mmol, 0.2 equiv).[12c] The mixture was stirred for 15 min then a solution of alkyne **9** (1.005 g, 5.91 mmol, 1.2 equiv) in THF (6 mL) was added dropwise over a period of 30 min. After being stirred for 16 h, the mixture was diluted with Et_2O (150 mL) and washed with saturated NH_4Cl solution (2 x 30 mL). The organic layer was dried over Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (1:9, EtOAc/petroleum spirit) to give the ene-yne 1**0** (874 mg, 70% yield) as a colourless oil. *Rf* = 0.62 (1:4, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 2956, 1710, 1168, 1022, 919. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.90 (dt, *J* = 10.7, 7.3 Hz, 1H, H4), 5.53 (d, *J* = 10.7 Hz, 1H, H5), 4.46 (s, 2H, H8), 3.68 (s, 3H, MeO), 2.61 (dd, *J* = 14.8, 7.4 Hz, 2H, H3), 2.42 (t, *J* = 7.5 Hz, 2H, H2), 0.91 (s, 9H, $(CH_3)_3C$), 0.13 (s, 6H, CH_3Si) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 173.6 (C1), 141.6 (C4), 110.6 (C5), 93.2 (C6), 81.4 (C7), 52.6 (C8), 52.0 (MeO), 33.6 (C3), 26.2 (C2), 25.9 ($(CH_3)_3C$), 18.7($(CH_3)_3C$), -4.8 (CH_3Si) ppm. ESIMS *m/z* 305 [(M+Na)$^+$ 100%]. HRESIMS calcd. for $C_{15}H_{26}O_3SiNa$: (M+H)$^+$ 305.1563; found: 305.1544.

Methyl 3-((2*R,3*S**)-3-(3-(*tert*-butyldimethylsilyloxy)prop-1-ynyl)oxiran-2-yl)propanoate (11):** *m*-Chloroperbenzoic acid (743 mg, 4.2 mmol, 1.4 equiv) was added to a solution of the alkene **10** (846 mg, 3 mmol) in CH_2Cl_2 (30 mL) and the mixture was stirred at rt for 14 h. The reaction was quenched with saturated $NaHCO_3$ solution (50 mL) and the aqueous phase was extracted with Et_2O (3 x 75 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (1:8, EtOAc/petroleum spirit) to give the epoxide **11** (439 mg, 56% yield) as a colourless oil and the starting alkene (200 mg, 27%). *Rf* = 0.58 (1:4, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 2955, 2239, 1767, 1251, 1185, 1041. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.34 (s, 2H, H8), 3.70 (s, 3H, MeO), 3.48 (d, *J* = 4.0 Hz, 1H, H5), 3.14 (ddd, *J* = 6.6, 5.5, 4.0 Hz, 1H, H4), 2.53 (t, *J* = 7.4 Hz, 2H, H2), 2.11 – 1.92 (m, 2H, H3), 0.90 (s, 9H, $(CH_3)_3C$), 0.11 (s, 6H, $(CH_3)_2Si$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 173.4 (C1), 85.0 (C7), 79.5 (C6), 57.2 (C4), 52.1 (MeO), 52.0 (C8), 45.7 (C5), 30.7 (C2), 26.1 ($(CH_3)_3C$), 25.3 (C3), 18.6 ($(CH_3)_3C$), -4.9 (CH_3Si) ppm. ESIMS *m/z* 321 [(M+Na)$^+$ 100%]. HRESIMS calcd. for $C_{15}H_{26}O_4SiNa$: (M+Na)$^+$ 321.1498; found 321.1488.

Aminolysis of epoxide 11 with pent-4-en-1-amine: Lithium triflate (162 mg, 1 mmol) and 4-penten-1-amine[15b] (170 mg, 2 mmol) were added to a solution of epoxide **11** (298 mg, 1 mmol) in CH_3CN (2 mL) in a microwave reaction vial. The mixture was heated in a microwave reactor at 110 ºC, 200 W for 1 h. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (1:3 to 100:0, EtOAc/petroleum spirit). Four compounds **12**-**15** were obtained.

(*R)-5-((*R**)-4-(*tert*-Butyldimethylsilyloxy)-1-(pent-4-enylamino)but-2-ynyl)dihydrofuran-2(3*H*)-one (12):** Colourless oil, 46 mg, 13% yield. *Rf* = 0.58 (1:4, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 3330, 2929, 1765, 1657, 1461, 1253, 1080, 814, 777. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.78 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4''), 5.00 (d, *J* = 17.0 Hz, 1H, H5''), 4.94 (d, *J* = 10.0 Hz, 1H, H5''), 4.54 (dd, *J* = 12.5, 4.5 Hz, 1H, H5), 4.31 (s, 2H, H4'), 3.53 (d, *J* = 4.5 Hz, 1H, H1'), 2.88 (dt, *J* = 11.5, 7.0 Hz, 1H, H1''), 2.65 – 2.55 (m, 2H, H1'' and H3), 2.51 (dt, *J* = 18.0, 9.0 Hz, 1H, H3), 2.36 – 2.27 (m, 1H, H4), 2.24 – 2.14 (m, 1H, H4), 2.09 (q, *J* = 7.0 Hz, 2H, H3''), 1.59 – 1.53 (m, 2H, H2''), 0.89 (s, 9H, $(CH_3)_3C$), 0.10 (s, 6H, $(CH_3)_2Si$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 177.1 (C2), 138.5 (C4''), 115.1 (C5''), 84.3 (C2'), 81.9 (C3'), 81.5 (C5), 54.7 (C1'), 52.0 (C4'), 47.5 (C1''), 31.7 (C3''), 29.4 (C2''), 28.7 (C3), 26.1 ($(CH_3)_3C$), 24.6 (C4), 18.6 ($(CH_3)_3C$), -4.8 (CH_3Si) ppm. ESIMS *m/z* 374 [(M+Na)$^+$ 100%]. HRESIMS calcd. for $C_{19}H_{33}O_3NNaSi$ (M+H)$^+$ 374.3127; found: 374.3137.

(5*R,6*R**)-6-(3-(*tert*-Butyldimethylsilyloxy)prop-1-ynyl)-5-hydroxy-1-(pent-4-enyl)piperidin-2-one (13):** Colourless oil, 92 mg, 26% yield. *Rf* = 0.58 (1:4, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 3250, 2928, 2857, 2310, 1635, 1471, 1251, 834. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.79 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4''), 5.02 (d, *J* = 17.0, 1H, H5''), 4.96 (d, *J* = 10.0 Hz, 1H, H5''), 4.35 (s, 2H, H3'), 4.32 (d, *J* = 4.5 Hz, 1H, H6), 3.99 (dt, *J* = 10.0, 4.5 Hz, 1H, H5), 3.77 (dt, *J* = 14.0, 8.0 Hz, 1H, H1''), 3.13 – 3.06 (m, 1H, H1''), 2.56 (ddd, *J* = 18.0, 6.5, 4.0 Hz, 1H, H3), 2.43 – 2.34 (ddd, *J* = 18.0, 10.0, 7.5 Hz, 1H, H3), 2.12 – 2.04 (m, 3H, H3'' and H4), 1.97 – 1.90 (m, 1H, H4), 1.70 – 1.62 (m, 2H, H2''), 0.89 (s, 9H, $(CH_3)_3C$), 0.10 (s, 6H, $(CH_3)_2Si$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.9 (C2), 138.1 (C4''), 115.6 (C5''), 86.1 (C3'), 80.0 (C2'), 66.9 (C5), 55.2 (C6), 51.9 (C3'), 46.1 (C1''), 31.4 (C3''), 29.6 (C3), 27.1 (C4), 26.8 (C2''), 26.1 ($(CH_3)_3C$), 18.6 ($(CH_3)_3C$), -4.9 (CH_3Si) ppm. ESIMS *m/z* 374 [(M+Na)$^+$ 100%]. HRESIMS calcd. for $C_{19}H_{33}O_3NNaSi$: (M+H)$^+$ 374.3127; found: 374.3127.

(*S)-5-((*S**)-4-(*tert*-Butyldimethylsilyloxy)-1-hydroxybut-2-ynyl)-1-(pent-4-enyl)pyrrolidin-2-one (14):** Colourless oil, 39 mg, 11% yield. *Rf* = 0.58 (1:4, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 3317, 2926, 1668, 1458, 1252, 1080, 1006, 998, 777. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.80 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4''), 5.02 (d, *J* = 17.0 Hz, 1H, H5''), 4.97 (d, *J* = 10.0 Hz, 1H, H5''), 4.56 (d, *J* = 3.0 Hz, 1H, H1'), 4.31 (s, 2H, H4'), 3.80 – 3.64 (m, 1H, H5), 3.66 (ddd, *J* = 14.0, 9.0, 8.0 Hz, 1H, H1''), 3.15 (ddd, *J* = 14.0, 9.0, 5.5 Hz, 1H, H1''), 2.57 – 2.48 (m, 1H, H3), 2.34 – 2.25 (m, 1H, H3), 2.18 – 2.00 (m, 4H, H2'' and H3''), 1.75 – 1.69 (m, H4), 1.64 – 1.60 (m, 1H, H4), 0.90 (s, 9H, $(CH_3)_3C$), 0.10 (s, 6H, $(CH_3)_2Si$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 176.1 (C2), 138.0 (C4''), 115.5 (C5''), 86.0 (C3'), 82.6 (C2'), 64.6 (C1'), 61.7 (C5), 51.9 (C4'), 41.8 (C1''), 31.4 (C3''), 30.5 (C3), 26.9 (C4), 26.1 ($(CH_3)_3C$), 21.2 (C2''), 18.6 ($(CH_3)_3C$), -4.9 (CH_3Si) ppm. ESIMS *m/z* 374 [(M+Na)$^+$ 100%]. HRESIMS calcd. for $C_{19}H_{33}O_3NNaSi$: (M+H)$^+$ 374.3127; found: 374.3115.

