1-1-2012

Model studies towards the total synthesis of the Stemona alkaloid 1-hydroxyprotostemonine: synthesis of ent-1-hydroxystemoamide

Nalivela Kumara Swamy
University of Wollongong

Stephen G. Pyne
University of Wollongong, spyne@uow.edu.au

Model studies towards the total synthesis of the Stemona alkaloid 1-hydroxyprotostemonine: synthesis of ent-1-hydroxystemoamide

Abstract

As part of a model study towards the total synthesis of Stemona alkaloid 1-hydroxyprotostemonine 1, we have achieved the synthesis an A-B-C ring precursor, ent-1-hydroxystemoamide. Key steps involve an ene-yne RCM reaction and a diastereoselective dihydroxylation-lactonization reaction.

Keywords

model, towards, total, synthesis, stemona, alkaloid, 1, hydroxyprotostemonine, ent, hydroxystemoamide, studies, CMMB

Disciplines

Medicine and Health Sciences | Social and Behavioral Sciences

Publication Details

Swamy, N. Kumara. & Pyne, S. G. (2012). Model studies towards the total synthesis of the Stemona alkaloid 1-hydroxyprotostemonine: synthesis of ent-1-hydroxystemoamide. Heterocycles, 84 (1), 473-492.

MODEL STUDIES TOWARDS THE TOTAL SYNTHESIS OF THE *STEMONA* ALKALOID 1-HYDROXYPROTOSTEMONINE: SYNTHESIS OF *ENT*-1 HYDROXYSTEMOAMIDE

Nalivela Kumara Swamy and Stephen G. Pyne*

School of Chemistry, University of Wollongong, New South Wales, 2522, Australia
e-mail: spyne@uow.edu.au

Abstract – As part of a model study towards the total synthesis of *Stemona* alkaloid 1-hydroxyprotostemonine **1**, we have achieved the synthesis an A-B-C ring precursor, *ent*-1-hydroxystemoamide. Key steps involve an ene-yne RCM reaction and a diastereoselective dihydroxylation-lactonization reaction.

This paper is dedicated to Prof. Al Padwa on the occasion of his 75th birthday in recognition of his many valuable contributions to heterocyclic chemistry.

The *Stemona* family of alkaloids includes more than 139 different natural products,[1-3] which have been structurally classified by Pilli into eight different groups.[1,3] The pyrrolo[1,2-*a*]azepine nucleus is common to six of these, while a pyrido[1,2-*a*]azepine ring system is found in the more recently discovered Stemocurtisine group of *Stemona* alkaloids.[1-6] Greger, on the other hand, has classified the *Stemona* alkaloids into three groups on the basis of biosynthetic considerations.[2] In 2010 the first two *Stemona* alkaloids with a pyrido[1,2-*a*]azonine skeleton were reported.[7] The *Stemona* alkaloid oxyprotostemonine **1**[4,5] was isolated in 2004 and more recently we reported the isolation of the structurally related alkaloid, 1-hydroxyprotostemonine **2**[8] which can be considered as a dihydro-derivative of **1** or a hydroxylated-derivative of protostemonine (Figure 1).

In this paper we report on a study into the synthesis of alkaloids **1** and **2** based on the retrosynthetic analysis shown in Scheme 1. This analysis suggested that the tricyclic compound **3** would be a suitable

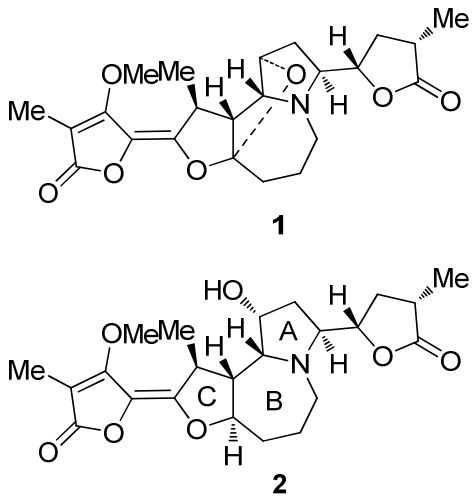
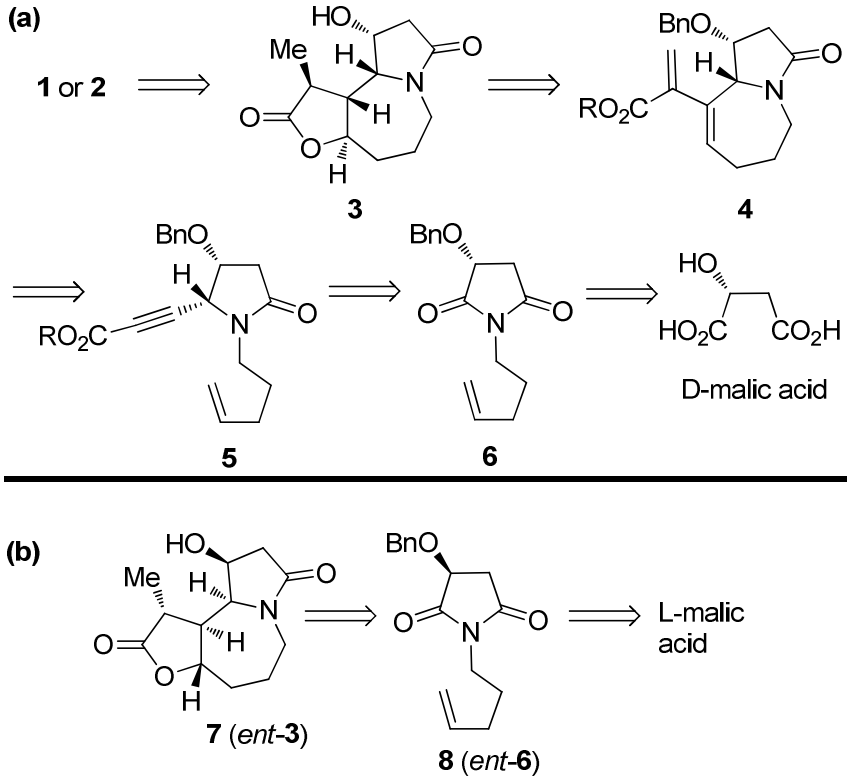


Figure 1. Structures of oxyprotostemonine **1** and 1-hydroxyprotostemonine **2**

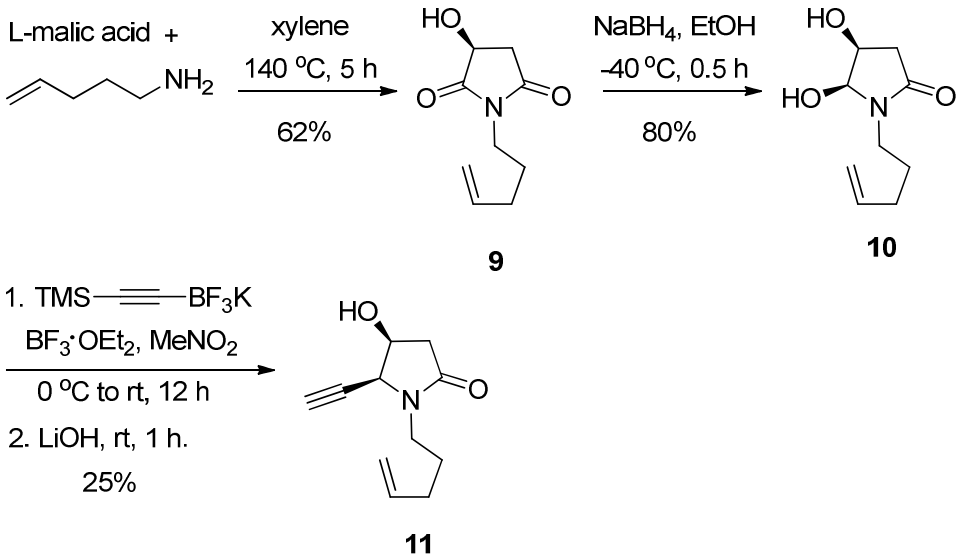
advanced intermediate to achieve the synthesis of the target molecules. This compound is the 1*R*-hydroxy analogue of stemoamide for which several successful syntheses have been reported for this natural product.[9] A formal synthesis of its enantiomer[10] and syntheses of the racemate have also been reported.[11] Our retrosynthetic analysis suggested that D-malic acid would be a suitable starting material. A ring-closing metathesis (RCM) reaction of the ene-yne **5** was expected to give the pyrrolo[1,2-a]azepine **5** based on Mori's earlier synthesis of stemoamide via de-benzyloxy **5**.[9g,h] However since L-malic acid is significantly less expensive than its D-form we performed our model studies on the enantiomeric series to that shown in Scheme 1(a). Here we report on the synthesis of the tricyclic compound **7** (Scheme 1(b)), the enantiomer of 1*R*-hydroxylstemoamide **3**, from L-malic acid.

Our initial studies to prepare a 4,5-*cis*-hydroxyl-alkynyl pyrrolidinone like **5** (in the enantiomeric series) involved a study of the synthesis of the 4,5-*cis*-hydroxyl-ethynylpyrrolidinone **11** (Scheme 2). A mixture of L-malic acid and 4-pentenylamine[12] in xylene were heated at 140 ^{o}C for 5 h to give the desired *N*-4-pentenylsuccinimide **9** in 62% yield. Regioselective reduction of **9** with $NaBH_4$ at -40 ^{o}C[13] gave the hemi-aminal **10** as the 4,5-*cis*-stereoisomer as evident from the relatively large geminal coupling constant $J_{4,5}$ of 6.5 Hz.[13] Treatment of the diol **10** with trimethylsilylethynyltrifluoroborate (3.0 equiv)/$BF_3{\cdot}OEt_2$ (4.0 equiv) gave the desired *cis*-alkyne **11**. Unfortunately the best yield we could obtain was 25% when the reaction was performed at 0 ^{o}C – rt with $MeNO_2$ as the solvent. When we used CH_2Cl_2 as the solvent no reaction was observed. The 4,5-*cis* stereochemistry was evident from the magnitude of $J_{4,5}$ which was 6.5 Hz.

