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RESEARCH ARTICLE

Studies Towards the Synthesis of the Pyrido[1,2-*a*]azepine Alkaloids

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Abstract: This study describes the synthesis of the pyrido[1,2-*a*]azepine alkaloids. The bicyclic compound **1** containing the A-B core ring structure was synthesized in 17 steps in 1.7% overall yield starting from 4-pentyn-1-ol. The key steps involve an oxidation of 1,4 diol to lactone and an ene-yne ring closing metathesis reaction.

Keywords: Pyrido[1,2-*a*]azepine, *Stemona* alkaloids, bromolactonization, aminolysis reaction, ene-yne lactam, vinyl iodide.

1. INTRODUCTION

The pyrido[1,2-*a*]azepine alkaloids, whose core structure is drawn in Fig. (**1**), is one of the eight groups of *Stemona* alkaloids classified by Pilli *et al*. [1]. These *Stemona* alkaloids have been exclusively isolated from the monocotyledonous family *Stemonaceae*, mainly distributed in South East Asia, Northern Australia, China, Japan, and Northern America [2] and have a wide range of bioactivities [3]. The dried roots from *S. tuberosa*, 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 treat coughing, and are claimed to have antituberculosis, antibacterial, antifungal and antihelmintic properties [4, 5]. The isolation and bioactivity of the pyrido[1,2-*a*]azepine alkaloids have received considerable attention of chemists and many reports on the isolation and bioactivity of these compounds have been found in the literature. In 2003, Greger *et al*., isolated five new pyrido[1,2-*a*]azepines alkaloids stemokerrin, methoxystemokerrin-*N*-oxide, oxystemokerrin, oxystemokerrin-*N*-oxide, and pyridostemin and tested them for insecticidal activity. Among these five compounds, oxystemokerrin was the most potent with the LC50 = 5.9 ppm [6]. Pyridostemine was also isolated by the Pyne group under another name, stemocurtisine and tested for larvicidal activity [7]. Later, this group reported the isolation and structure determination of stemocurtisinol [8]. In 2007, Ye group isolated four new [1,2-*a*]azepine alkaloids, namely cochinchistemonine, cochinchistemoninone, stemokerrin-*N*-oxide and oxystemokerrilactone from *S. cochinchinensis* and *S. saxorum* grown in Vietnam (Fig. **2**) [9, 10].

The interesting structure and diverse biological activities of *Stemona* alkaloids have attracted intensive research and numerous studies on the total synthesis of these alkaloids have been reported in the literature [2]. However, these studies focused on the construction of pyrrolo[1,2-*a*]azepine alkaloids. None of them involves the synthesis of a member of the pyrido[1,2-*a*]azepine alkaloids, although their biosynthesis has been documented [11]. Actually, studies on the synthesis of these alkaloids have been very limited. In 2015, Bach *et al*., reported the synthesis of the tricyclic precursor of pyrido[1,2-*a*]azepine alkaloids starting from 2,6-pyridinedicarboxylic acid in 17 synthetic steps [12]. Previously, I reported the construction of an A-B bicyclic ring system of stemocurtisine starting from glutamic acid [13]. Herein, the study reports on the synthesis of pyrido[1,2-*a*]azepine alkaloids by constructing the A-B ring core structure 1, following the retrosynthesis outlined in Scheme **1**.

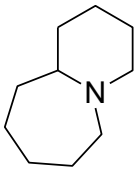

Fig. (1). Core structure of pyrido[1,2-*a*]azepine alkaloids.