(4*R,5*R**)-8-(*tert*-Butyldimethylsilyloxy)-4-hydroxy-*N*-(pent-4-enyl)-5-(pent-4-enylamino)oct-6-ynamide (15):** Yellow solid, 161 mg, 37% yield. Mp = 79-81 ºC. *Rf* = 0.58 (1:4, EtOAc/Petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 3401, 2952, 2931, 1460, 1562, 1249, 1168, 1030, 835. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.63 (bs, 1H, NH amide), 5.82 – 5.72 (m, 2H, H4' and H4''), 5.00 (d, *J* = 17.0 Hz, 2H, H5' and H5''), 4.95 (d, *J* = 10.0 Hz, 2H, H5' and H5''), 4.31 (s, 2H, H8), 3.58 – 3.53 (m, 1H, H4), 3.25 (d, *J* = 9.0 Hz, 1H, H5), 3.20 (dd, *J* = 13.0, 6.5 Hz, 2H, H1'), 2.91 – 2.84 (m, 1H, H1''), 2.64 – 2.56 (m, 1H, H1'''), 2.46 – 2.35 (m, 2H, H2), 2.14 – 2.02 (m, 5H, H3', H3'' and H3), 1.75 (td, *J* = 14.5, 7.0 Hz, 1H, H3), 1.66 – 1.54 (m 4H, H2' and H2''), 0.89 (s, 9H, $(CH_3)_3C$), 0.09 (s, 6H, $(CH_3)_2Si$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 174.8 (C1), 138.2 (C4'), 138.0 (C4''), 115.4 (C5'),115.3 (C5''), 85.4 (C7), 81.9 (C6), 73.3 (C4), 55.8 (C5), 52.0 (C8), 46.9 (C1'), 39.7 (C1''), 32.9 (C2), 31.6 (C3'), 31.3 (C3''), 29.3 (C3), 28.7 (C2'), 28.6 (C2''), 26.1 ($(CH_3)_3C$), 18.6 ($(CH_3)_3C$), -4.9 (C-Si) ppm. ESIMS *m/z* 437 [(M+H)$^+$ 100%]. HRESIMS calcd. for $C_{24}H_{45}O_3N_2Si$: (M+H)$^+$ 437.3183; found: 437.3199.

Preparation of lactam 13 from the amino-lactone 12: To solution of the amino-lactone **12** (43 mg, 0.13 mmol) in MeOH (1.5 mL) was added Et_3N (337 µL, 25% volume in MeOH) and the mixture was stirred at reflux temperature for 3 d. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (9:1, EtOAc/petroleum spirit) to afford the lactam **13** (41 mg, 96% yield) as a pale yellow oil.

(*Z*)-8-(4-Methoxybenzyloxy)oct-4-en-6-yn-1-ol (17): To a solution of the vinyl iodide **7** (1.484 g, 7 mmol) in Et_3N (50 mL), were added $PdCl_2(PPh_3)_2$ (112 mg, 0.154 mmol, 0.02 equiv) and CuI (267 mg, 1.54 mmol, 0.2 equiv) under a nitrogen atmosphere. The mixture was stirred for 15 min then a solution of alkyne **16** (1.48 g, 8.4 mmol) in THF (25 mL) was added dropwise over period of 30 min. After being stirred for 14 h, the mixture was diluted with Et_2O (150 mL) and washed with saturated NH_4Cl solution (2x 50 mL). The organic layer was dried over Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (3:7, EtOAc/petroleum spirit) to give the ene-yne **17** (1.438 g, 79% yield) as a colourless oil. *Rf* = 0.61 (1:1, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 3412, 2937, 1713, 1608, 1512, 1246, 1173, 1029, 818. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.30 (d, *J* = 8.5 Hz, 2H, ArH), 6.90 (d, *J* = 8.5 Hz, 2H, ArH), 5.97 (dt, *J* = 10.5, 7.5 Hz, 1H, H4), 5.57 (d, *J* = 10.5 Hz, 1H, H5), 4.56 (s, 2H, OCH_2Ar), 4.30 (s, 2H, H8), 3.82 (s, 3H, OMe), 3.67 (t, *J* = 6.5 Hz, 2H, H1), 2.44 (q, *J* = 7.5 Hz, 2H, H3), 1.73 – 1.67 (m, 2H, H2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.7 (ArC), 143.9 (C4), 130.1 (ArCH), 129.8 (ArC), 114.2 (ArCH), 109.7 (C5), 90.0 (C7), 83.4 (C6), 71.5 (OCH_2Ar), 62.4 (C1), 57.9 (C8), 55.6 (OMe), 31.9 (C2), 26.9 (C3) ppm. ESIMS *m/z* 283 [(M+Na)$^+$ 100%]. HRESIMS calcd. for $C_{16}H_{20}O_3Na$: (M+Na)$^+$ 283.1316; found 283.1316.

(*Z*)-*tert*-Butyl(8-(4-methoxybenzyloxy)oct-4-en-6-ynyloxy)dimethylsilane (18): Imidazole (2.176 g, 32 mmol) and TBSCl (2.215 g, 14.72 mmol) were added to a solution of alcohol **17** (3.33 g, 12.8 mmol) in DMF (40 mL) at rt under a N_2 atmosphere and the mixture was stirred at rt for 6 h. The mixture was then poured into a beaker containing water (70 mL) and then extracted with EtOAc (3 x 100 mL). The organic extracts were combined, washed with water (2 x 100 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (1:9, EtOAc/petroleum spirit) to give the TBS ether **18** (4.453 g, 93% yield) as a colourless oil. *Rf* = 0.61 (1:3, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 2931, 2856, 1512, 1426, 1248, 1107, 819, 741. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.29 (d, *J* = 8.5 Hz, 2H, ArH), 6.88 (d, *J* = 8.6 Hz, 2H, ArH), 5.96 (dt, *J* = 10.7, 7.4 Hz, 1H, H4), 5.52 (d, *J* = 10.7 Hz, 1H, H5), 4.55 (s, 2H, OCH_2Ar), 4.29 (s, 2H, H8), 3.80 (s, 3H, OMe), 3.64 (t, *J* = 6.5 Hz, 2H, H1), 2.38 (q, *J* = 7.3 Hz, 2H, H3), 1.68 – 1.61 (m, 2H, H4), 0.89 (s, 9H, $(CH_3)_3C$), 0.05 (s, 6H, $(CH_3)_2Si$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.7 (ArC), 144.4 (C4), 130.1 (ArCH), 130.0 (ArC), 114.2 (ArCH), 109.1 (C5), 89.8 (C7) , 83.5 (C6), 71.4 (OCH_2Ar), 63.0 (C1), 57.9 (C8), 55.6 (OMe), 32.4 (C2), 27.2 (C3), 26.3 ($(CH_3)_3C$), 18.7 ($(CH_3)_3C$), -4.9 (CH_3Si) ppm. ESIMS *m/z* 397 [(M+Na)$^+$]. HRESIMS calcd. for $C_{22}H_{34}O_3SiNa$: (M+Na)$^+$ 397.2175; found: 397.2156.

***tert*-Butyl(3-((2*R**,3*S**)-3-(3-(4-methoxybenzyloxy)prop-1-ynyl)oxiran-2-yl)propoxy)dimethylsilane (19):** Purified *m*-chloroperbenzoic acid (2.38 g, 13.8 mmol) was added to solution of the alkene **18** (4.3 g, 11.5 mmol) in CH_2Cl_2 (150 mL) and the mixture was stirred at rt for 14 h. The reaction was quenched with saturated $NaHCO_3$ solution (100 mL) and the aqueous phase was extracted with Et_2O (3 x 150 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered through a short column loaded with Al_2O_3. The solvent was removed *in vacuo* and the residue was purified by column chromatography (1:8, EtOAc/petroleum spirit) to give the epoxide **19** (2.825 g, 63% yield) as a colourless oil and the starting alkene **18** (0.989 g, 23%). *Rf* = 0.59 (1:3, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 3312, 2930, 2856, 1612, 1513, 1465, 1248, 1094, 834, 755. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.27 (d, *J* = 8.0 Hz, 2H, ArH), 6.88 (d, *J* = 8.0 Hz, 2H, ArH), 4.52 (s, 2H, OCH_2Ar), 4.17 (s, 2H, H8), 3.80 (s, 3H, OMe), 3.72 – 3.64 (m, 2H, H1), 3.49 (d, *J* = 3.5 Hz, 1H, H5), 3.10 (dd, *J* = 7.0, 3.5 Hz, 1H, H4), 1.80-1.71 (m, 4H, H2 and H3), 0.89 (s, 9H, $(CH_3)_3C$), 0.05 (s, 6H, $(CH_3)_2Si$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.8 (ArC), 130.1 (ArCH), 129.6 (ArC), 114.2 (ArCH), 82.0 (C6), 81.8 (C7), 71.6 (OCH_2Ar), 63.0 (C1), 58.3 (C4), 57.3 (C8), 55.6 (OMe), 45.5 (C5), 29.5 (C3), 26.6 (C2), 26.3 ($(CH_3)_3C$), 18.6 ($(CH_3)_3C$), -5.0 (CH_3Si) ppm. ESIMS *m/z* 413 [(M+Na)$^+$ 100%]. HRESIMS calcd. for $C_{22}H_{34}O_4SiNa$: (M+Na)$^+$ 413.2124; found: 413.2126.