An alternative route was then sort. The known *N*-PMB succinimide **12**, prepared in two steps from L-malic acid,[14] was treated with CAN in acetonitrile/water (3:1) to provide the *N*-deprotected succinimide **13** in 82% yield (Scheme 3) which was further transformed to the *N*-4-pentenylsuccinimide **8** (84% yield)



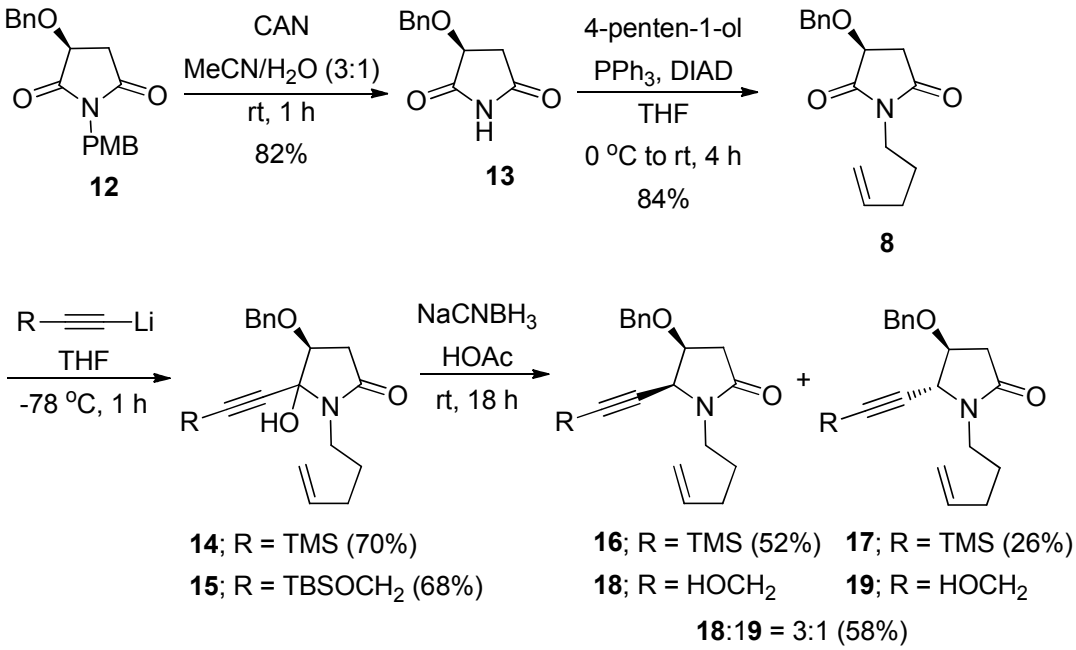
Scheme 1. Retrosynthetic analysis



Scheme 2. Synthesis of the 4,5-*cis*-hydroxyl-ethynylpyrrolidinone **11**

by treatment with 4-penten-1-ol under Mitsunobu's reaction conditions[15] (Scheme 3). Treatment of **8** with lithium 2-trimethylsilylacetylide gave a diastereomeric mixture (dr = 67:33) of carbinol adducts **14** which

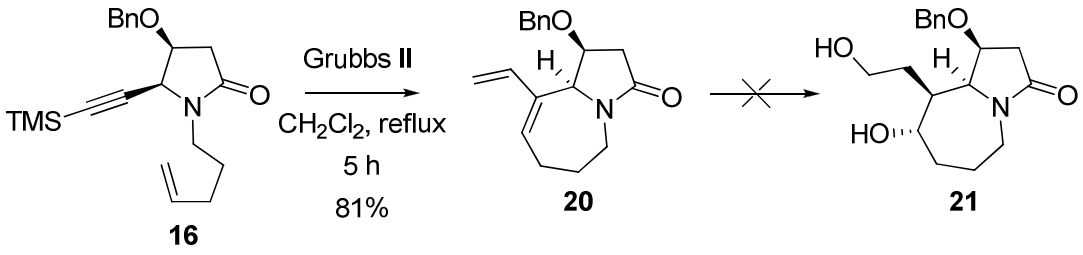
upon reduction with $NaBH_3CN$ (5.0 eq) in AcOH afforded a separable mixture of the *cis* and *trans* products **16** (52% yield) and **17** (26% yield), respectively (Scheme 3). The major isomer **16** showed $J_{4,5}$ = 6.0 Hz, indicative of 4,5-*cis* stereochemistry[13] while the minor *trans* isomer had $J_{4,5}$ = 0.0 Hz. Under similar reaction conditions the reaction of **8** and lithium 3-*tert*-butyldimethylsilyloxypropynilide followed by treatment of **15** (dr = 70:30) with $NaBH_3CN$ (5.0 eq) in AcOH afforded a 3:1 inseparable mixture of the *cis* and *trans* TBS deprotected products **19** and **20**, respectively, in 58% yield. The stereochemistry of the major isomer was confirmed from the magnitude of its coupling constant between H4 and H5 in its ^1H NMR spectrum. The major isomer **10** showed $J_{4,5}$ = 6.5 Hz, indicative of 4,5-*cis* stereochemistry.[13] However obtaining the coupling constant $J_{4,5}$ for the minor isomer proved difficult because of overlapping signals.



Scheme 3. Synthesis of alkynes **16 – 19**

Compound **16** underwent a smooth ene-yne RCM reaction with Grubbs' II catalyst to give the desired pyrrolo[1,2-*a*]azepine **20** in 81% yield (Scheme 4). We had planned to convert **20** to the diol **21** which upon oxidation was expected to produce the desired lactone C ring. However, attempts to convert **20** to the diol **21** by chemoselective hydroboration reactions using BH_3•DMS were not successful due to competing reduction of the lactam carbonyl. Somfi reported similar difficulties during his studies on the synthesis of stemoamide.[9b]

In contrast to ene-yne **16**, the mixture of ene-ynes **18/19** was unreactive to either Grubbs' I or II catalyst (Scheme 5). This mixture was then oxidized with Jones reagent[16] and the crude acid was not purified but



Scheme 4. Attempted synthesis of diol **21**

was esterified[17] using DCC (1.0 eq), DMAP (0.1 eq) and EtOH (1.3 eq) in CH_2Cl_2. This gave a mixture (3:1) of separable *cis* and *trans* products from which the major *cis* isomer **22** ($J_{4,5}$ = 6.5 Hz) could be isolated in 47% overall yield. When **22** was treated with Grubbs' I catalyst in CH_2Cl_2 at rt for 5 h then the desired pyrrolo[1,2-*a*]azepine **23** was isolated in 82% yield (Scheme 5). Compound **23** was converted to the tricyclic compound **25** using the procedures employed by Mori in the synthesis of stemoamide.[9g,h] Reduction of the terminal alkene of **22** went as expected and gave **24** was an inseparable 4:1 mixture of diastereomers. The ester group was then hydrolysed to the corresponding acid which was treated with $CuBr_2$ on alumina at 65 ^oC according to Mori's bromo-lactonization procedure.[9g,h] The resulting mixture was then treated with Et_3N to effect complete elimination of HBr from the bromo-lactone intermediate. Unfortunately, this resulted in a 1:1 diastereomeric mixture of the tricyclic molecule **25** and **26** which could be separated by column chromatography in low overall yields (Scheme 5). In the de-benzyloxy series of Mori this reaction was highly diastereoselective in favour of the desired stereoisomer.[9g,h] Clearly the extra *O*-benzyl group in our substrate **24** is responsible for the poor diasteoselectivity of this reaction sequence. Evidence for the configuration of **25** was obtained from NOESY NMR experiments which showed a significant correlation between H3a and H10a. In compound **26** however, no NOESY correlation between H3a and H10a was observed. Correlations were also observed between H10 and H10a in both compounds (Figure 2).

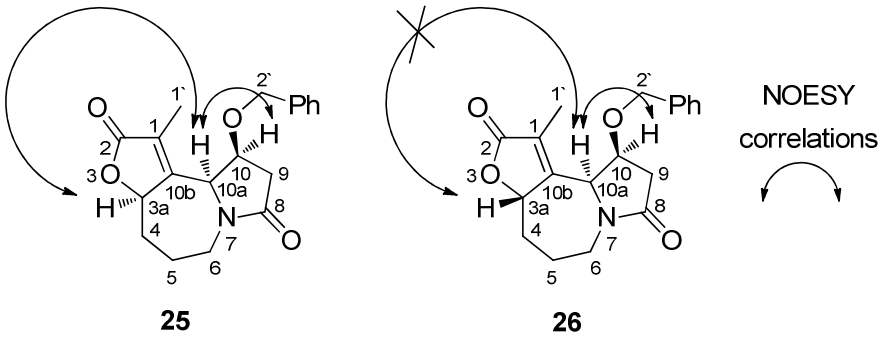
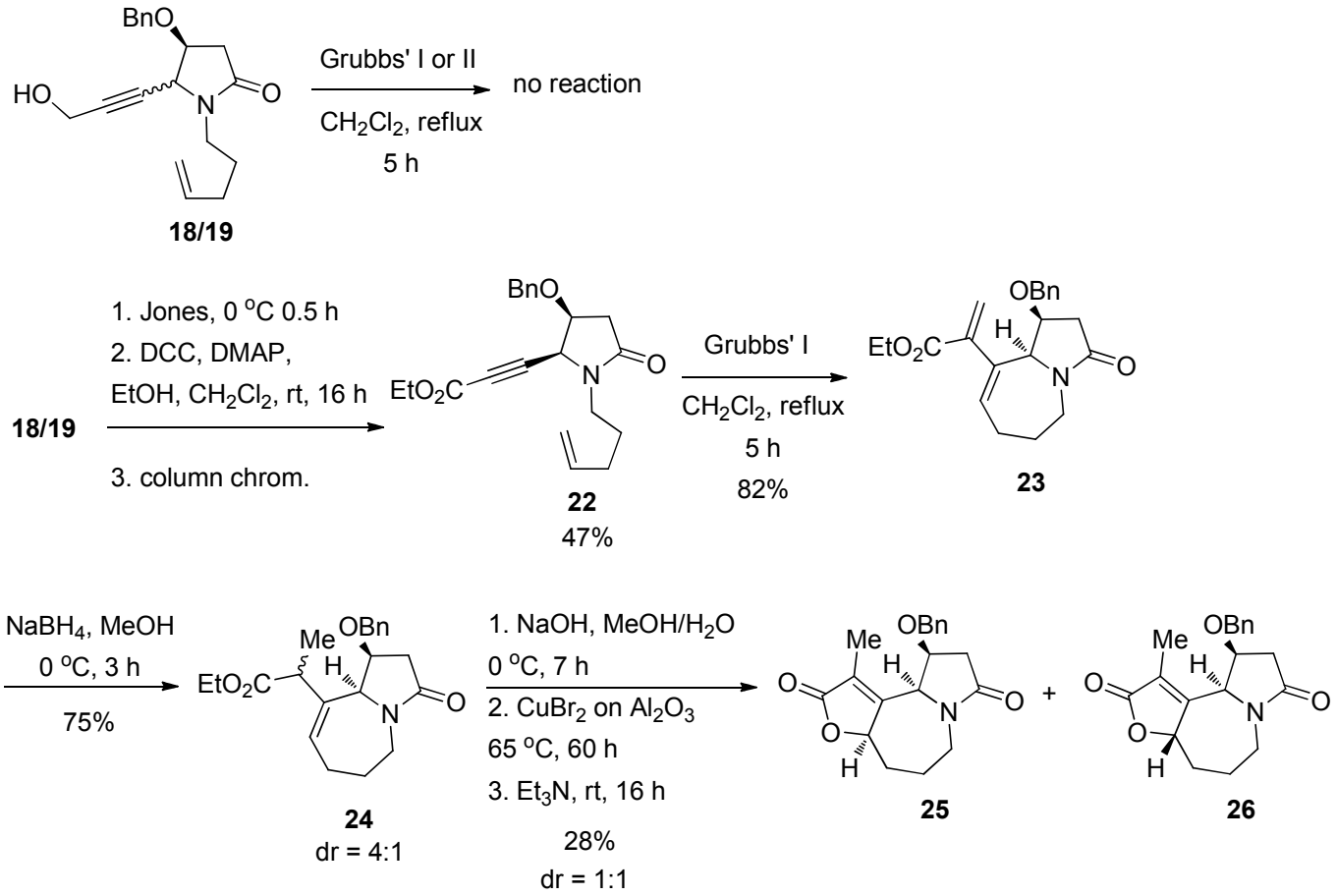
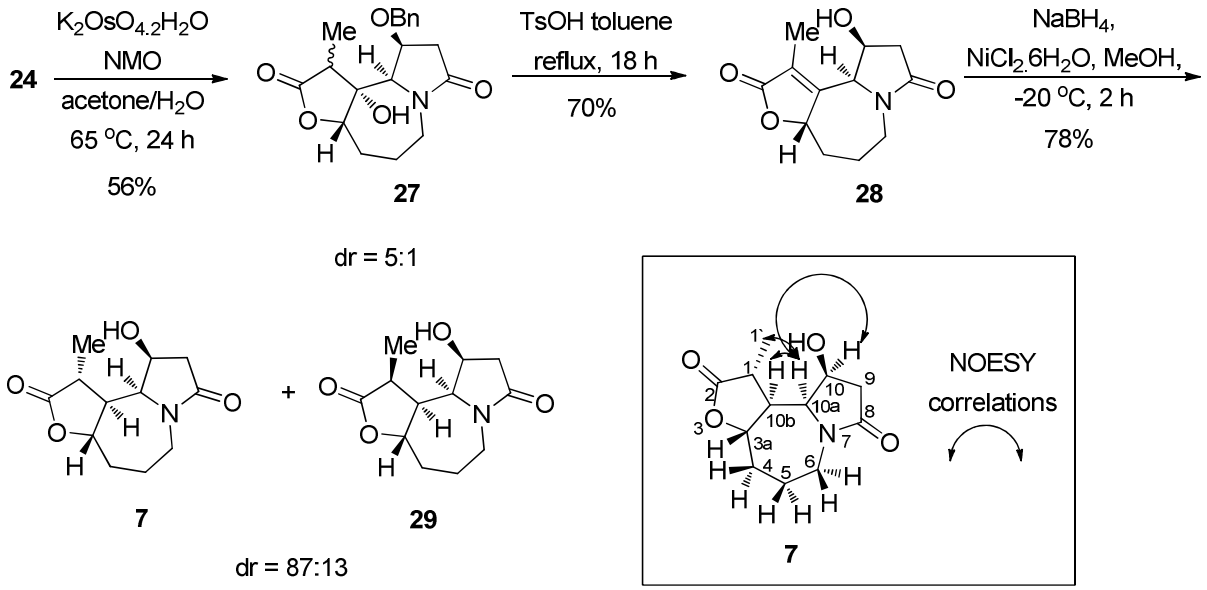