In principle, the bicyclic compound **1** could be obtained from the ene-yne lactam **2** by a sequence of ene-yne ring-closing metathesis (RCM)/1,4-hydride reduction. Compound 2 could be synthesized from compound **3** in four synthetic steps. Compound **3** could be prepared from the epoxide **4** in six steps. This epoxide could be achieved from the *cis*-vinyl iodide **5** *via* a sequence of TBDPS (tert-butyldiphenylsillyl) protection, Sonogashira coupling and epoxidation. The vinyl

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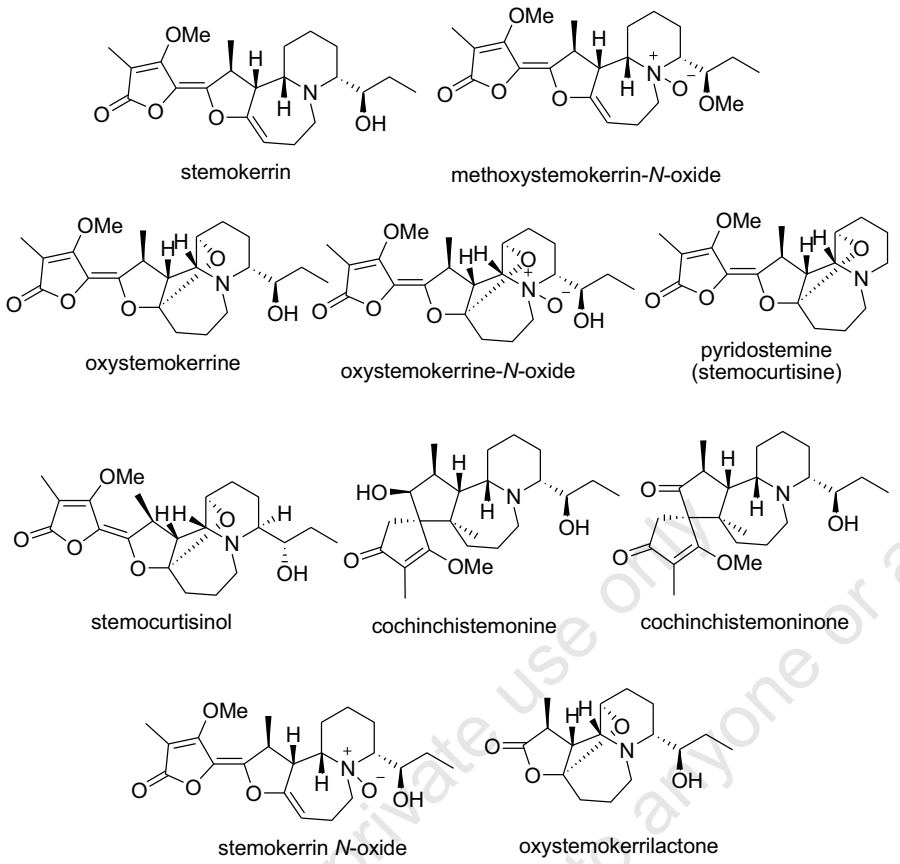
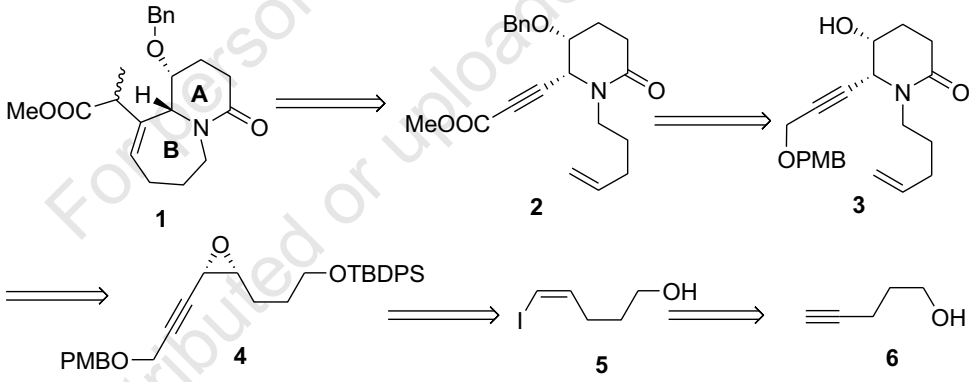


Fig. (2). Some isolated pyrido[1,2-*a*]azepine alkaloids.