(4*R,5*R**)-1-(*tert*-Butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)-5-(pent-4-enylamino)oct-6-yn-4-ol (20):** Lithium triflate (162 mg, 1 mmol) and 4-penteneamine (340 mg, 3 mmol) were added to solution of the epoxide **19** (390 mg, 1 mmol) in CH_3CN (2 mL) in a microwave reactor vial. The mixture was heated in a microwave reactor at 110 ºC, 200 W for 1.5 h. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (3:7, EtOAc/petroleum spirit) to give the amine **20** (352 mg, 74% yield) as a pale yellow oil. *Rf* = 0.60 (1:1, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 3370, 2930, 2855, 1513, 1465, 1248, 1091, 833, 755. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.29 (d, *J* = 8.0 Hz, 2H, ArH), 6.90 (d, *J* = 8.0 Hz, 2H, ArH), 5.83 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4'), 5.05 (d, *J* = 17.0 Hz, 1H, H5'), 4.98 (d, *J* = 10.0 Hz, 1H, H5'), 4.53 (s, 2H, OCH_2Ar), 4.18 (s, 2H, H8), 3.83 (s, 3H, OMe), 3.69 (t, *J* = 6.0 Hz, 2H, H1), 3.46 (dd, *J* = 8.5, 6.0 Hz, 1H, H4), 3.17 (d, *J* = 8.5 Hz, 1H, H5), 2.91 (dt, *J* = 11.5, 7.0 Hz, 1H, H1'), 2.64 (dt, *J* = 11.5, 7.0 Hz, 1H, H1'), 2.15 (q, *J* = 7.0 Hz, 2H, H3'), 1.97 – 1.88 (m, 1H, H3), 1.83-1.74 (m, 1H, H2), 1.73 – 1.67 (m, 1H, H2), 1.66-1.57 (m, 2H, H2'), 1.54 – 1.45 (m, 1H, H3), 0.91 (s, 9H, $(CH_3)_3C$), 0.07 (s, 6H, $(CH_3)_2Si$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.8 (ArC), 138.6 (C4'), 130.1 (ArCH), 129.8 (ArC), 115.2 (C5'), 114.2 (ArCH), 85.7 (C6), 81.3 (C7), 73.2 (C4), 71.6 (OCH_2Ar), 63.6 (C1), 57.5 (C8), 56.3 (C5), 55.6 (OMe), 47.0 (C1'), 31.8 (C3'), 30.7 (C3), 29.6 (C2), 29.3 (C2'), 26.3 ($(CH_3)C$), 18.7 ($(CH_3)_3C$), -4.9 (CH_3Si) ppm. ESIMS *m/z* 476 [(M+H)$^+$ 100%]. HRESIMS calcd. for $C_{27}H_{46}O_4NSi$: (M+H)$^+$ 476.3196; found: 476.3198.

(4*R,5*R**)-8-(4-Methoxybenzyloxy)-5-(pent-4-enylamino)oct-6-yne-1,4-diol (21):** 1M tetrabutylamonium fluoride solution in THF (3.8 mL, 3.8 mmol) was added dropwise to a solution of the TBS ether **20** (1.19 g, 2.5 mmol) in THF (30 mL) at 0 ^{0}C and the mixture was warmed to rt and stirred for 4 h. Saturated $NaHCO_3$ (50 mL) was added and the aqueous phase was extracted with EtOAc (3 x 100 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (9:1 to 100:0, EtOAc/petroleum spirit) to give the diol **21** (890 mg, 91% yield) as a colourless oil. *Rf* = 0.69 (1:9, MeOH/EtOAc). IR (neat, ν_{max}/cm^{-1}): 3310, 2944, 1779, 1696, 1450, 1410, 1247, 1066, 1030, 740. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.28 (d, *J* = 8.5 Hz, 2H, ArH), 6.90 (d, *J* = 8.5 Hz, 2H, ArH), 5.82 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4'), 5.04 (d, *J* = 17.0, 1H, H5'), 4.98 (d, *J* = 10.0 Hz, 1H, H5'), 4.52 (s, 2H, OCH_2Ar), 4.17 (s, 2H, H8), 3.82 (s, 3H, OMe), 3.74-3.64 (m, 2H, H1), 3.48 – 3.43 (m, 1H, H4), 3.15 (d, *J* = 9.0 Hz, 1H, H5), 2.90 (dt, *J* = 11.5, 7.0 Hz, 1H, H1'), 2.63 (dt, *J* = 11.5, 7.0 Hz, 1H, H1'), 2.14 (q, *J* = 7.0 Hz, 2H, H3'), 2.04 – 1.95 (m,

1H, H3), 1.83 – 1.74 (m, 2H, H2), 1.63-1.59 (m, 2H, H2'), 1.58 – 1.48 (m, 1H, H3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.8 (ArC), 138.5 (C4'), 130.1 (ArCH), 129.7 (ArC), 115.3 (C5'), 114.2 (ArCH), 85.2 (C6), 81.7 (C7), 73.0 (C4), 71.6 (OCH_2Ar), 63.2 (C1), 57.4 (C8), 56.0 (C5), 55.6 (OMe), 46.9 (C1'), 31.7 (C3'), 31.1 (C3), 29.7 (C2), 29.6 (C2') ppm. ESIMS *m/z* 362 [$(M+H)^+$ 100%]. HRESIMS calcd. for $C_{21}H_{32}O_4N$: $(M+H)^+$ 362.2321; found: 362.2331.

(9*H*)-Fluoren-9-yl)methyl (4*R,5*R**)-5,8-dihydroxy-1-(4-methoxybenzyloxy)oct-2-yn-4-yl(pent-4-enyl)carbamate (22):** To a solution of the amine **21** (975 mg, 2.7 mmol) in THF (40 mL), was added a saturated solution of Na_2CO_3 (20 mL) and the mixture was allowed to cool to 0 ^{0}C. FmocCl (768 mg. 2.97 mmol) was added portionwise at 0 ^{0}C and the reaction mixture was stirred at rt for 4 h. The organic phase was removed *in vacuo* and the aqueous layer was extracted with EtOAc (3 x 50 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (3:2, EtOAc/petroleum spirit) to give the Fmoc-diol **22** (1.511 g, 96% yield) as a waxy solid. *Rf* = 0.60 (9:1, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 3436, 2927, 1687, 1611, 1458, 1248, 1066, 1032, 739. ^{1}H NMR (500 MHz, $CDCl_3$, rotamers evident) δ = 7.76 (*J* = 8.5 Hz, 2H, ArH), 7.59 (*J* = 8.5 Hz, 2H, ArH), 7.39 (t, *J* = 8.5 Hz, 2H, ArH), 7.31 (t, *J* = 8.5 Hz, 2H, ArH), 7.23 (*J* = 9.0 Hz, 2H, ArH), 6.87 (*J* = 9.0 Hz, 2H, ArH), 5.72-5.62 (bm, 1H, H4''), 5.01-4.90 (bm, 2H, H5''), 4.77-4.72 (bm, 1H, $FmocCH_2O$), 4.67-4.57 (bm, 2H, $FmocCH_2O$ and H1'), 4.47 (s, 2H, OCH_2Ar), 4.23 (t, *J* = 6.0 Hz. 1H, FmocCH), 4.12 (s, 2H, H4'), 3.80 (s, 3H, OMe), 3.67-3.58 (bm, 3H, H1 and H4), 3.12-2.97 (bm, 2H, H1'), 1.90-1.80 (bm, 2H, H3'), 1.75-1.65 (bm, 2H, H2'), 1.55-1.40 (bm, 4H, H2 and H3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ rotamers evident) δ = 159.7 (Ar), 144.1 (Ar), 141.6 (Ar), 138.0 (C4'), 129.9 (Ar), 129.5 (Ar), 127.9 (Ar), 127.3 (Ar), 124.9 (Ar), 120.2 (Ar), 115.2 (C5''), 114.1 (Ar), 82.5 (C7), 82.2 (C6), 73.0 (b, C4), 71.5 (OCH_2Ar), 67.2 ($FmocCH_2O$), 63.0 (C1), 57.2 (C8), 55.5 (OMe), 54.9 (b,C5), 47.7 (FmocCH), 45.6 (b, C1''), 31.4 (C3'), 31.2 (C2'), 29.4 (C3), 28.8 (b, C2) ppm. ESIMS *m/z* 606 [$(M+Na)^+$ 100%]. HRESIMS calcd. for $C_{36}H_{41}O_6NNa$: $(M+Na)^+$ 606.2832; found: 606.2822.