Figure 2. Significant NOESY correlations for compounds **25** and **26**

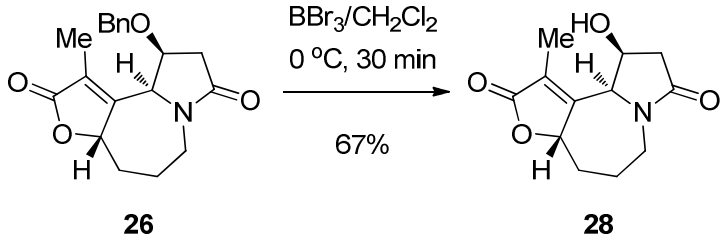


Scheme 5. Synthesis of the tricyclic compounds **25** and **26**

Osmium catalysed *syn*-dihydroxylation of **24** resulted in formation of the lactone **27** (dr 5:1) in a highly diastereoselective process since dehydration of **27** under acid conditions gave the unsaturated lactone **28** as a single diastereomer in 70% yield (Scheme 6). No other diastereomer of **27** could be detected by NMR analysis of the crude reaction mixture or could be isolated. The conversion of **27** to **28** also involved cleavage of the *O*-benzyl protecting group. Finally, reduction of **28** with $NaBH_4/NiCl_2$[9g,h] gave in 78% yield an inseparable mixture (dr = 87:13) of **7** and its diastereomer **29** (Scheme 6). The stereochemical assignment of **7** was based on the NOESY correlations observed between H-10 and H-10a, H-10a and H-10b and H-10a and the C-1 Me group and the lack of correlations between H-3a and H-10b (Scheme 6 (inset)). Further supportive evidence for the stereochemical relationship between H-1 and H-10b in **7** was the magnitude of $J_{1,10b}$ (12.3 Hz) which was almost identical to that found in stemoamide (12.4 Hz).[18] The stereochemical relationship between **26** and **28** came from the *O*-debenzylation reaction of **26** with BBr_3 which gave, in 67% yield, a product identical to compound **28** that was prepared according to Scheme 6 (Scheme 7). The stereochemistry assigned to **29** is not certain because a diastereomerically pure sample could not be obtained. Its stereochemistry at C-10b is based on literature precedent for the reduction of related molecules.[9g,h]



Scheme 6. Synthesis of **7** and its significant NOESY correlations (inset)



Scheme 7. Stereochemical correlations between compounds **26** and **28**

In conclusion, as part of a model study towards the total synthesis of the *Stemona* alkaloid 1-hydroxyprotostemonine **1**, we have achieved the synthesis an A-B-C ring precursor, *ent*-1-hydroxystemoamide **7** starting with L-malic acid. The bromolactonization method employed by Mori in the synthesis of stemoamide was not diasteoselective in the corresponding *O*-benzyl analogues prepared in this study. An alternative route was developed using a highly diastereoselective *syn*-dihydroxylation reaction to prepare the lactone C-ring of **7**. In principle this method could be used to prepare compound **3** from D-malic acid which could then be converted to 1-hydroxyprotostemonine **1** by the addition of the two butyrolactone rings.[19-21]

EXPERIMENTAL

General methods

All reactions were performed in oven dried glassware under an atmosphere of nitrogen, unless otherwise stated. Anhydrous CH_2Cl_2 and MeOH were obtained from Sigma-Aldrich Chemical Co. Anhydrous THF

was obtained by distillation from sodium wire/benzophenone. "Evaporation" refers to the removal of solvent under reduced pressure using a rotory evaporator and then the removal of the last traces of solvent under high vacuum. Commercial substances were used without further purification. Petrol refers to the hydrocarbon fraction of bp 45-55 ^{o}C. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova NMR Spectrometer (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz) or Varian Unity-300 (1H NMR at 300 (1H NMR at 300 MHz, ^{13}C NMR at 75 MHz) instruments. $CDCl_3$ (internal reference at 7.26 for ^{1}H NMR and δ 77.00 for ^{13}C NMR) was used as the NMR unless otherwise stated. The following abbreviations were used; s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublet, br = broad. NMR assignments were based on COSY, HSQC, HMBC, NOESY and DEPT experiments. TLC analyses were performed using aluminium backed Merk silica gel TLC plates. Flash column chromatography was performed using Merk silica gel (40 – 63 μm) packed by the slurry method. Melting points were obtained using a Gallenkamp MF-370 capillary tube melting point apparatus and are uncorrected. Optical rotations were measured using a 1 cm cell, in a Jasco DIP-370 digital polarimeter. Specific rotations were calculated by using the average value of 10 optical rotation measurements. Low-resolution mass spectra were obtained on a Shimadzu GC mass spectrometer (EI) or Waters LCZ single quadropole (ESI). High-resolution mass spectra (exact masses) were obtained on a VG Autospec mass spectrometer (EI) or Water QTOF (ESI). HRMS were obtained in lieu of elemental analysis and ^{1}H and ^{13}C NMR spectroscopy were used as the criteria for purity. Infrared spectra were obtained as neat samples on a Smart Omni-Sampler Avator ESP Nicolet-Brand.

(*S*)-3-Hydroxy-1-(pent-4-enyl)pyrrolidine-2,5-dione (9)

To a solution of L-malic acid (0.10 g, 0.74 mmol) in xylene (50 mL) in a round bottom flask equipped with a Dean-Stark trap and a condenser was added pent-4-en-1-amine[12] (0.095 g, 1.12 mmol) at rt. The resulting suspension was heated at 140 ^{o}C for 5 h, and then xylene was removed *in vacuo.* The crude product was purified by column chromatography (2:1, EtOAc/petrol) to give compound **9** (0.085 g, 62%) as a pale yellow oil. R_f = 0.52 (2:1, EtOAc/petrol). $[\alpha]_D^{27}$ -65.4 (*c* 3.62, $CHCl_3$). IR (neat, ν_{max}/cm^{-1}): 3449, 2939, 1694, 1404, 1182, 909. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82 – 5.70 (1H, m, H4`), 5.04 (1H, dd, *J* = 1.0, 17.0 Hz, H5`), 5.01 (1H, d, *J* = 10.0 Hz, H5`), 4.65 (1H, dd, *J* = 5.0, 8.5 Hz, H3), 4.24 (1H, bs, OH), 3.52 (2H, t, *J* = 7.5 Hz, H1`), 3.06 (1H, dd, *J* = 8.5, 18.0 Hz, H4), 2.67 (1H, dd, *J* = 5.0, 18.0 Hz, H4), 2.08 – 2.04 (2H, m, H3`), 1.71 – 1.65 (2H, m, H2`). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.7 (C5), 174.3 (C2), 136.9 (C4`), 115.4 (C5`), 66.7 (C3), 38.4 (C1`), 37.1 (C4), 30.8 (C3`), 26.5 (C2`). ESIMS *m/z* 184 [$(M+H)^+$ 100%]. HRESIMS calcd. for $C_9H_{14}NO_3$, $(M+H)^+$ 184.0937, found: 184.0933.

(4*S*,5*S*)-4,5-Dihydroxy-1-(pent-4-enyl)pyrrolidin-2-one (10)

The cyclic imide **9** (0.085 g, 0.46 mmol) was dissolved in EtOH (20 mL), and the solution was cooled to –40 ^{o}C. $NaBH_4$ (0.088 g, 2.36 mmol) was added portionwise and the resulting suspension was stirred at –40 ^{o}C for 30 min. Then the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (30 mL) and was extracted with EtOAc (3 x 70 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (0.5:10, MeOH/EtOAc) to give product **10** (0.068 g, 80%) as a colourless oil. R_f = 0.40 (0.5:10, MeOH/EtOAc). $[\alpha]_D^{23}$ + 29.3 (*c* 0.12, $CHCl_3$). IR (neat, ν_{max} /cm^{-1}): 3329, 2960, 1664, 1465, 1413, 1259, 1081, 1016, 799. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.83-5.76 (1H, m, H4), 5.09-4.97 (2H, m H5`), 4.35 (1H, dd, *J* = 6.5, 7.0 Hz, H4), 4.21 (1H, d, *J* = 7.0 Hz, H5), 3.50-3.42 (1H, m, H1`), 3.22-3.13 (1H, m, H1), 2.83 (1H, dd, *J* = 6.5, 17.5 Hz, H3), 2.09-2.04 (2H, m, H3), 1.73-1.60 (1H, m , H2`). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 173.7 (C2), 137.5 (C4`), 115.3 (C5`), 82.9 (C5), 71.8 (C4), 39.7 (C1`), 38.5 (C3), 31.0 (C3`), 26.7 (C2`). EIMS *m/z* 185 (M^+, 70%). HREIMS calcd. for $C_9H_{15}NO_3$ (M^+) 185.1044, found: 185.1038.