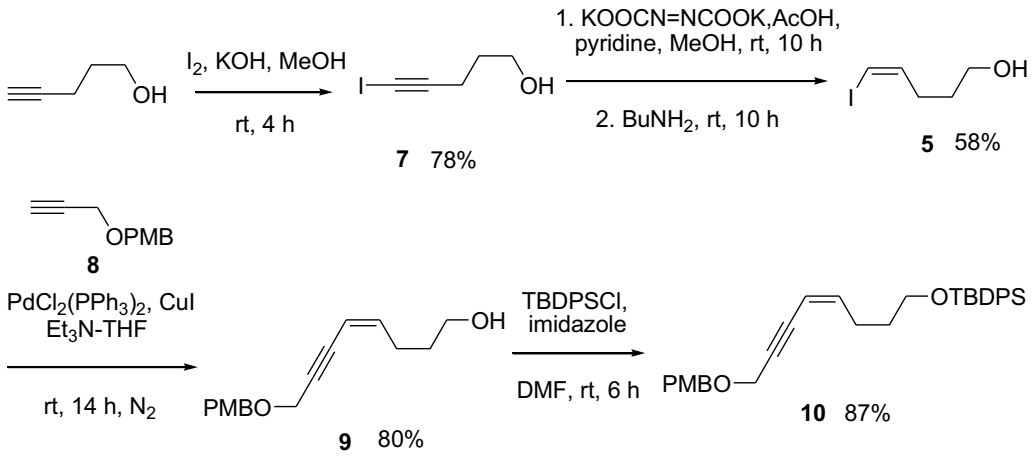
Scheme 1. Retrosynthetic analysis of the bicyclic compound 1.

iodide **5** could be obtained from the commercially available 4-pentyn-1-ol **6**.

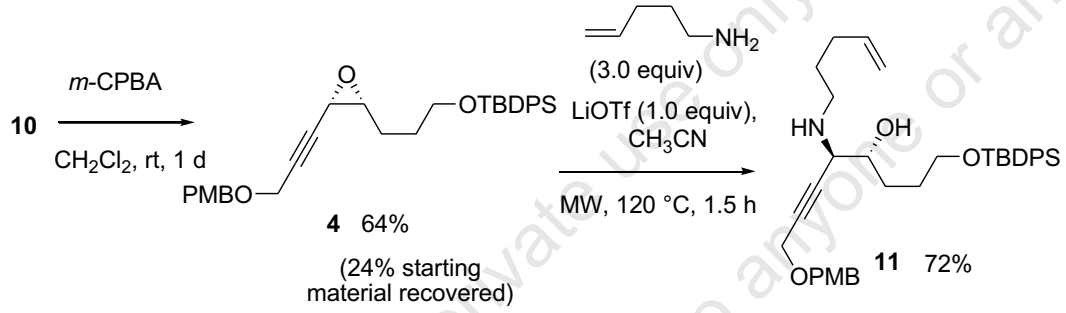
2. RESULTS AND DISCUSSION

The synthesis of *cis* iodine **5** was started from commercially available 4-pentyn-1-ol **6** following a procedure described by Denmark *et al*. [14]. Treatment of this alcohol with I_2/KOH in methanol (MeOH) led to the iodide **7**, which underwent *syn*-reduction of the alkyne by diimide (NH=NH), prepared *in situ* from potassium azodicarboxylate and acetic acid (AcOH), to give the known (*Z*)-vinyl iodide **5** in 58% yield (Scheme **2**). The Sonogashira coupling reaction between iodide **5** and the alkyne **8**, which was prepared from 4-methoxybenzyl chloride (PMBCl) and propargyl alcohol in two steps in high yields, worked smoothly with a favourable yield (80%) to provide the ene-yne **9**. Under TBDPS protection condition, compound **10** was provided in 87% yields from **9** (Scheme **2**).