(9*H*)-Fluoren-9-yl)methyl (*R)-4-(4-methoxybenzyloxy)-1-((*R**)-5-oxotetrahydrofuran-2-yl)but-2-ynyl(pent-4-enyl)carbamate (23):** To a solution of the diol **22** (1.28 g, 2.2 mmol) in anhydrous CH_2Cl_2 (30 mL) were added TEMPO (69 mg, 0.44 mmol) and BAIB (2.83 g, 8.8 mmol) at rt and the mixture was stirred at rt for 18 h. The reaction was quenched by 0.1 N $Na_2S_2O_3$ solution (20 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (3:2, EtOAc/petroleum spirit) to give the Fmoc-lactone **23** (813 mg, 84% yield) as a waxy solid. *Rf* = 0.65 (3:2, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 3346, 2935, 1773, 1612, 1513, 1455, 1451, 1246, 1713, 1067, 1029, 919, 817. ^{1}H NMR (500 MHz, $CDCl_3$, rotamers evident) δ = 7.79 (d, *J* = 7.5 Hz, 2H, ArH), 7.63 (t, *J* = 7.0 Hz, 2H, ArH), 7.43 (t, *J* = 7.5 Hz, 2H, ArH), 7.35 (t, *J* = 7.0 Hz, 2H, ArH), 7.27 (d, *J* = 8.5 Hz, 2H, ArH), 6.91 (d, *J* = 8.5 Hz, 2H, ArH), 5.72-5.3 (bm, 1H, H4''), 5.15-5.05 (bm, 3H, H5'' and H1'), 4.71-4.63 (bm, 2H, H5 and $FmocCH_2O$), 4.62-4.57 (bm, 1H, $FmocCH_2O$), 4.50 (bs, 2H, OCH_2Ar), 4.27 (t, *J* = 5.0 Hz, 1H, FmocCH), 4.16 (bs, 2H, H4'), 3.84 (s, 3H, OMe), 3.34-3.26 (bm, 1H, H1'), 3.13-3.07 (bm, 1H, H1''), 2.59-2.52 (bm, 1H, H3), 2.12-2.03 (bm, 3H, H3 and 2H3''), 1.89-1.83 (bm, 1H, H4), 1.58-1.52 (bm, 1H, H2''), 1.45-1.38 (bm, 1H, H2'') ppm. ^{13}C NMR (126 MHz, $CDCl_3$, rotamers evident) δ = 176.2 (C2), 159.5 (Ar), 156.3 (b, FmocCO), 143.8 (Ar), 141.4 (Ar), 137.7 (C4''), 129.7 (Ar), 129.1 (Ar), 127.4 (Ar), 127.1 (Ar), 124.7 (Ar), 120.0 (Ar), 115.1 (b, C3''), 113.9 (Ar), 83.2 (C3'), 79.4 (b, C5), 78.8 (b, C2'), 71.4 (OCH_2Ar), 67.1 (b, $FmocCH_2O$), 56.8 (C4'), 55.3 (OMe), 52.4 (b, C1'), 47.3 (FmocCH), 31.1 (C3''), 28.2 (C2''), 28.1 (b,C3), 24.9 (C4) ppm. ESIMS *m/z* 602 [$(M+Na)^+$ 100%]. HRESIMS calcd. for $C_{36}H_{37}O_6NNa$: $(M+Na)^+$ 602.25143; found: 602.2519.

(*R)-5-((*R**)-4-(4-Methoxybenzyloxy)-1-(pent-4-enylamino)but-2-ynyl)dihydrofuran-2(3*H*)-one (24):** Triethyamine (5 mL) was added to a solution of the Fmoc-lactone **23** (2.432 g, 4.2 mmol) in CH_3CN (20 mL) at rt and the mixture was allowed to stir at rt for 14 h. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (4:1, EtOAc/petroleum spirit) to give the lactone **24** (1.289 g, 86% yield) as a pale yellow oil. *Rf* = 0.63 (9:1, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 3343, 2935, 2841, 1773, 1611, 1512, 1247, 1067, 1029, 816. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.28 (d, *J* = 8.5 Hz, 2H, ArH), 6.89 (d, *J* = 8.5 Hz, 2H ArH), 5.82 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4''), 5.03 (d, *J* = 17.0 Hz, 1H, H5''), 4.97 (d, *J* = 10.0 Hz, 1H, H5'')), 4.60 (dd, *J* = 7.0, 5.5 Hz, 1H, H5), 4.52 (s, 2H, OCH_2Ar), 4.17 (s, 2H, H4'), 3.81 (s, 3H, OMe), 3.59 (d, *J* = 5.5 Hz, 1H, H1'), 2.92 (dt, *J* = 11.5, 7.0 Hz, 1H, H1''), 2.67 – 2.59 (m, 2H, H1'' and H3), 2.54 (m, 1H, H3), 2.39 – 2.31 (m, 1H, H4), 2.27 – 2.19 (m, 1H, H4), 2.12 (q, *J* = 7.0 Hz, 2H, H3''), 1.64 – 1.55 (m, 2H, H2'') ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 177.1 (C1), 159.7 (ArC), 138.5 (C4''), 130.0 (ArCH), 129.6 (ArC), 115.1 (C5''), 114.2 (ArCH), 83.7 (C2'), 81.7 (C3'), 81.4 (C5), 71.6 (OCH_2Ar), 57.3 (C4'), 55.6 (OMe), 54.7 (C1'), 47.6 (C1''), 31.7 (C3''), 29.4 (C2''), 28.7 (C3), 24.5 (C4) ppm. ESIMS *m/z* 380 [$(M+Na)^+$ 100%]. HRESIMS calcd. for $C_{21}H_{27}O_4NSiNa$: $(M+Na)^+$ 380.1838; found: 380.1842.

(5*R,6*R**)-5-Hydroxy-6-(3-(4-methoxybenzyloxy)prop-1-ynyl)-1-(pent-4-enyl)piperidin-2-one (25):** To solution of the amino-lactone **24** (1.086 g, 3.3 mmol) in MeOH (12 mL) was added Et_3N (3 mL) and the mixture was stirred at reflux temperature for 3 d. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (9:1, EtOAc/petroleum spirit) to afford the lactam **25** (920 mg, 84% yield) as a pale yellow oil. *Rf* = 0.63 (1:9, MeOH/EtOAc). IR (neat, ν_{max}/cm^{-1}): 3361, 2930, 1614, 1513, 1438, 1413, 1247, 1067, 1031, 817. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.24 (d, *J* = 7.5 Hz, 2H, ArH), 6.87 (d, *J* = 7.5 Hz, 2H, ArH), 5.79 (ddt, *J* = 17.0, 10.0, 4.5 Hz, 1H, H4''), 5.01 (d, *J* = 17.0 Hz, 1H, H5''), 4.95 (d, *J* = 10.0 Hz, 1H, H5''), 4.49 (s, 2H, OCH_2Ar), 4.32 (s, 1H, H6), 4.17 (s, 2H, H3'), 4.01 – 3.95 (m, 1H, H5), 3.79 (s, 3H, OMe), 3.81 – 3.71 (m, 1H, H1''), 3.12 (dt, *J* = 14.0, 7.0 Hz 1H, H1''), 2.59-2.53 (m, 1H, H3), 2.38 (dt, *J* = 11.5, 7.0 Hz, 1H, H3), 2.14 – 2.02 (m, 3H, H4 and H3''), 1.95-1.88 (m, 1H, H4), 1.76 – 1.62 (m, 2H, H2'') ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 169.0 (C1), 159.8 (ArC), 138.0 (C4''), 130.2 (ArCH), 129.3 (ArC), 115.4 (C5''), 114.2 (ArCH), 83.2 (C2'), 81.8 (C1'), 71.9 (OCH_2Ar), 66.8 (C5), 57.3 (C3'), 55.6 (OMe), 55.2 (C6) 46.2 (C1''), 31.4 (C3''), 29.8 (C3), 27.1 (C4), 26.7 (C2'') ppm. ESIMS *m/z* 380 [$(M+Na)^+$ 100%]. HRESIMS calcd. for $C_{21}H_{27}O_4NSiNa$: $(M+Na)^+$ 380.1838; found: 380.1839.