(4*S*,5*S*)-5-Ethynyl-4-hydroxy-1-(pent-4-enyl)pyrrolidin-2-one (11)

To a stirred solution of **10** (0.60 g, 3.00 mmol) and potassium trimethylsilylethynyltrifluoroborate (1.84 g, 9.00 mmol) in $MeNO_2$ (1.3 mL) at 0 ^{o}C under a N_2 atmosphere was added $BF_3{\cdot}Et_2O$ (1.55 mL, 12.0 mmol). The resulting mixture was stirred for 1 h before warming to rt and stirring for a further 12 h. The reaction mixture was then diluted with EtOAc (8 mL) and washed with saturated aqueous $NaHCO_3$ (8 mL). The separated organic phase was dried ($MgSO_4$) then concentrated under reduced pressure. The resulting residue was dissolved in THF (5 mL) then treated with LiOH (2 mL of a saturated aqueous solution) and the resulting mixture was stirred for 1 h before being diluted with EtOAc (8 mL). The separated organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude residue was purified by column chromatography (2:1, EtOAc/petrol) to afford the title compound **11** (0.15 g, 25%) as a pale yellow liquid. R_f = 0.53 (2:1, EtOAc/petrol). $[\alpha]_D^{26}$ -12.6 (*c* 1.5, $CHCl_3$). IR (neat, ν_{max}/cm^{-1}): 3287, 2930, 2361, 2332, 1676, 1425, 1261, 826. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.84 – 5.77 (1H, m, H4`), 5.05 (1H, d, *J* = 17.5 Hz, H5`), 4.98 (1H, d, *J* = 10.5 Hz, H5`), 4.48 (1H, dd, *J* = 2.0, 5.5 Hz, H5), 4.44 (1H, apparent q, *J* = 5.5 Hz, H4), 3.67 – 3.61 (1H, m, H1`), 3.19 – 3.13 (1H, m, H1`), 2.68 – 2.61 (2H, m, H3, H7`), 2.06 (2H, apparent q, *J* = 7.0 Hz, H3`), 1.74 – 1.61 (2H, m, H2`). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1 (C2), 137.4 (C4`), 115.1 (C5`), 77.7, 76.4 (C≡CH), 65.7 (C4), 56.1 (C5), 40.7 (C1`), 39.1 (C3), 30.9 (C3`), 26.3 (C2`). ESIMS *m/z* 194 [$(M+H)^+$ 100%]. HRESIMS calcd. for $C_{11}H_{16}NO_2$, $(M+H)^+$ 194.1122, found: 194.1127.

(*S*)-3-(Benzyloxy)pyrrolidine-2,5-dione (13)

To a solution of **12**[14] (6.20 g, 19.0 mmol) in CH_3CN/H_2O (3:1, 400 mL) at rt was added CAN (41.81 g, 76.00 mmol). The reaction mixture was stirred at rt for 1 h. The mixture was diluted with water and extracted with EtOAc (3 x 50 mL). The organic extracts were washed with saturated aqueous $NaHCO_3$ solution (30 mL), dried ($MgSO_4$) and the solvent was concentrated *in vacuo*. The crude product was purified by column chromatography (1:1, EtOAc/petrol) to afford compound **13** (3.24 g, 82%) as a colourless oil. R_f = 0.45 (2:1, EtOAc/petrol). $[\alpha]_D^{25}$ -98.5 (*c* 5.75, $CHCl_3$). IR (neat, ν_{max}/cm^{-1}): 3232, 3084, 2360, 1790, 1712, 1329, 1191, 1113, 741, 698. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.17 (1H, bs, NH), 7.36 – 7.30 (5H, m, ArH), 4.93 (1H, d, *J* = 11.5 Hz, H1`), 4.74 (1H, d, *J* = 11.5 Hz, H1`), 4.37 (1H, dd, *J* = 4.0, 8.0 Hz, H3), 2.94 (1H, dd, *J* = 8.0, 18.0 Hz, H4), 2.69 (1H, dd, *J* = 4.0, 18.0 Hz, H4). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.7 (C5), 174.8 (C2), 136.5 (ArC), 128.5 (ArCH), 128.2 (ArCH), 128.18 (ArCH), 72.9 (C1`), 72.8 (C3), 37.2 (C4). ESIMS *m/z* 206 [$(M+H)^+$ 100%]. HRESIMS calcd. for $C_{11}H_{12}NO_3$, $(M+H)^+$ 206.0779, found: 206.0777.

(*S*)-3-(Benzyloxy)-1-(pent-4-enyl)pyrrolidine-2,5-dione (8)

To a solution of **13** (0.10 g, 0.48 mmol) in THF (5 mL) were added 4-penten-1-ol (0.06 mL, 0.58 mmol), PPh_3 (0.153 g, 0.58 mmol), and DIAD (0.12 mL, 0.58 mmol) at 0 ^{o}C under a N_2 atmosphere. The mixture was stirred for 5 min and then warmed to rt and stirring was continued for 4 h. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (1:9, EtOAc/petrol) to afford compound **8** (0.112 g, 84%) as a colourless oil. R_f = 0.67 (2:8, EtOAc/petrol). $[\alpha]_D^{25}$ -61 (*c* 4.26, $CHCl_3$). IR (neat, ν_{max}/cm^{-1}): 2936, 2360, 1704, 1403, 1269, 1113, 741, 698. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 – 7.31 (5H, m, ArH), 5.82 – 5.74 (1H, m, H4`), 5.04 (1H, d, *J* = 17.5 Hz, H5`), 4.98 (1H, d, *J* = 11.5 Hz, H5`), 4.98 (1H, d, *J* = 11.5 Hz, H6`), 4.78 (1H, d, *J* = 11.5 Hz, H6`), 4.34 (1H, dd, *J* = 4.0, 8.0 Hz, H3), 3.51 (2H, t, *J* = 8.5 Hz, H1`), 2.92 (1H, dd, *J* = 8.0, 18.0 Hz, H4), 2.63 (1H, dd, *J* = 4.0, 18.0 Hz, H4), 2.05 (2H, apparent q, *J* = 7.0 Hz, H3`), 1.71 – 1.65 (2H, m, H2`). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.8 (C5), 174.1 (C2), 137.0 (ArC), 136.6 (C4`), 128.5 (ArCH), 128.2 (ArCH), 128.18 (ArCH), 128.1 (ArCH), 115.3 (C5`), 72.9 (C6`), 72.0 (C3), 38.2 (C1`), 36.1 (C4), 30.8 (C3`), 26.5 (C2`). ESIMS *m/z* 274 [$(M+H)^+$ 100%]. HRESIMS calcd. for $C_{16}H_{20}NO_3$, $(M+H)^+$ 274.1403, found: 274.1394.

(4*S*)-4-(Benzyloxy)-5-hydroxy-1-(pent-4-enyl)-5-((trimethylsilyl)ethynyl)pyrrolidin-2-one (14)

To a solution of trimethylsilylacetylene (3.58 g, 36.63 mmol) in dry THF (20 mL) at – 78 ^{o}C, was added dropwise *n*-BuLi (2.5 M in hexanes, 11.7 mL, 29.0 mmol). After stirring for 15 min a solution of **8** (4.00 g, 14.0 mmol) in dry THF (5 mL) was added dropwise over 15 min at – 78 ^{o}C. Then stirring was

continued for 1 h at – 78 ^{o}C under a N_2 atmosphere. Saturated aqueous NH_4Cl solution (15 mL) was added at – 78 ^{o}C and then the mixture was extracted with EtOAc (3 x 40 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (2.5:1 EtOAc/petrol)) to afford **14** as a 67:33 mixture of two diastereomeric products (3.80 g, 70%) as a pale yellow gum. R_f = 0.52 (2.5:1, EtOAc/petrol). IR (neat, ν_{max}/cm^{-1}): 3278, 2944, 2359, 2344, 1698, 1404, 1327, 1251, 845, 738, 698. ^{1}H NMR (500 MHz, $CDCl_3$): δ *major isomer* 7.37 – 7.26 (5H, m, ArH), 5.85 – 5.77 (1H, m, H4`), 5.04 (1H, dd, *J* = 1.0, 17.0 Hz, H5`), 4.96 (1H, d, *J* = 10.5 Hz, H5`), 4.90 (1H, d, *J* = 11.5, H6`), 4.66 (1H, d, *J* = 11.5, H6`), 4.04 – 4.00 (2H, m, H4, OH), 3.46 – 3.32 (2H, m, H1`), 2.74 (1H, dd, *J* = 6.5, 17.0 Hz, H3), 2.41 (1H, dd, *J* = 6.5, 17.0 Hz, H3), 2.10 (2H, apparent q, *J* = 7.0 Hz, H3`), 1.83 – 1.77 (2H, m, H2`), 0.18 (9H, s, (C*H*$_3$)$_3$Si); *minor isomer* 7.39 – 7.31 (5H, m, ArH), 5.85 – 5.77 (1H, m, H4`), 5.03 (1H, dd, *J* = 1.0, 17.0 Hz, H5`), 4.95 (1H, d, *J* = 10.5 Hz, H5`), 4.77 (1H, d, *J* = 11.5, H6`), 4.75 (1H, d, *J* = 11.5, H6`), 4.22 (1H, t, *J* = 5.5, 7.0 Hz, H4), 4.09 (1H, s, OH), 3.48 – 3.33 (2H, m, H-1`), 2.61 (1H, dd, *J* = 7.0, 17.0 Hz, H3), 2.44 (1H, dd, *J* = 5.5, 17.0 Hz, H3), 2.08 (2H, apparent q, *J* = 7.5 Hz, H3`), 1.82 – 1.75 (2H, m, H2`), 0.25 (9H, s, (C*H*$_3$)$_3$Si).

^{13}C NMR (125 MHz, $CDCl_3$): δ *major isomer* 172.6 (C2), 138.3 (ArC), 138.1 (C4`), 128.8 (ArCH), 128.3 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 115.4 (C5`), 100.3 (C≡C), 94.9 (C5), 88.8 (C≡C), 81.2 (C4), 72.8 (C6`), 40.4 (C1`), 36.7(C3), 31.8 (C3`), 28.3 (C2`), -0.00 (*C*H$_3$)$_3$Si); *minor isomer* 170.8 (C2), 137.8 (ArC), 136.3 (C4`), 128.6 (ArCH), 128.4 (ArCH), 128.0 (ArCH), 114.7 (C5`), 102.2 (C≡C), 91.6 (C5), 83.8 (C≡C), 78.1 (C4), 72.7 (C6`), 40.0 (C1`), 35.3 (C3), 31.2 (C3`), 27.7 (C2`), -0.45 (*C*H$_3$)$_3$Si). ESIMS *m/z* 372 [(M+H)$^+$ 100%].

HRESIMS calcd. for $C_{21}H_{30}NO_3Si$, (M+H)$^+$ 372.1985, found: 372.1995.

(4*S*,5*S*)-4-(Benzyloxy)-1-(pent-4-enyl)-5-((trimethylsilyl)ethynyl)pyrrolidin-2-one (16) and (4*S*,5*R*)-4-(Benzyloxy)-1-(pent-4-enyl)-5-((trimethylsilyl)ethynyl)pyrrolidin-2-one (17)

To a solution of **14** (6.00 g, 16.0 mmol) in AcOH (40 mL) was added $NaCNBH_3$ (5.00 g, 80 mmol) portionwise and the mixture was stirred at rt for 18 h. The mixture was quenched with water (50 mL) and extracted with EtOAc (2 x 100 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$) and the solvent was removed in *vacuo.* The crude product, which was a 2:1 mixture of *cis*:*trans* diastereomers, was purified by column chromatography (2:1 EtOAc/petrol) to give the *cis* compound **16** (2.99 g, 52%) as pale yellow gum and the *trans* compound **17** (1.51 g, 26%) as a pale yellow gum.

(16): R_f = 0.52 (2:1, EtOAc/petrol). $[\alpha]_D^{25}$ -7.7 (*c* 0.96, $CHCl_3$). IR (neat, ν_{max}/cm^{-1}): 2936, 2176, 2359, 2340, 1701, 1251, 1108, 843, 789, 697. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.27 (5H, m, ArH), 5.84 –

5.76 (1H, m, H4`), 5.04 (1H, d, *J* = 17.0 Hz, H5`), 4.97 (1H, d, *J* = 10.0 Hz, H5`), 4.73 (1H, d, *J* = 11.5, H6`), 4.57 (1H, d, *J* = 11.5, H6`), 4.51 (1H, d, *J* = 6.0, H5), 4.21 (1H, apparent q, *J* = 6.5, H4), 3.62 – 3.56 (1H, m, H1`), 3.23 – 3.17 (1H, m, H-1`), 2.63 – 2.54 (2H, m, H3), 2.07 (2H, apparent q, *J* = 7.0 Hz, H3`), 1.75 – 1.59 (2H, m, H2`), 0.18 (9H, s, (C*H*$_3$)$_3$Si). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 172.0 (C2), 137.5 (ArC), 137.4 (C4`), 128.4 (ArCH), 128.3 (ArCH), 127.6 (ArCH), 115.0 (C5`), 98.4 (C≡CSi), 93.6 (C≡CSi), 72.6 (C4), 71.6 (C6`), 54.8 (C5), 40.8 (C1`), 37.0 (C3), 31.0 (C3`), 28.3 (C2`), -0.29 (*C*H$_3$)$_3$Si). ESIMS *m/z* 356 [(M+H)$^+$ 100%]. HRESIMS calcd. for $C_{21}H_{30}NO_2Si$, (M+H)$^+$ 356.2032, found: 356.2046. **(17)**: R_f = 0.54 (2:1, EtOAc/petrol). $[\alpha]_D^{25}$ +7.8 (*c* 4.05, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.26 (5H, m, ArH), 5.84 – 5.76 (1H, m, H4`), 5.04 (1H, d, *J* = 17.0 Hz, H5`), 4.97 (1H, d, *J* = 10.0 Hz, H5`), 4.63 (2H, s, H6`), 4.28 (1H, s, H5), 4.20 – 4.17 (1H, m, H4), 3.62 – 3.50 (1H, m, H1`), 3.17 – 3.11 (1H, m, H1`), 2.75 (1H, dd, *J* = 7.0, 17.0 Hz, H3), 2.48 (1H, dd, *J* = 3.0, 17.0 Hz, H3), 2.07 (2H, q, *J* = 4.0 Hz, H3`), 1.72 – 1.61 (2H, m, H2`), 0.17 (9H, s, H9`). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 172.2 (C2), 137.9 (ArC), 137.5 (C4`), 128.8 (ArCH), 128.3 (ArCH), 128.0 (ArCH), 115.4 (C5`), 101.2 (C≡C), 92.2 (C≡C), 78.0 (C4), 71.7 (C6`), 56.7 (C5), 40.8 (C1`), 37.6 (C3), 31.2 (C3`), 26.5 (C2`), 0.02 (C9`). ESIMS *m/z* 356 [(M+H)$^+$ 100%].

(4*S*)-4-(Benzyloxy)-5-(3-(*tert*-butyldimethylsilyloxy)prop-1-ynyl)-5-hydroxy-1-(pent-4-enyl)pyrrolidin-2-one (15)

To a solution of *tert*-butyldimethyl(prop-2-ynyloxy)silane (1.86 g, 10.0 mmol) in dry THF (10 mL) at – 78 ^{o}C, was added dropwise *n*-BuLi in hexane (2.93 mL, 2.5 M, 7.32 mmol). After stirring for 15 min a solution of **8** (1.0 g, 3.66 mmol) in dry THF (5 mL) was added dropwise over 15 min at – 78 ^{o}C. Then stirring was continued for 1 h at – 78 ^{o}C under a N_2 atmosphere. Saturated aqueous NH_4Cl solution (15 mL) was added at – 78 ^{o}C and then the mixture was extracted with EtOAc (3 x 40 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography (1:3, EtOAc/petrol)) to afford **15** as a 70:30 mixture of two diastereomeric products (1.00 g, 68%) and as a pale yellow gum. R_f = 0.67 (1:3, EtOAc/petrol). IR (neat, ν_{max}/cm^{-1}): 3089, 2928, 1659, 1400, 1367, 1254, 1099, 834, 779, 738, 696. ^{1}H NMR (500 MHz, $CDCl_3$): δ *major isomer* 7.27 – 7.16 (5H, m, ArH), 5.74 – 5.63 (1H, m, H4`), 4.90 (1H, dd, *J* = 1.5, 17.0 Hz, H5`), 4.84 (1H, dd, *J* = 2.0, 10.0 Hz, H5`), 4.65 (1H, d, *J* = 12.0 Hz, H6`), 4.58 (1H, d, *J* = 12.0 Hz, H6`), 4.25 (2H, s, H9`), 4.09 (1H, dd, *J* = 5.5, 7.0 Hz, H4), 3.39 – 3.15 (2H, m, H1`), 2.51 (1H, dd, *J* = 7.0, 17.0 Hz, H3), 2.35 (1H, dd, *J* = 5.5, 17.0 Hz, H3), 1.98 -1.91 (2H, m, H3`), 1.69 – 1.63 (2H, m, H2`), 0.92 (9H, s, (C(C*H*$_3$)$_3$), 0.00 (6H, s, (C*H*$_3$)$_2$Si); *minor isomer* 7.26 – 7.16 (5H, m, ArH), 5.74 – 5.66 (1H, m, H4`), 4.93 (1H, dd, *J* = 1.5, 17.0 Hz, H5`), 4.86 (1H, dd, *J* = 2, 10.0 Hz, H5`), 4.77 (1H, d, *J* = 11.5 Hz, H6`), 4.55

(1H, d, *J* = 11.5 Hz, H6`), 4.27 (2H, s, H9`), 3.93 (1H, dd, *J* = 5.5 7.0 Hz, H4), 3.36 – 3.20 (2H, m, H1`), 2.63 (1H, dd, *J* = 7.0, 17.0 Hz, H3), 2.30 (1H, dd, *J* = 5.5, 17.0 Hz, H3), 2.00 – 1.96 (2H, m, H3`), 173 – 1.65 (2H, m, H2`), 0.79 (9H, s, (C(CH_3)$_3$), 0.00 (6H, s, (CH_3)$_2$Si).

^{13}CNMR (125 MHz, $CDCl_3$): δ *major isomer* 170.7 (C2), 137.8 (ArC), 136.3 (C4`), 128.5 (ArCH), 128.3 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 127.9 (ArCH), 114.7 (C5`), 84.8, 84.1 (C≡C), 81.8 (C5), 78.0 (C4), 72.7 (C6`), 51.3 (C9`), 40.0 (C1`), 35.3 (C3), 31.1 (C3`), 27.8 (C2`), 25.6 (C($CH_3$)$_3$), 18.1 ($C$($CH_3$)$_3$), -5.2 ($CH_3$)$_2$Si); *minor isomer* 171.7 (C2), 137.8 (ArC), 137.5 (C4`), 128.3 (ArCH), 127.7 (ArCH), 127.6 (ArCH), 114.8 (C5`), 84.4, 84.0 (C≡C), 80.8 (C4), 79.7 (C5), 72.3 (C6`), 51.4 (C9`), 39.8 (C1`), 36.1 (C3), 31.2 (C3`), 27.8 (C2`), 25.6 (C(CH_3)$_3$), 18.1 (C(CH_3)$_3$), -5.3 (CH_3)$_2$Si). ESIMS *m/z* 444 [(M+H)$^+$ 100%]. HRESIMS calcd. for $C_{25}H_{38}NO_4Si$, (M+H)$^+$ 444.2559, found: 444.2570.