(5*R,6*R**)-5-(*tert*-Butyldimethylsilyloxy)-6-(3-(4-methoxybenzyloxy)prop-1-ynyl)-1-(pent-4-enyl)piperidin-2-one (26):** To a solution of the alcohol **25** (990 mg, 2.77 mmol) in CH_2Cl_2 (30 mL) were added TBSOTf (10.43 mL, 1.85 mmol) and 2,6-lutidine (0.32 mL, 2.77 mmol) at 0 ^{0}C. The mixture was warmed to rt and stirred for 1 h. This step was repeated three times and the reaction mixture was stirred at rt for 12 h. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (3:2, EtOAc/petroleum spirit) to give compound **26** (1.16 g, 81% yield) as a colourless oil. *Rf* = 0.62 (9:1, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 2936, 1742, 1635, 1610, 1462, 1231, 1170, 1032. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.29 (d, *J* = 8.5 Hz, 2H, ArH), 6.90 (d, *J* = 8.5 Hz, 2H, ArH), 5.84 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4''), 5.06 (d, *J* = 17.0 Hz, 1H, H5''), 5.00 (d, *J* = 10.0 Hz, 1H, H5''), 4.55 (s, 2H, OCH_2Ar), 4.23 (d, *J* = 3.0 Hz, 1H, H6), 4.20 (s, 2H, H3'), 4.08 – 4.03 (m, 1H, H5), 3.83 (s, 3H, OMe), 3.79 (dt, *J* = 14.0, 7.0 Hz, 1H, H1''), 3.18 (dt, *J* = 14.0, 7.0 Hz, 1H, H1''), 2.64-2.58 (ddd, *J* = 18.0, 7.0, 3.5 Hz, 1H, H3), 2.61 (ddd, *J* = 18.0, 10.0, 7.0 Hz, 1H, H3), 2.25 – 2.15 (m, 1H, H4), 2.10 (q, *J* = 7.0 Hz, 2H, H3''), 1.89 – 1.83 (m, 1H, H4), 1.72 (quin, *J* = 7.5 Hz, 2H, H2''), 0.94 (s, 9H, $(CH_3)_3C$)), 0.15 (s, 6H, $(CH_3)_2Si$)) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 169.0 (C2), 159.7 (ArC), 138.2 (C4''), 130.0 (ArCH), 129.7 (ArC), 115.3 (C5''), 114.2 (ArCH), 82.8 (C2'), 81.6 (C1'), 71.3 (OCH_2Ar), 68.2 (C5), 57.2 (C3'), 55.6 (OMe), 55,5 (C6), 46.1 (C1''), 31.4 (C3''), 29.7 (C3), 27.5 (C4), 27.0 (C2''), 26.0 (($CH_3)_3C$), 18.4 (($CH_3)_3C$), -4.2 (CH_3Si) ppm. ESIMS *m/z* 494 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{27}H_{41}O_4NSiNa$: $(M+Na)^+$ 494.2708; found: 494.2703.

(5*R,6*R**)-5-(*tert*-Butyldimethylsilyloxy)-6-(3-hydroxyprop-1-ynyl)-1-(pent-4-enyl)piperidin-2-one (27):** To a mixture of the PMB ether **26** (1.178 g, 2.5 mmol) in CH_2Cl_2 (50 mL) and water (5 mL,) was added DDQ (1.022 g, 4.5 mmol) portionwise at 0 ^{0}C and the mixture was allowed to stirred at rt for 18 h. Then the mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (2 x 50 mL). The organic layer was dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (4:1, EtOAc/petroleum spirit) to give the primary alcohol **27** (694 mg, 79% yield) as a yellow oil. *Rf* = 0.57 (9:1, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 3326, 2926, 2869, 2361, 1622, 1454, 1126, 1024, 913. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4''), 5.03 (d, *J* = 17.0 Hz, 1H, H5''), 4.98 (d, *J* = 10.0 Hz, 1H, H5'), 4.34 (s, 1H, H6), 4.31 (s, 2H, H3'), 4.05-4.00 (m, 1H, H5), 3.77 (dt, *J* = 13.5, 8.0 Hz, 1H, H1''), 3.16 (dt, *J* = 13.5, 8.0 Hz, 1H, H1''), 2.59 (ddd, dt, *J* = 18.0, 6.5, 4.0 Hz 1H, H3), 2.40 (dt, *J* = 17.5, 7.5 Hz 1H, H3), 2.20-2.13 (m, H, H4), 2.12-2.08 (m, 1H, H3'), 1.98-1.91 (m,1H, H4), 1.67 (quin, *J* = 7.5 Hz, 2H, H2''), 0.86 (s, 9H, $(CH_3)_3C$), 0.10 (s, 6H, $(CH_3)_2Si$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0 (C2), 137.8 (C4''), 111.1 (C5''), 82.5 (C2'), 81.4 (C1'), 68.7 (C5), 57.3 (C6), 55.9 (C3'), 45.9 (C1''), 31.0 (C3), 29.7 (C3''), 27.3 (C2''), 26.5 (C4), 26.1 ($(CH_3)_3C$), 18.5 ($(CH_3)_3C$), -4.7 (CH_3Si). ESIMS *m/z* 374 [$(M+Na)^+$ 100%]. HRESIMS calcd. for $C_{19}H_{33}O_3NSiNa$, $(M+Na)^+$ 374.2127, found:374.2123.

Methyl 3-((2*R,3*R**)-3-(*tert*-butyldimethylsilyloxy)-6-oxo-1-(pent-4-enyl)piperidin-2-yl)propiolate (5):** To a solution of the primary alcohol **27** (635 mg, 1.81 mmol) in acetone (20 mL) was added Jones' reagent (2.7 mL) dropwise at 0 ^{0}C. After stirring for 30 min at 0 ^{0}C, CH_3OH (0.5 mL) was added and the reaction mixture was stirred for additional 10 min at 0 ^{0}C. Water (40 mL) was added and the mixture then was extracted with CH_2Cl_2 (4 x 60 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* to give the crude acid (594 mg, 90% yield) as a yellow solid, which was used in the next step without further purification. To a solution of this acid (594 mg, 1.63 mmol) in anhydrous DMF (20 mL), was added K_2CO_3 (450 mg, 3.26 mmol) at rt and the mixture was stirred for 15 min under a N_2 atmosphere. Then MeI (610 µL, 9.8 mmol) was added and the reaction mixture was allowed to stirred at rt for 14 h. Water (40 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 60 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (2:3, EtOAc/petroleum spirit) to give the ester **5** (413 mg, 67% yield) as a pale yellow oil. NMR analysis indicated approximately 90% purity. *Rf* = 0.65 (4:1, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 2930, 1717, 1635, 1436, 1249, 858, 751. NMR (500 MHz, $CDCl_3$) δ = 5.82 (ddt, *J* = 17.5, 10.5, 6.0 Hz, 1H, H4''), 5.04 (d, *J* = 17.5 Hz, 1H, H5''), 4.98 (d, *J* = 10.0 Hz, 1H, H5'), 4.27 (d, *J* = 3.5 Hz, 1H, H2), 4.10-4.05 (m, 1H, H3), 3.78 (s, 3H, OMe), 3.74 (dt, *J* = 13.5, 8.0 Hz, 1H, H1''), 3.15 (dt, *J* = 13.5, 7.5 Hz, 1H, H1''), 2.63-2.57 (ddd, dt, *J* = 18.0, 7.0, 6.5, Hz 1H, H5), 2.38 (ddd, *J* = 18.0, 10.0, 7.0 Hz 1H, H5), 2.16-2.10 (m, 1H, H4), 2.07 (quin, *J* = 6.5 Hz, 2H, H3''), 1.91-1.85 (m, 1H , H4), 1.72-1.65 (m , 2H, H2''), 0.91 (s, 9H, $(CH_3)_3C$), 0.12 (s, 6H, $(CH_3)_2Si$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.8 (C6), 153.8 (C3'), 138.0 (C4''), 115.5 (C5''), 84.0 (C1'), 77.2 (C2'), 67.8 (C3), 55.7 (C5), 53.1 (OMe), 46.4 (C1''), 31.4 (C3''), 29.5 (C5), 27.7 (C4),26.8 (C2''), 25.9 ($(CH_3)_3C$), 18.3 ($(CH_3)_3C$), -4.2 (CH_3Si) ppm. ESIMS *m/z* 402 [$(M+Na)^+$ 100%]. HRESIMS calcd. for $C_{20}H_{33}O_4NSiNa$: $(M+Na)^+$ 402.2084; found: 402.2077.

Methyl 2-((1*R,10a*R**)-1-(*tert*-butyldimethylsilyloxy)-4-oxo-1,2,3,4,6,7,8,10a-octahydropyrido[1,2-*a*]azepin-10-yl)acrylate (28):** To a solution of the ene-yne **5** (872 mg, 2.3 mmol) in anhydrous CH_2Cl_2 (80 mL) was added Grubb's 1st generation Ru catalyst (189 mg, 0.23 mmol) under a N_2 atmosphere and the mixture was stirred at rt for 8 h. The reaction mixture then was exposed to open air for 30 min. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (3:2, EtOAc/petroleum spirit) to give the bicyclic compound **28** (680 mg, 78% yield) as a yellow oil. *Rf* = 0.69 (4:1, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 2952, 2929, 1720, 1639, 1251, 1222, 1202, 1074, 990, 812, 774. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.12 (s, 1H, H4'), 5.94 – 5.87 (t, *J* = 8.0 Hz, 1H, H9), 5.73 (s, 1H, H4'), 4.27 (s, 1H, H10a), 4.23 (dd, *J* = 13.0, 7.5 Hz, 1H, H6), 4.00 (s, 1H, H1), 3.77 (s, 3H, OMe), 3.20 (td, *J* = 13.0, 6.5 Hz, 1H, H6), 2.75 – 2.64 (m, 2H, H3 and H8), 2.34 (dd, *J* = 17.7, 5.7 Hz, 1H, H3), 2.23 – 2.13 (m, 1H, H7), 1.96 – 1.90 (m, 1H, H2), 1.90 – 1.76 (m, 2H, H8 and H2), 1.58 – 1.49 (m, 1H, H7), 0.88 (s, 9H, $(CH_3)_3C$), 0.02 (s, 6H, $(CH_3)_2Si$) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 169.5 (C4), 167.5 (C2'), 142.3 (C10), 136.1 (C1'), 132.8 (C9), 127.4 (C4'), 67.6 (C10a), 66.5 (C1), 52.5 (OMe), 42.3 (C6), 28.1 (C2), 27.1 (C3), 26.2 ($(CH_3)_3C$), 24.0 (C7), 22.1 (C8), 18.5 ($(CH_3)_3C$), -4.7 (CH_3Si) ppm. ESIMS *m/z* 380 [$(M+H)^+$ 100%]. HRESIMS calcd. for $C_{20}H_{34}O_4NSi$: $(M+H)^+$ 380.2261; found: 380.2257.

Methyl 2-((1*R,10a*R**)-1-(*tert*-butyldimethylsilyloxy)-4-oxo-1,2,3,4,6,7,8,10a-octahydropyrido[1,2-*a*]azepin-10-yl)propanoate (4):** Sodium borohydride (532 mg, 14 mmol) was added portionwise to a solution of the enone **28** (663 mg, 1.75 mmol) in anhydrous MeOH (20 mL) at 0 ^{0}C under a N_2 atmosphere and the mixture was stirred at 0 ^{0}C for 3 h. Saturated aqueous $NaHCO_3$ solution (30 mL) was added at 0 ^{0}C and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic extract was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (3:2, EtOAc/petroleum spirit) to give an inseparable mixture of diastereomers **4** (517 mg, 78% yield) as a pale yellow oil. *Rf* = 0.69 (4:1, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 2948, 2930, 1736, 1631, 1462, 1251, 1202, 1166, 1095, 993, 836. ^{1}H NMR (500 MHz, $CDCl_3$) *major diastereomer* δ = 5.86-5.79 (m, 1H, H9), 4.26-4.19 (m, H1 and H6), 3.93 (s, 1H, H10a), 3.69 (s, 3H, OMe), 3.04-2.96 (m, 1H, H1'), 2.85-2.69 (m, 2H, H6 and H3), 2.69-2.56 (m, 1H, H8), 2.41-2.32 (m, 1H, H3), 2.16-2.07 (m, 1H, H7), 2.02-1.94 (m, 1H, H2), 1.91-1.83 (m, 1H, H2), 1.83-1.75 (m, 1H, H8), 1.34 (d, *J* = 7.5 Hz, 3H, H4'), 0.86 (s, 9H, $(CH_3)_3C$), 0.11 (s, 6H, $(CH_3)_2Si$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 174.5 (C2'), 169.5 (C4), 135.9 (C10), 127.8 (C9), 69.2 (C1), 66.9 (C10a), 52.1 (OMe), 44.8 (C1'), 42.1 (C6), 28.4 (C2), 27.1 (C3), 26.1 ($(CH_3)_3C$), 23.9 (C7), 21.5 (C8), 19.0 (C4'), 18.5 ($(CH_3)_3C$), -4.7 (CH_3Si) ppm. ^{1}H NMR (500 MHz, $CDCl_3$) *minor diastereomer* (*in part*) δ = 5.86-5.79 (m, 1H, H9), 4.19-4.13 (m, H1 and H6), 3.97 (s, 1H, H10a), 3.70 (s, 3H, OMe), 3.04-2.96 (m, 1H, H1'), 2.94-2.86 (m, 1H, H6), 2.85-2.69 (m, 1H, H3), 2.69-2.56 (m, 1H, H8), 2.41-2.32 (m, 1H, H3), 2.16-2.07 (m, 1H, H7), 2.02-1.94 (m, 1H, H2), 1.91-1.83 (m, 1H, H2), 1.83-1.75 (m, 1H, H8), 1.35 (d, *J* = 7.5 Hz, 3H, H4'), 0.86 (s, 9H, $(CH_3)_3C$), 0.1 (s, 6H, $(CH_3)_2Si$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 174.4 (C2'), 169.5 (C4),134.7 (C10), 127.5 (C9), 69.8 (C1), 65.8 (C10a), 52.4 (OMe), 43.2 (C1'), 42.1 (C6), 28.2 (C2), 27.0 (C3), 26.1 ($(CH_3)_3C$), 23.8 (C7), 21.5 (C8), 19.0 (C4'), 18.5 ($(CH_3)_3C$), -4.7 (CH_3Si) ppm. ESIMS *m/z* 382 [$(M+H)^+$ 100%]. HRESIMS calcd. for $C_{20}H_{36}NO_4Si$: $(M+H)^+$ 382.2414; found: 382.2411.

Bromolactonization of 4: To a solution of **4** (648 mg, 1.3 mmol) in MeOH (15 mL), was added slowly 1M aqueous NaOH solution (13.7 mL) at 0 ^{0}C and the mixture was stirred at 0 ^{0}C for 8 h. The mixture was acidified to pH = 5 with 1M HCl solution and extracted with EtOAc (4 x 50 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* to afford a diastereomeric mixture of acids, which was used in the step without further purification. To a solution of this acid in CH_3CN (4 mL) was added diphenyl diselenide (21 mg, 0.65 mmol) and the resulting mixture was cooled to -30 ^{0}C. *N*-bromosuccinimide (277 mg, 1.69 mmol) was added with stirring, and the resulting reaction mixture was stirred at -30 ^{0}C for 3 h. The resulting solution was concentrated to <1 mL *in vacuo*, and EtOAc (60 mL) was added. The resulting organic layer was washed with water (2 x 10 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* to afford a yellow residue, which then was dissolved in EtOAc (10 mL). Et_3N (0.2 mL) was added and the solution was stirred at rt for 18 h.[13] The solution was then diluted with EtOAc (40 mL), washed with water (2 x 10 mL), dried over $MgSO_4$ and filtered. Purification by column chromatography (6:4 to 9:1, EtOAc/petroleum spirit) of the resulting

residue gave the tricyclic compounds **29** (192 mg, 31% yield) and **30** (124 mg, 20% yield) as white solids.

(3a*R,11*R**,11a*R**)-11-(*tert*-Butyldimethylsilyloxy)-1,3a,11a-trimethyl-3a,4,5,6,9,10,11,11a-octahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepine-2,8-dione (29):** NMR analysis indicated approximately 90% purity. Mp = 137-139 ºC. *Rf* = 0.69 (4:1, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 2951, 2930, 1751, 1630, 1253, 1196, 1148, 1082, 993, 835, 776. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.97 (d, *J* = 9.5 Hz, 1H, H3a), 4.71 (s, 1H, H11a), 4.52 (d, *J* = 10.5 Hz, 1H, H6), 4.21 (s, 1H, H11), 2.79 – 2.69 (m, 1H, H9), 2.54 – 2.47 (m, 1H, H4), 2.42-2.36 (m, 1H, H9), 2.27 – 2.15 (m, 1H, H6), 2.02-1.96 (m, 2H, H10), 1.90 (s, 3H, CH_3), 1.88-1.81 (m, 1H, H5), 1.75-1.65 (m, 1H, H5), 1.22 – 1.14 (m, 1H, H4), 0.84 (s, 9H, $(CH_3)_3C$), 0.03 (s, 6H, $(CH_3)_2$ Si) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 173.5 (C2), 169.9 (C8), 163.6 (C11b), 124.2 (C1), 83.9 (C3a) , 67.7 (C11), 63.2 (C11a), 47.6 (C6), 36.5 (C4) , 28.4 (C10), 26.6 (C9), 26.0 ($(CH_3)_3C$), 25.1 (C5), 18.2 ($(CH_3)_3C$), 9.74 (C1'), -4.6 (CH_3Si), -4.9 (CH_3Si) ppm. ESIMS *m/z* 366 [(M+H)$^+$ 100%]. HRESIMS calcd. for $C_{19}H_{32}NO_4Si$: (M+H)$^+$ 366.2101; found: 366.2099.

(3a*S,11*R**,11a*R**)-11-(*tert*-Butyldimethylsilyloxy)-1-methyl-3a,4,5,6,9,10,11,11a-octahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepine-2,8-dione (30):** NMR analysis indicated approximately 90% purity. Mp = 140-142 ºC. *Rf* = 0.69 (4:1, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 2954, 2930, 1749, 1628, 1254, 1160, 1103, 938, 834, 777. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.80 (d, *J* = 11.0 Hz, 1H, H3a), 4.51 – 4.45 (m, 1H, H11), 4.37-4.30 (m, 1H, H6), 4.27 (d, *J* = 3.0 Hz, 1H, H11a), 2.94 – 2.87 (m, 1H, H6), 2.57 (dt, *J* = 17.5, 7.0 Hz, 1H, H9), 2.44 (dt, *J* = 17.5, 7.0 Hz 1H, H9), 2.33 – 2.26 (m, 1H, H4), 2.19 – 2.07 (m, 3H, H10 and H5), 2.10 (s, 3H, H1'), 1.74 – 1.63 (m, 1H, H5), 1.60-1.54 (m, 1H, H4), 0.86 (s, 9H, $(CH_3)_3C$), 0.12 (s, 3H, CH_3Si), 0.07 (s, 3H, CH_3Si) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 174.5 (C2), 170.1 (C8), 157.3 (C11b), 123.3 (C1), 83.4 (C3a), 68.3 (C11), 62.3 (C11a), 46.1 (C6), 29.3 (C9), 28.3 (C4), 27.9 (C10), 26.0 ($(CH_3)_3C$), 21.5 (C5), 18.3 ($(CH_3)_3C$), 12.6 (C1'), -4.2 (CH_3Si), -4.6 (CH_3Si) ppm. ESIMS *m/z* 366 [(M+H)$^+$ 100%]. HRESIMS calcd. for $C_{19}H_{32}NO_4Si$: (M+H)$^+$ 366.2101; found: 366.2110.