(4*S*)-4-(Benzyloxy)-5-(3-hydroxyprop-1-ynyl)-1-(pent-4-enyl)pyrrolidin-2-one (18/19)

To a solution of **15** (1.0 g, 2.26 mmol) in HOAc (25 mL) was added $NaCNBH_3$ (071 g, 11.0 mmol) portionwise and the mixture was stirred at rt for 18 h. The mixture was quenched with water (50 mL) and extracted with EtOAc (2 x 80 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$) and the solvent was removed in *vacuo.* The crude product was purified by column chromatography (1:1, EtOAc/petrol)) to afford inseparable mixture (*cis*:*trans* = 3:1*)* of two diastereomeric products **18/19** (0.41 g, 58%) and as a colourless gum. R_f = 0.58 (1:1, EtOAc/petrol). IR (neat, ν_{max}/cm^{-1}): 3375, 2935, 2360, 2337, 1674, 1454, 1409, 1073, 1027, 742, 697. ^{1}H NMR (500 MHz, $CDCl_3$): δ *major cis diastereomer* 7.38 – 7.26 (5H, m, ArH), 5.85 – 5.75 (1H, m, H4`), 5.04 (1H, d, *J* = 16.5 Hz, H5`), 4.98 (1H, d, *J* = 10.0 Hz, H5`), 4.70 (1H, d, *J* = 11.5 Hz, H6`), 4.60 (1H, d, *J* = 11.5 Hz, H6`), 4.54 (1H, d, *J* = 6.5 Hz, H5), 4.32 (2H, s, H9`), 4.24 (1H, apparent q, *J* = 7.0 Hz, H4), 3.70 – 3.61 (1H, m, H1`), 3.16 – 3.01 (1H, m, H1`), 2.60 (2H, d, *J* = 7.5 Hz, H3), 2.09 – 2.02 (2H, m, H3`), 1.73 – 1.59 (2H, m, H2`); *minor trans diastereomer* (in part) 7.38 – 7.26 (5H, m, ArH), 4.29 (2H, s, H9`), 3.70 – 3.61 (1H, m, H1`), 3.16 – 3.01 (1H, m, H1`), 2.77 (1H, d, *J* = 7.0, 17.0 Hz, H3), 2.50 (1H, d, *J* = 17.0 Hz, H3), 2.09 – 2.02 (2H, m, H3`), 1.73 – 1.59 (2H, m, H2`). $^{13}$C NMR (125 MHz, $CDCl_3$): δ *major cis diastereomer* 171.7 (C2), 137.5 (ArC), 137.0 (C4`), 128.4 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 127.9 (ArCH), 127.7 (ArCH), 115.1 (C5`), 86.5, 78.5 (C≡C), 72.5 (C4), 71.8 (C6`), 54.0 (C5), 50.8 (C9`), 40.7 (C1`), 36.8 (C3), 30.9 (C3`), 26.3 (C2`); *minor trans diastereomer* (in part) 171.7 (C2), 137.5 (ArC), 137.0 (C4`), 128.4 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 127.9 (ArCH), 127.7 (ArCH), 71.4 (C6`), 55.8 (C5), 50.6 (C9`), 40.4 (C1`), 37.2 (C3), 30.7 (C3`), 26.1 (C2`). ESIMS *m/z* 314 [(M+H)$^+$ 100%]. HRESIMS calcd. for $C_{19}H_{24}NO_3$, (M+H)$^+$ 314.1743, found: 314.1756.

(1*S*,9a*S*)-1-(Benzyloxy)-9-vinyl-5,6,7,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]azepin-3(2*H*)-one (20)

A solution of **16** (2.00 g, 5.63 mmol) and Grubbs' 2nd generation catalyst (0.034 g, 0.56 mmol) in CH_2Cl_2 (400 mL) was heated at reflux for 5 h under a N_2 atmosphere. The solution was then concentrated and the residue was purified by column chromatography (1:1, EtOAc/petrol) to give a title compound **20** (1.29 g, 81%) as a pale yellow oil. R_f = 0.54 (1:1, EtOAc/petrol). $[\alpha]_D^{25}$ -42.4 (*c* 1.13, $CHCl_3$). IR (neat, ν_{max}/cm^{-1}): 2931, 1674, 1453, 1404, 1267, 1069, 735, 697. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.21 (5H, m, ArH), 6.38 (1H, dd, *J* = 11.0, 18.0 Hz, H1`), 6.09 (1H, t, *J* = 7.0 Hz, H8), 5.08 (1H, d, *J* = 18.0 Hz, H2`), 5.01 (1H, d, *J* = 11.0 Hz, H2`), 4.65 (1H, d, *J* = 4.0 Hz, H9a), 4.48 (2H, s, H3`), 4.23 (1H, apparent t, *J* = 4.5 Hz, H1), 4.07 (1H, dd, *J* = 8.5, 14.0 Hz, H5), 2.92 – 2.85 (1H, m, H5), 2.79 – 2.71 (1H, m, H7), 2.65 – 2.56 (2H, m, H2), 2.11 – 2.04 (1H, m, H6), 2.02 – 1.96 (1H, m, H7), 1.67 – 1.60 (1H, m, H6). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5 (C3), 139.0 (C1`), 138.0 (C9), 134.8 (C8), 134.2 (ArC), 128.2 (ArCH), 127.4 (ArCH), 127.2 (ArCH), 110.7 (C2`), 74.1 (C1), 71.5 (C3`), 66.0 (C9a), 38.6 (C2), 38.1 (C5), 23.9 (C6), 22.1 (C7). ESIMS *m/z* 284 [$(M+H)^+$ 100%]. HRESIMS calcd. for $C_{18}H_{22}NO_2$, $(M+H)^+$ 284.1626, found: 284.1651.

Ethyl 3-((4*S*,5*S*)-4-(benzyloxy)-2-oxo-1-(pent-4-enyl)pyrrolidin-5-yl)propiolate (22)

To a solution of alcohols **18/19** (50 mg, 0.16 mmol) in acetone (6 mL), was added Jones reagent[16] at 0 °C dropwise until disappearance of starting material by TLC analysis. The reaction mixture was diluted with water (10 mL), extracted with EtOAc (3 x 30 mL) and the combined organic extracts washed with brine solution, dried ($MgSO_4$) and concentrated in *vacuo*. The crude product (48 mg, 92%) was dissolved in CH_2Cl_2 (10 mL) and treated with EtOH (0.011 mL, 0.19 mmol), DCC (30 mg, 0.14 mmol) and DMAP (1.8 mg, 0.014 mmol) at 0 °C under a N_2 atmosphere. The reaction mixture was warmed to rt and stirring was continued for 6 h. The mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$) and concentrated *in vacuo*. The crude compound was purified by column chromatography (2 : 1, EtOAc/petrol), to give the *cis* diastereomer **22** (26 mg, 47%) as pale yellow gum and the *trans* diastereomer (8.5 mg, 15%) as a pale yellow gum.

(22): R_f = 0.57 (2:1, EtOAc/petrol). $[\alpha]_D^{27}$ +10 (*c* 1.4, $CHCl_3$); IR (neat, ν_{max}/cm^{-1}): 2930, 2359, 2334, 2236, 1705, 1408, 1250, 1073, 749, 698. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 – 7.30 (5H, m, ArH), 5.83 - 5.75 (1H, m, H4`), 5.05 (1H, dd, *J* = 1.5, 17.0 Hz, H5`), 4.99 (1H, d, *J* = 10.5 Hz, H5`), 4.70 (1H, d, *J* = 11.5 Hz, H6`), 4.60 (1H, d, *J* = 11.5 Hz, H6`), 4.59 (1H, d, *J* = 6.5 Hz, H5), 4.30 – 4.23 (3H, m, H4 and H10`), 3.67 – 3.61 (1H, m, H1`), 3.18 – 3.13 (1H, m, H1`), 2.62 (2H, d, *J* = 7.5 Hz, H3), 2.11 – 2.01 (2H, m, H3`), 1.74 – 1.57 (2H, m, H2`), 1.32 (3H, t, *J* = 7.0 Hz, H11`). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 171.2 (C2), 152.8 (C9`), 137.3 (ArC), 136.8 (C4`), 128.5 (ArCH), 128.1 (ArCH), 127.9 (ArCH), 115.4 (C5`),

80.4, 79.3 (C≡C), 72.5 (C4), 72.0 (C6`), 62.2 (C10`), 53.9 (C5), 40.9 (C1`), 36.7 (C3), 30.9 (C3`), 26.3 (C2`), 13.9 (C11`). ESIMS *m/z* 356 [$(M+H)^+$ 100%]. HRESIMS calcd. for $C_{21}H_{26}NO_4$, $(M+H)^+$ 356.1862, found: 356.1864.

Ethyl 2-((1*S*,9a*S*)-1-(benzyloxy)-3-oxo-2,3,5,6,7,9a-1*H*-pyrrolo[1,2-*a*]azepin-9-yl)acrylate (23)

A solution of **22** (0.15 g, 0.42 mmol) and Grubbs' 1st generation catalyst (0.034 g, 0.042 mmol) in CH_2Cl_2 (30 mL) was stirred at rt for 5 h under a N_2 atmosphere. The solution was quenched by opening to the air and was then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (2:1, EtOAc/petrol) to give a title compound **23** (0.122 g, 82%) as a light brown gum. R_f = 0.52 (2:1, EtOAc/petrol). $[\alpha]_D^{22}$ -11.8 (*c* 0.76, $CHCl_3$). IR (neat, ν_{max}/cm^{-1}): 2936, 2359, 2337, 1671, 1453, 1270, 1069, 910, 731, 699. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 – 7.24 (5H, m, ArH), 6.07 (1H, s, H1`), 6.00 (1H, t, *J* = 6.0 Hz, H8), 5.61 (1H, s, H1`), 4.57 (1H, d, *J* = 6.0 Hz, H9a), 4.55 (1H, d, *J* = 12.0, H6`), 4.41 (1H, d, *J* = 12.0 Hz, H6`), 4.26 – 4.17 (2H, m, H4`), 4.09 – 4.04 (2H, m, H1, H5), 3.16 – 3.09 (1H, m, H5), 2.75 – 2.67 (1H, m, H7), 2.60 (1H, d, *J* = 17.0 Hz, H2), 2.52 (1H, dd, *J* = 5.0, 17.0 Hz, H2), 2.09 - 1.38 (3H, m, H7, H6), 1.31 (3H, t, *J* = 7.0 Hz, H5`). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3 (C3), 166.6 (C3`), 141.8 (C2`), 137.9 (ArC), 134.1 (C8), 133.2 (C9), 128.3 (ArCH), 127.5 (ArCH), 127.1 (ArCH), 126.6 (C1`), 74.5 (C1), 71.1 (C6`), 67.5 (C9a), 61.1 (C4`), 38.2 (C5), 37.8 (C2), 24.0 (C6), 22.2 (C7), 14.1 (C5`). ESIMS *m/z* 356 [$(M+H)^+$ 100%]. HRESIMS calcd. for $C_{21}H_{26}NO_4$, $(M+H)^+$ 356.1860, found: 356.1862.

Ethyl 2-((1*S*)-1-(benzyloxy)-3-oxo-2,3,5,6,7,9a-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-9-yl)propanoate (24)

To a solution of **23** (0.12 g, 0.33 mmol) in MeOH (10 mL) was added $NaBH_4$ (0.10 g, 2.70 mmol) at 0 °C, and the solution was stirred at the same temperature for 3 h. After completion of the reaction, saturated aqueous NH_4Cl solution was added, and the aqueous layer was extracted with EtOAc (3 x 30 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (2:1, EtOAc/petrol) to give **24** (0.09 g, 75%) as a 4:1 inseparable mixture of diastereomeric products and as a colourless oil. R_f = 0.50 (2:1, EtOAc/petrol). IR (neat, ν_{max}/cm^{-1}): 2937, 2360, 2342, 1722, 1688, 1454, 1181, 1095, 1071, 741, 697. ^{1}H NMR (500 MHz, $CDCl_3$): δ *major diastereomer* 7.32 – 7.23 (5H, m, ArH), 5.95 (1H, t, *J* = 8.5 Hz, H8), 4.28 (1H, d, *J* = 11.5 Hz, H6`), 4.45 (1H, d, *J* = 11.5 Hz, H6`), 4.28 (1H, d, *J* = 4.5 Hz, H9a), 4.16 (1H, t, *J* = 4.5 Hz, H1), 4.10 (2H, q, *J* = 7.0 Hz, H4`), 4.05 – 3.97 (1H, m, H5), 3.15 (1H, q, *J* = 7.5 Hz, H2`), 2.97 – 2.90 (1H, m, H5), 2.71 – 2.65 (1H, m, H7), 2.64 (1H, d, *J* = 17.0 Hz, H2), 2.55 (1H, dd, *J* = 5.0, 17.0 Hz, H2), 2.04 – 1.59 (3H, m, H7,

6), 1.26 (3H, d, *J* = 7.0 Hz, H1`), 1.20 (3H, t, *J* = 7.0 Hz, H5`); *minor diastereomer (in part)* 7.32 – 7.23 (5H, m, ArH), 5.93 (1H, t, *J* = 8.5 Hz, H8), 4.54 (1H, d, *J* = 12.0 Hz, H6`), 4.38 (1H, d, *J* = 12.0 Hz, H6`), 4.35 (1H, d, *J* = 5.5 Hz, H9a), 4.19 (1H, t, *J* = 5.0 Hz, H1), 4.13 (2H, q, *J* = 6.5 Hz, H4`), 4.05 – 4.02 (1H, m, H5), 2.98 – 2.88 (2H, m, H5, 2`), 2.71 – 2.54 (3H, m, H2, H7), 2.06 – 1.58 (3H, m, H6, H7), 1.32 (3H, d, *J* = 7.5 Hz, H1`), 1.21 (3H, t, *J* = 7.5 Hz, H5`). ^{13}C NMR (125 MHz, $CDCl_3$): δ *major diastereomer* 174.2 (C3), 172.3 (C3`), 137.9 (ArC), 134.0 (C9), 130.4 (C8), 128.2 (ArCH), 127.5 (ArCH), 127.4 (ArCH), 127.1 (ArCH), 127.0 (ArCH), 75.6 (C1), 70.7 (C-Bn), 68.0 (C9a), 60.8 (C4`), 46.3 (C2`), 37.9 (C5), 37.7 (C2), 23.6 (C6), 21.5 (C7), 16.6 (C1`), 14.1 (C5`). ESIMS *m/z* 358 [$(M+H)^+$ 100%]. HRESIMS calcd. for $C_{21}H_{28}NO_4$, $(M+H)^+$ 358.2009, found: 358.2018.

(3a*R*,10*S*,10a*S*)-10-(Benzyloxy)-1-methyl-3a,4,5,6,10,10a-hexahydro-2*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepine-2,8(9H)-dione (25) and (3a*S*,10*S*,10a*S*)-10-(Benzyloxy)-1-methyl-3a,4,5,6,10,10a-hexahydro-2*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepine-2,8(9*H*)-dione (26)

A solution of **24** (0.20 g, 0.56 mmol) in MeOH (8 mL) and aqueous 1N NaOH solution (5.92 mL) was stirred at 0 ^oC for 8 h. The solution was acidified with 10% HCl and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (50 mL), and $CuBr_2$ on alumina[9g,h] (3.0 g) was added. The mixture was heated at 65 ^oC for 60 h. After filtration, the solid was washed with MeOH, and the filterate was concentrated. Water was added to the residue, and the aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic extracts were washed with brine solution, dried ($MgSO_4$) and concentrated. The residue was dissolved in EtOAc (15 mL), and Et_3N (0.155 mL, 1.10 mmol) was added and the solution was stirred at rt for 16 h. The reaction solution was then washed with 10% HCl, brine and saturated $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (2:1, EtOAc/petrol) to give **25** (0.0247 g, 13.5%) as a colourless gum and **26** (0.0247 g, 13.5%) as a colorless gum.

(25): R_f = 0.53 (2:1, EtOAc/petrol). $[\alpha]_D^{26}$ +27.4 (*c* 2.81, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 – 7.16 (5H, m, ArH), 5.00 (1H, d, *J* = 11.5 Hz, H3a), 4.71 (1H, d, *J* = 5.0 Hz, H10a), 4.62 (1H, d, *J* = 11.5 Hz, H2`), 4.57 – 4.54 (1H, m, H10), 4.37 (1H, d, *J* = 11.5 Hz, H2`), 4.20 – 4.16 (1H, m, H6), 2.90 – 2.83 (1H, m, H6), 2.78 (1H, dd, *J* = 3.0, 17.0 Hz, H9), 2.63 (1H, dd, *J* = 6.0, 17.0 Hz, H9), 2.22 – 2.16 (1H, m, H5), 1.96 – 1.84 (2H, m, H4, H5), 1.83 (3H, s, H1`, Me), 1.79 – 1.68 (1H, m, H4). $^{13}$C NMR (125 MHz, $CDCl_3$): 173.6 (C2), 171.6 (C8), 156.5 (1a), 136.6 (ArC), 128.5 (ArCH), 128.2 (ArCH), 127.4 (ArCH), 124.2 (C1), 80.6 (C3a), 73.0 (C10), 71.3 (C2`), 61.5 (C10a), 40.0 (C6), 36.3 (C9), 26.1 (C5), 22.0 (C4), 10.4 (C1` Me). ESIMS *m/z* 328 [$(M+H)^+$ 100%].

(26): R_f = 0.54 (2:1, EtOAc/petrol). $[\alpha]_D^{26}$ +18.0 (*c* 1.6, $CHCl_3$). IR (neat, ν_{max}/cm^{-1}): 2927, 2360, 2337, 1749, 1689, 1454, 1255, 1108, 737, 698. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 – 7.11 (5H, m, ArH), 5.01 (1H, d, *J* = 11.5 Hz, H-3a), 4.80 (1H, d, *J* = 5.0 Hz, H10a), 4.56 (1H, d, *J* = 12.0 Hz, H2`), 4.32 (1H, d, *J* = 14.0 Hz, H6), 4.23 – 4.14 (2H, m, H10, H2`), 2.63 (1H, d, *J* = 17.0 Hz, H9), 2.57 (1H, dd, *J* = 5.0, 17.0 Hz, H9), 2.51 – 2.42 (2H, m, H4, H6), 1.90 – 1.87 (1H, m, H5), 1.67 – 1.57 (4H, m, H5, H1`). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 173.1 (C2), 172.2 (C8), 160.4 (1a), 136.3 (ArC), 128.6 (ArCH), 128.3 (ArCH), 127.9 (ArCH), 124.8 (C1), 83.8 (C3a), 72.1 (C10), 71.1 (C2`), 62.0 (C10a), 42.7 (C6), 37.2 (C9), 34.7 (C4), 25.6 (C5), 8.6 (C1` Me). ESIMS *m/z* 328 [$(M+H)^+$ 100%]. HRESIMS calcd. for $C_{21}H_{26}NO_4$, $(M+H)^+$ 328.1534, found: 328.1549.

(3a*S*,10*S*,10a*R*,10b*R*)-10-(Benzyloxy)-10b-hydroxy-1-methylhexahydro-1*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepine-2,8(9*H*, 10b*H*)-dione (27)

To a solution of **24** (0.20 g, 0.56 mmol) in acetone/water (9:1) was added $K_2OsO_4.2H_2O$ (12 mg, 0.03 mmol) and NMO (98.0 mg, 0.84 mmol) at rt and reaction mixture warmed to 60 ^oC and stirred for 24 h. The solution was cooled to rt and the reaction mixture was quenched with saturated aqueous potassium bisulfite solution (15 mL), After stirring for 10 min, water (30 mL) was added and the mixture was extracted with EtOAc (3x50 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent concentrated *in vacuo.* The crude product was purified by flash column chromatography (0.5:10, MeOH/EtOAc) to give the title compound **27** as a 5:1 mixture of inseperable diastereomers (0.109 g, 56%) and as a colourless liquid.

R_f = 0.45 (0.5:10, MeOH/EtOAc). $[\alpha]_D^{27}$ +98.1 (*c* 1.1, $CHCl_3$). IR (neat, ν_{max}/cm^{-1}): 3327, 2935, 2960, 2337, 1770, 1670, 1454, 1330, 1197, 1012, 975, 739, 697. ^{1}H NMR (500 MHz, $CDCl_3$): δ *major isomer* 7.38 – 7.20 (5H, m, ArH), 4.79 (1H, dd, *J* = 6.0, 10.0 Hz, H3a), 4.60 (1H, d, *J* =11.5 Hz, H2`), 4.28 (1H, d, *J* = 11.5 Hz, H2`), 4.20 -4.14 (1H, m, H6), 4.08 (1H, apparent t, *J* = 4.0 Hz, H10), 3.75 (1H, d, *J* = 3.5 Hz, H10a), 3.19 (1H, q, *J* = 7.5 Hz, H1), 3.05 (1H, t, *J* = 13.0 Hz, H6), 2.67 (1H, d, *J* = 17.0 Hz, H9), 2.47 (1H, dd, *J* = 4.0, 17.0 Hz, H9), 2.04 – 1.98 (2H, m, H4), 186 – 1.83 (1H, m, H5), 1.49 – 1.40 (1H, m, H5), 1.09 (3H, d, *J* = 7.5 Hz, H1` Me); *minor isomer* (in part) 7.37 – 7.20 (5H, m, ArH), 5.02 (1H, dd, *J* = 4.0, 12.0 Hz, H3a), 4.51 (1H, d, *J* = 12.0 Hz, H2`), 4.38-4.36 (1H, m, H10), 4.27 (1H, d, *J* = 12.0 Hz, H2`), 4.21-4.18 (1H, m, H6), 4.07 (1H, d, *J* = 4.0 Hz, H10a), 3.29 (1H, t, *J* = 13.0 Hz, H6), 2.93 (1H, q, *J* = 7.0 Hz, H1), 2.70 (1H, d, *J* = 17.0 Hz, H9), 2.45 (1H, dd, *J* = 5.0, 17.0 Hz, H9), 2.07 – 1.80 (2H, m, H4), 1.48 (3H, d, *J* = 8.0 Hz, H1` Me), 1.40 – 1.16 (2H, m, H5). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.3 (C2), 172.1 (C8), 135.8 (ArC), 128.8 (ArCH), 128.5 (ArCH), 128.2 (ArCH), 83.9 (C3a), 80.2 (C10b), 72.9 (C10a), 70.4 (C2` Bn), 66.1 (C10), 42.6 (C1), 40.2 (C6), 36.8 (C9), 26.2 (C4), 25.7 (C5), 7.7 (C1`);

minor isomer (in part) 178.7 (C2), 172.1 (C8), 136.4 (ArC), 128.6 (ArCH), 128.0 (ArCH), 127.3 (ArCH), 84.2 (C3a), 80.7 (C10b), 74.9 (C10), 69.6 (C2` Bn), 67.6 (C10a), 52.0 (C1), 40.1 (C6), 36.5 (C9), 26.7 (C4), 26.2 (C5), 12.8 (C1`). ESIMS *m/z* 346 [$(M+H)^+$ 100%]. HRESIMS calcd. for $C_{19}H_{23}NO_5$, $(M+H)^+$ 346.1645, found: 346.1654.