Synthesis of 29 from 30: To a solution of compound **30** (104 mg, 0.28 mmol) in $CHCl_3$ (2 mL), was added DBU (3 drops) and the mixture was stirred at rt for 2 d. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (4:1, EtOAc/petroleum spirit) to give compound **29** (61 mg, 60% yield).

(1S*,3a*R,11*R**,11a*R**,11b*R**)-11-(*tert*-Butyldimethylsilyloxy)-1-methyldecahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepine-2,8-dione (31):** Magnesium turnings (39 mg, 1.64 mmol) were added to a solution of the α,β-unsaturated lactone **29** (40 mg, 0.11 mmol) in MeOH (1.2 mL) at 0 ^{0}C. The mixture was warmed to rt and stirred for 1 d. After cooling to 0 ^{0}C, acetic acid (12 µL, 0.22 mmol) was added and the resulting mixture was stirred at rt for 30 min. Water (5 mL) was added and the mixture was extracted with EtOAc (3 x 15 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (7:3, EtOAc/petroleum spirit) to provide compound **31** (29 mg, 71% yield) as a white solid. Recrystalization for X-ray structural analysis was performed using a solvent mixture of CH_2Cl_2 and *n*-hexane at rt. Mp = 160-162 ºC *Rf* = 0.65 (9:1, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 3233, 2957, 2318, 1765, 1632, 1448, 1390, 1253, 1185, 1101, 1065, 1014, 774. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.79 (td, *J* = 11.5, 2.5 Hz, IH, H3a), 4.48 (d, *J* = 13.5 Hz, IH, H6), 4.25 (s, 1H, H11), 3.73 (d, *J* = 7 Hz, 1H, H11a), 2.86 (dq, *J* = 14.0, 7.0 Hz, 1H, H1), 2.71-2.60 (m, 2H, H6 and H9), 2.43-2.31 (m , 3H, H9, H4 and H11b), 2.09-2.03 (m, 1H, H10), 1.92-1.84 (m, 2H, H10 and H5), 1.68-1.58 (m, 1H, H5), 1.43-1.33 (m, 1H, H4), 1.30 (d, *J* = 7.0 Hz, 3H, H1'), 0.88 (s, 9H, $(CH_3)_3C$), 0.16 (s, 3H, CH_3Si), 0.12 (s, 3H, CH_3Si) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 177.9 (C2), 169.9 (C8), 79.7 (C3a), 66.0 (C11), 59.3 (C11a), 53.4 (C11b), 43.1 (C6), 37.9 (C1), 28.0 (C9), 26.8 (C10), 26.2 ($(CH_3)_3C$), 25.1 (C5), 18.3 ($(CH_3)_3C$), 15.2 (C1'), -2.9 (CH_3Si), -4.7 (CH_3Si) ppm. ESIMS *m/z* 368 [(M+H)$^+$ 100%]. HRESIMS calcd. for $C_{19}H_{34}O_4NSi$: (M+H)$^+$ 368.2257; found: 368.2256.

(1S*,3a*R,11*R**,11a*R**,11b**R**)-11-Hydroxy-1-methyldecahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepine-2,8-dione (3):** To a solution of the TBS ether **31** (30 mg, 0.082 mmol) and acetic acid (12 µL, 0.206 mmol, 3 equiv) at 0 ºC was added a solution of 1M TBAF in THF (206 µL, 0.206 mmol, 3 equiv). The mixture then was warmed to rt and stirred for 14 h. The reaction was quenched with saturated $NaHCO_3$ solution (5 mL) and extracted with EtOAc (3 x 15 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (4:1, EtOAc/petroleum spirit) to give the alcohol **3** (16 mg, 80% yield) as a pale yellow solid. Mp = 254-256 ºC. *Rf* = 0.68 (9:1, EtOAc/MeOH). IR (neat, ν_{max}/cm^{-1}): 3340, 2957, 2856, 1765, 1624, 1183, 1104, 1067, 1012, 870, 794. ^{1}H NMR (500 MHz, CD_3OD) δ = 4.86 – 4.78 (m, 1H, H3a), 4.28 (d, *J* =13.5 Hz, 1H, H6β), 4.22 (s, 1H, H11), 3.85 (dd, *J* =7.5, 2.0 Hz 1H, H11a), 3.18 (dq, *J* = 14.0, 7.0 Hz, 1H, H1), 2.84 (t, *J* = 13.5 Hz, 1H, H6α), 2.71 – 2.61 (m, 1H, H9), 2.61-2.54 (m, 1H, H10), 2.30 (m, 1H, H9), 2.25-2.19 (m, 1H, H4), 2.01 – 1.88 (m, 1H, H10), 1.85-1.79 (m, 1H, H5), 1.59 (m, 1H, H5), 1.46 (m, 1H, H4), 1.27 (d, *J* = 7.0 Hz, 3H, H1') ppm. ^{13}C NMR (125 MHz, CD_3OD) δ = 181.1 (C2), 172.9 (C8), 81.9 (C3a), 64.6 (C11), 59.5 (C11a), 53.90 (C11b), 44.2 (C6), 39.1 (C1), 36.0 (C4), 28.3 (C10), 27.7 (C9), 25.7 (C5), 15.0 (C1') ppm. ESIMS *m/z* 354 [(M+H)$^+$ 100%]. HRESIMS calcd. for $C_{13}H_{20}O_4N$: (M+H)$^+$ 254.1392; found: 254.1396.

Attempted synthesis of 2: To a solution of **3** (15.7 mg) in CH_2Cl_2 (3 mL) were added BIAB (24 mg, 0.07 mmol) and I_2 (16.6 mg, 0.065 mmol). The mixture the was irradiated with a UV lamp at rt, 500 W for 30 min. The reaction was quenched with 1M $Na_2S_2O_3$ (3 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (2:3, EtOAc/petroleum spirit) to give the major product **32** (3.4 mg, 16% yield) as a pale yellow oil and as a mixture of diastereomers (dr = 2.3:1). *Rf* = 0.69 (4:1, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 2924, 1764, 1640, 1501, 1448, 1397, 1244, 973. ^{1}H NMR (500 MHz, $CDCl_3$) *major isomer* δ = 9.79 (s, 1H, CHO), 7.06 (d, *J* = 9.0 Hz, 1H, H4), 4.24-4.13 (m, 2H, H8a and H6), 3.02-2.80 (m, 3H, H2', H6 and H3'), 2.80-2.62 (m, 3H, H3, H2' and H3'), 2.42-2.37 (m, 1H, H3a and H8), 2.11 (s, 3H, CH_3CO), 180-1.75 (m, 1H, H7), 1.68-1.56 (m, 2H, H8 and H7), 1.25 (d, *J* = 7.0 Hz, 3H, H3"). ^{13}C NMR (125 MHz, $CDCl_3$) *major isomer* δ = 200.9 (C4'), 177.0 (C2), 171.5 (C1), 170.0 (CH_3CO), 82.6 (C4), 78.1 (C8a), 55.2 (C3a), 41.0 (C6), 39.1 (C2'), 34.4 (C8), 25.4 (C3'), 23.5 (C7), 21.0 (CH_3CO), 14.7 (C3") ppm. ^{1}H NMR (500 MHz, $CDCl_3$) *minor isomer* (in part) δ = 9.81 (s, 1H, CHO), 6.66 (d, *J* = 8.0 Hz, 1H, H4), 4.13-4.07 (m, 2H, H8a and H6), 2.34-2.27 (m, 1H, H3a), 2.03 (s, 3H, CH_3CO), 1.21 (d, *J* = 7.0 Hz, 3H, H3") ppm. ^{13}C NMR (125 MHz, $CDCl_3$) *minor isomer* δ = 200.6 (C4'), 177.4 (C2), 171.8 (C1), 169.0 (CH_3CO), 78.2 (C4), 77.3 (C8a), 54.0 (C3a), 41.0 (C6), 38.5 (C2'), 34.0 (C8), 25.9 (C3'), 23.5 (C7), 20.8 (CH_3CO), 15.0 (C3") ppm. ESIMS *m/z* 366 [(M+Na)$^+$ 100%]. HRESIMS calcd. for $C_{15}H_{21}O_8NNa$: (M+Na)$^+$ 366.1158; found: 366.1165.