(3a*S*,10*S*)-10-Hydroxy-1-methyl-3a,4,5,6,10,10a-hexahydro-2*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepine-2,8(9*H*)-dione (28)

Method 1: To a solution of **27** (0.08 g, 0.23 mmol) in toluene (8 mL) in a flask equipped with a Dean-Stark apparatus and a condenser, was added PTSA (66 .0 mg, 0.34 mmol) at rt. The resulting reaction mixture was heated at reflux temperature and stirred for 18 h. The reaction mixture was then cooled to rt and diluted with water (4 mL) and extracted with EtOAc (3x30 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$) and the solvent concentrated in *vacuo*. The crude product was purified by column chromatography (0.5:10, MeOH/EtOAc) to give compound **28** (38.0 mg, 70%) as an off white solid. Mp = 210 – 212 ^oC. R_f = 0.46 (0.5:10, MeOH/EtOAc). $[\alpha]_D^{23}$ +20.5 (*c* 0.34, $CHCl_3$). IR (neat, ν_{max}/cm^{-1}): 3401, 2932, 2359, 2343, 1742, 1697, 1429, 1058, 1016.

^1H NMR (300 MHz, $CDCl_3$): δ 5.07 – 5.02 (1H, m, H3a), 4.78 (1H, d, *J* = 4.2 Hz, H10a), 4.61 (1H, apparent q, *J* = 5.1 Hz, H10), 4.33 – 4.27 (1H, m, H6), 3.91 (1H, d, *J* = 4.2 Hz, OH), 2.74 (1H, dd, *J* = 5.7, 17.1 Hz, H9), 2.54 – 2.41 (3H, m, H4, H6, H9), 1.91 (3H, s, H1`, Me), 1.90 – 1.87 (1H, m, H5), 1.70 – 1.61 (1H, m, H5), 1.32 – 1.18 (1H, m, H4). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 174.1 (C2), 172.9 (C8), 161.2 (C1a), 125.1 (C1), 84.5 (C3a), 66.4 (C10), 63.5 (C10a), 42.9 (C6), 40.2 (C9), 34.6 (C4), 25.5 (C5), 8.9 (C1` Me). ESIMS *m/z* 238 [$(M+H)^+$ 100%]. HRESIMS calcd. for $C_{12}H_{16}NO_4$, $(M+H)^+$ 238.1041, found: 238.1059.

Method 2: To a solution of **26** (0.015 g, 0.045 mmol) in dichloromethane (1.0 mL) at 0 ^oC was added borontribromide (0.101 g, 0.412 mmol). After 30 min the mixture was diluted with CH_2Cl_2 (10 mL) and the solution was washed with a saturated solution of $NaHCO_3$ (2 x 10 mL) and then brine. The solution was then dried ($MgSO_4$) and the solvent concentrated in *vacuo*. The crude product was purified by column chromatography (0.5:10, MeOH/EtOAc) to give compound **28** (6.6 mg, 68%) as an off white solid. The ^1H NMR spectrum of this material was identical to that prepared via method 1.

(1*R*,3a*S*,10*S*,10a*S*,10b*S*)-10-Hydroxy-1-methylhexahydro-1*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepine-2,8(9H,10b*H*)-dione (7) and (1*S*,3a*S*,10*S*,10a*S*,10b*S*)-10-Hydroxy-1-methylhexahydro-1*H*-furo[3,2-

***c*]pyrrolo[1,2-*a*]azepine-2,8(9*H*,10*bH*)-dione (29)**

To a solution of **28** (23.0 mg, 0.097 mmol) in MeOH (2.5 mL) was added $NiCl_2.6H_2O$ (8.77 mg, 0.034 mmol) and $NaBH_4$ (25.0 mg, 0.67 mmol) at -30 ^oC, and the mixture was stirred at same temperature for 2 h. The resulting mixture was then diluted with CH_2Cl_2 and the solution was washed with brine and saturated aqueous $NaHCO_3$ solution, and dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by small column chromatography (0.6:10, MeOH/EtOAc) to give a 87:13 mixture of inseparable diastereomeric products **7** and **29** (18.0 mg, 78%) as a colourless solid. Mp = 150 – 152 ^oC. R_f = 0.43 (0.6:10, MeOH/EtOAc). $[\alpha]_D^{24}$ +7.8 (*c* 0.38, $CHCl_3$). IR (neat, ν_{max}/cm^{-1}): 3402, 2961, 2360, 2340, 1759, 1670, 1439, 1167, 1009. ^1H NMR (500 MHz, $CDCl_3$): δ *major diastereomer* 4.92 – 4.86 (1H, m, H3a), 4.52 (1H, m, H10), 4.20 (1H, d, *J* = 14.5 Hz, H6), 3.85 – 3.82 (2H, m, H10a, OH), 3.30 (1H, dq, *J* = 12.3, 7.2 Hz, H1), 2.68 – 2.58 (2H, m, H6, H9), 2.39 (1H, d, *J* = 17.0 Hz, H9), 2.36 – 2.30 (2H, m, H1a, H4), 1.90 – 1.83 (1H, m, H5), 1.57 – 1.37 (2H, m, H5, H9), 1.32 (3H, d, *J* = 7.2 Hz, Me (H1`)); *minor diastereomer* (in part) 4.80 – 4.76 (1H, m, H3a), 4.29 (1H, apparent t, *J* = 6.5 Hz, H10), 4.10 (1H, d, *J* = 14.5 Hz, H6), 3.75 – 3.68 (1H, m, H10a), 3.23 – 3.18 (1H, m, H1), 2.84 (1H, dd, *J* = 7.5, 18.0 Hz, H9), 1.28 (3H, d, *J* = 7.0 Hz, Me (H1`)). ^{13}C NMR (125 MHz, $CDCl_3$): δ *major diastereomer* 178.7 (C2), 173.1 (C8), 80.3 (C3a), 67.2 (C10), 59.8 (C10a), 51.9 (C1a), 42.1 (C9), 40.5 (C6), 36.9 (C1), 35.0 (C4), 25.7 (C5), 14.6 (C1`); *minor diastereomer* (in part) 79.2 (C3a), 71.6 (C10), 62.1 (C10a), 43.7 (C9), 43.5 (C6), 37.4 (C1), 24.6 (C5), 12.6 (C1`) ESIMS *m/z* 240 [$(M+H)^+$ 100%]. HRESIMS calcd. for $C_{12}H_{18}NO_4$, $(M+H)^+$ 240.1148, found: 240.1169.

ACKNOWLEDGEMENTS

We thank the Australian Research Council and the University of Wollongong for financial support.

REFERENCES

1. R. A. Pilli, G. B. Rosso, and M. C. F. de Oliveira, *The Alkaloids*, Vol. 62; G. A. Cordell, Ed; Elsevier; San Diego, 2005; Chapter *2*, pp 77–173.
2. H. Greger, *Planta Med.,* 2006, **72**, 99.
3. R. A. Pilli, G. B. Rosso, and M. C. F. de Oliveira, *Nat. Prod. Rep.,* 2010, **27**, 1908.
4. P. Mungkornasawakul, S. G. Pyne, A. Jatisatienr, D. Supyen, W. Lie, A. T. Ung, B. W. Skelton, and A. H. White, *J. Nat. Prod.,* 2003, **66**, 980.
5. E. Kaltenegger, B. Brem, K. Mereiter, H. Kalchhauser, H. Kahlig, O. Hofer, S. Vajrodaya, and H. Greger, *Phytochemistry,* 2003, **63**, 803.
6. P. Mungkornasawakul, S. G. Pyne, A. Jatisatienr, D. Supyen, C. Jatisatienr, W. Lie, A. T. Ung, B. W.

Skelton, and A. H. White, *J. Nat. Prod.,* 2004, **67**, 675.

7. Y. Hitosuyanagai, G. Uemura, and K. Takeya, *Tetrahedron Lett*., 2010, **51**, 5694.
8. S. Chaiyong, A. Jatisatienr, P. Mungkornasawakul, T. Sastraruji, S. G. Pyne, A. T. Ung, T. Urathamakul, and W. Lie, *J. Nat. Prod.,* 2010, **73***,* 1833.
9. (a) T. Honda, T. Matsukawa, and K. Takahashi, *Org. Biomol. Chem.,* 2011, **9**, 673; (b) S. Torssell, E. Wanngren, and P. Somfai, *J. Org. Chem*., 2007, **72**, 4246; (c) H. F. Olivo, R. Tovar-Miranda, and E. Barragan, *J. Org. Chem*., 2006, **71**, 3287; (d) M. P. Sibi and T. Subramanian, *Synlett,* 2004, 1211; (e) formal synthesis: M. K. Gurjar and D. S. Reddy, *Tetrahedron Lett.,* 2002, **43**, 295; (f) P. A. Jacobi and K. Lee, *J. Am. Chem. Soc*., 2000, **122**, 4295; (g) A. Kinoshita and M. Mori, *Heterocycles,* 1997, **46**, 287; (h) A. Kinoshita and M. Mori, *J. Org. Chem.,* 1996, **61**, 8356; (i) D. R. Williams, J. P. Reddy, and G. S. Amato, *Tetrahedron Lett.,* 1994, **35**, 6417.
10. N. Bogliotti, P. I. Dalko, and J. Cossy, *Synlett,* 2006, 2664.
11. (a) Y. Wang, L. Zhu, Y. Zhang, and R. Hong, *Angew. Chem., Int. Ed*., 2011, **50**, 2787; (b) R. W. Bates and S. Sridhar, *Synlett,* 2009, **12**, 1979; (c) reference 9f (d) P. A. Jacobi, K. Lee, K. *J. Am. Chem. Soc*., 1997, **119**, 3409.
12. J. Y. Kim and T. Livinghouse, *Org. Lett.,* 2005, **7**, 1737.
13. I. R. Morgan, A. Yazici, and S. G. Pyne, *Tetrahedron*, 2008, **64**, 1409.
14. P. Q. Huang, Q. F. Chen, C. L. Chen, and H. K. Zhang, *Tetrahedron: Asymmetry,* 1999, **10**, 3827.
15. J. G. Pierce, D. L. Waller, and P. Wipf, *J. Organomet. Chem.,* 2007, **692**, 4618.
16. E. Fillion, E. T. Vincent, L. G. Mercier, A. A. Remorova, and R. J. Carson, *Tetrahedron Lett.,* 2005, **46**, 1091.
17. P. V. Ramachandran, T. R. Michael, and M. V. Reddy, *Tetrahedron Lett.,* 2005, **46**, 2547.
18. W.-H. Lin, Y. Ye, and R.-S. Xu, *J. Nat. Prod.,* 1992, **55**, 571.
19. F. Velazquez and F. O. Horacio, *Org. Lett*., 2002, **4**, 3175.
20. S. F. Martin and K. J. Barr, *J. Am. Chem. Soc*., 1996, **118**, 3299.
21. S. F. Martin, K. J. Barr, D. W. Smith, and S. K. Bur, *J. Am. Chem. Soc*., 1999, **121**, 6990.