(1S*,3a*R,11*R**,11a*R**,11b**R**)-11-(*tert*-Butyldimethylsilyloxy)-1-methyl-8-thioxodecahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepin-2(8*H*)-one (33):** Lawessons' reagent (21.2 mg, 0.053 mmol) was added to a solution of the lactam **31** (35 mg, 0.095 mmol) in THF (12 mL) and the reaction mixture was heated at reflux temperature for 3 h. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (3:1, EtOAc/petroleum spirit) to give the thiolactam **33** (29 mg, 80% yield) as a white solid. Mp = 154-156 ºC. *Rf* = 0.61 (4:1, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 2952, 1736, 1493, 1254, 1177, 1154, 1066, 1010, 980, 794. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.31 (dd, *J* = 13.5, 4.0 Hz, 1H, H6β), 4.69 (dt, *J* = 11.5, 3.5 Hz, 1H, H3a), 4.34 (s, 1H, H11), 3.76 (dd, *J* = 7.5, 2.0 Hz 1H, H11a), 3.19-3.09 (m, 3H, H6 and H9), 2.88 (dq, *J* = 14.0, 7.0 Hz, 1H, H1), 2.60 – 2.52 (m, 1H, H11b), 2.40-2.33 (m, 1H, H4), 2.10 – 1.83 (m, 4H, H5 and H10), 1.47 (qd, *J* =

13.0, 5.5 Hz, 1H, H4), 1.31 (d, *J* = 7.0 Hz, 3H, H1'), 0.87 (s, 9H, $(CH_3)_3C$), 0.15 (s, 3H, CH_3Si), 0.11 (s, 3H, CH_3Si) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 201.1 (C8), 177.4 (C2), 79.3 (C3a), 66.1 (C11), 62.2 (C11a), 52.9 (C11b), 51.2 (C6), 38.0 (C1), 37.0 (C9), 35.4 (C4), 28.0 (C3), 26.2 ($(CH_3)_3C$), 23.1 (C5), 18.3 ($(CH_3)_3C$), 15.3 (C1'), -2.9 (CH_3Si), -4.8 (CH_3Si) ppm. ESIMS *m/z* 384 $[(M+H)^+$ 100%]. HRESIMS calcd. for $C_{19}H_{34}O_3NSiS$: $(M+H)^+$ 384.2036; found: 384.2029.

(1*S,3a*R**,11*R**,11a*R**,11b*R**)-11-(*tert*-Butyldimethylsilyloxy)-1-methyldecahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepin-2(8*H*)-one (34):** An excess amount of Raney Ni (*ca* 20 mg) was added to a solution of the thiolactam **33** (26.5 mg, 0.07 mmol) in EtOH (4 mL) and the mixture was heated at reflux temperature for 4 h. The mixture was filtered through a small pad of celite and the filtered cake was washed with EtOH (60 mL). The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (4:1, EtOAc/petroleum spirit) to give the amine **34** (19 mg, 75% yield) as a pale yellow solid. Mp = 117-119 ºC. *Rf* = 0.58 (4:1, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 2946, 2927, 1762, 1465, 1325, 1209, 1165, 1025. ^1H NMR (500 MHz, $CDCl_3$) δ = 5.01 (dt, *J* = 10.5, 3.0, 1H, H3a), 3.94 (s, 1H, H11), 2.88 (d, *J* = 11.1 Hz, 1H, H8), 2.78 (dq, *J* = 14.0, 7.0 Hz, 1H, H1), 2.62 (dd, *J* = 19.0, 8.0 Hz, 1H, H6), 2.48-2.40 (m, 2H, H6 and H8), 2.36 (d, *J* = 7.5 Hz, 1H, H11a), 2.28 (dd, *J* = 10.0, 5.0 Hz, 1H, H4), 2.19 (apparent dt, *J* = 12.0, 9.0 Hz, 1H, H11b), 2.00 – 1.91 (m, 1H, H3), 1.91 – 1.83 (m, 1H, H3), 1.69 (dt, *J* = 16.0, 8.0 Hz, 2H, H5), 1.41 – 1.33 (m, 2H, H9), 1.31 – 1.21 (m, 1H, H4), 1.30 (d, *J* = 7.0 Hz, 3H, H1'), 0.89 (s, 9H, $(CH_3)_3C$), -0.11 (s, 6H $(CH_3)_2Si$,) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 179.3 (C2), 80.5 (C3a), 67.7 (C11), 63.7 (C11a), 58.8 (C8), 55.0 (C6), 53.8 (C11b), 37.6 (C1), 36.1 (C4), 32.7 (C10), 27.7 (C5), 26.3 ($(CH_3)_3C$), 21.5 (C9), 18.5 ($(CH_3)_3C$) 15.2 (C1'), -3.0 (CH_3Si), -4.6 (CH_3Si) ppm. ESIMS *m/z* 354 $[(M+H)^+$ 100%]. HRESIMS calcd. for $C_{19}H_{36}O_3NSi$: $(M+H)^+$ 354.24564; found: 354.2452.

(1*S,3a*R**,11*R**,11a*R**,11b*R**)-11-Hydroxy-1-methyldecahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepin-2(8*H*)-one (35):** To a solution of the TBS ether **34** (23 mg, 0.065 mmol) and acetic acid (11 µL, 0.195 mmol) at 0 ºC was added a 1M solution of TBAF in THF (195 µl, 0.195 mmol). The mixture then was warmed to rt and stirred for 14 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with EtOAc (3 x 15 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (4:1, EtOAc/petroleum spirit) to give the alcohol **35** (17 mg, 78% yield) as a pale yellow solid. NMR analysis indicated some impurities wee present. .Mp = 210-212 ºC. *Rf* = 0.61 (9:1, EtOAc/petroleum spirit). IR (neat, ν_{max}/cm^{-1}): 3431, 2928, 1762, 1453, 1261, 1182, 1165, 1125, 1102, 1075, 1025, 769, 682. ^1H NMR (500 MHz, $CDCl_3$) δ = 4.77 (dt, *J* = 11.0, 3.5 Hz, 1H, H3a), 3.86 (s, 1H, H11), 2.96-2.84 (m, 2H, H1 and H8), 2.75 – 2.68 (m, 1H, H6), 2.56 – 2.46 (m, 2H, H6 and H8), 2.46 – 2.42 (m, 1H, H11a), 2.31 (d, *J* = 10.0 Hz, 1H, H4), 2.20 (apparent ddd, *J* = 12.5, 11.0, 8.0 Hz, 1H, H11b), 1.89 – 1.76 (m, 3H, H10, H9 and H5), 1.70 – 1.58 (m, 1H, H5), 1.54 – 1.48 (m, 1H, H9), 1.43 – 1.32 (m, 1H, H10), 1.32 – 1.23 (m, 1H, H4), 1.22 (d, *J* = 7.0 Hz, 3H, H1') ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 178.7 (C2), 80.6 (C3a), 65.7 (C11), 64.1 (C11a), 59.3 (C8), 55.3 (C6), 53.4 (C11b), 37.7 (C1), 35.7 (C4), 32.0 (C10), 27.8 (C5), 21.2 (C9), 14.4 (C1') ppm. ESIMS *m/z* 240 $[(M+H)^+$ 100%]. HRESIMS calcd. for $C_{13}H_{22}O_3N$: $(M+H)^+$ 240.1600; found: 240.1601.

Attempted photochemical cyclization reaction of 35: To a solution of **35** (14.4 mg, 0.06 mmol) in CH_2Cl_2 (2 mL) were added BIAB (24 mg, 0.07 mmol) and I_2 (16.6 mg, 0.065 mmol). The mixture the was irradiated with a UV lamp at rt, 500 W for 15 min. The reaction was quenched with 1M $Na_2S_2O_3$ (3 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo*. ^1H NMR and TLC analysis analysis of the crude reaction mixture showed a complex mixture of products.

CCDC 1419726 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra of all new compounds.

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Keywords: Stemona alkaloid •synthesis • piperidinone • alkynyl epoxide • azepine

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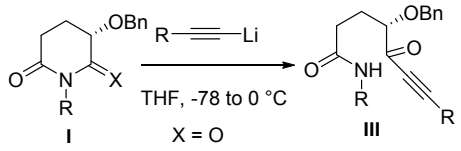

I **III**

I X = O
II X = H, OH

An alternative method employing hemiaminal **II** and potassium alkynyl trifluroborate salts was not pursued because of the reported low yields of the desired *cis*-products, see: (b) J. C. Jury, K. S. Nalivera, A. Yazici, A. C. Willis, S. G. Pyne, *J. Org. Chem*. **2009**, *74*, 5523- 5527.

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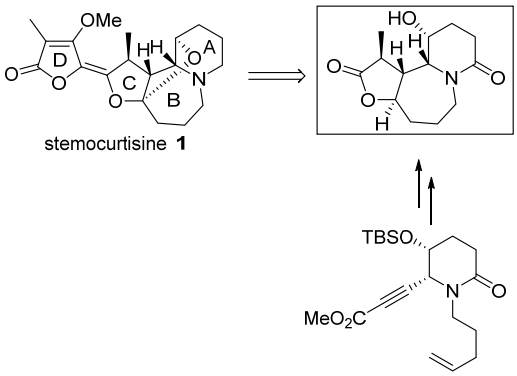
Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

Text for Table of Contents

The diastereoselective synthesis of the A-B-C tricylic ring structure of the *Stemona* alkaloid stemocurtisine has been developed.



Key Topic* Natural Product Synthesis

Xuan Duc Dau, Anthony C. Willis, Stephen G. Pyne*

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Title Diasteroselective Synthesis of the A-B-C Tricyclic Ring Structure of Stemocurtisine

*Natural Product Synthesis

Layout 2:

FULL PAPER

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*one or two words that highlight the emphasis of the paper or the field of the study