Epoxidation of **10** using *m*- chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 gave the racemic epoxide **4** in 64% yield. From here, all products were obtained as racemic mixtures, however, only one enantiomer was displayed for convenience. The aminolysis reaction of **4** with pent-4-en-1-amine (3.0 equiv) and LiOTf (1.0 equiv) under microwave (MW)



Scheme 2. Synthesis of alkyne **10**.



Scheme 3. Synthesis of amino alcohol **11**.

heating at 120ºC for 1.5 h afforded the racemic amine **11** in 72% yield (Scheme **3**).

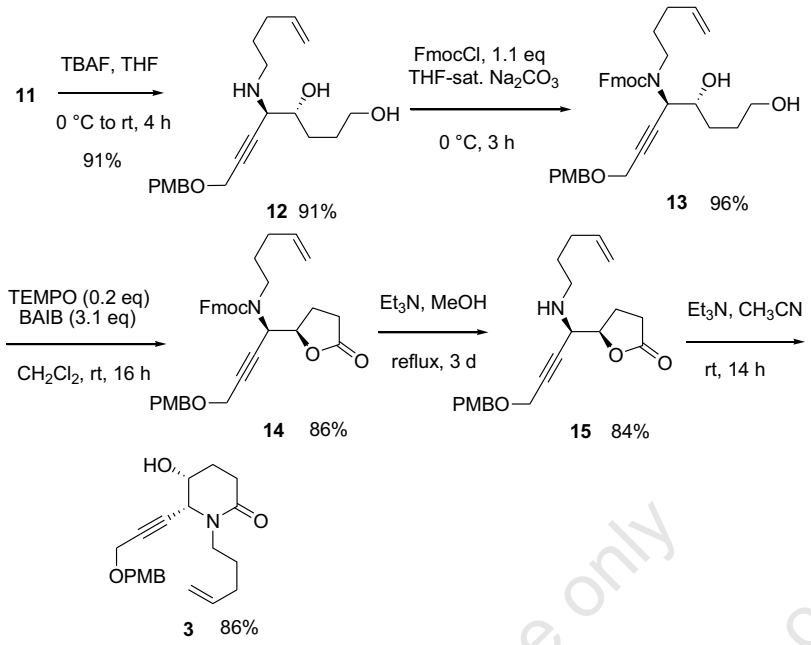
Removal of the TBDPS group of **11** by treatment with tetrabutylamoniumfluoride (TBAF) in tetrahedrofuran (THF) provided the diol **12** in 91% yield. Unfortunately, oxidation of **12** by various oxidation systems (TEMPO(2,2,6, 6-tetramethylpiperidin-1-yl)-oxyl)/BAIB (Bis(acetoxy) iodobenzene), TPAP (Tetrapropylammonium perruthenate)/NMO (N-methyl morpholine oxide)) gave a complex mixture of products instead of the desired lactone **15**. Thus, the diol **12** was converted into the Fmoc (fluorenylmethoxycarbonyl) derivative **13** in excellent yield (96%) by treatment with FmocCl in THF-sat. Na_2CO_3 at 0ºC for 4 h. Oxidation of the 1,4-diol **13** with TEMPO/BAIB in CH_2Cl_2 led to the corresponding δ-lactone **14** in good yield (86%). Finally, the Fmoc group of **14** was easily removed by treatment with Et_3N in CH_3CN in 89% yield, and the resulting lactone **15** was converted into the expected lactam **3** by heating with Et_3N in MeOH at reflux temperature in 86% yield (Scheme **4**).

The lactam **3** was converted into the ester **2** in four steps. Benzylation of the lactam **3** with benzyl bromide (BnBr), Ag_2O in Et_2O gave the corresponding benzyl ether **16** in very poor yield (29%). However, a great improvement was achieved (65% yield and 19% starting material recovered) under William's type conditions for benzylation [15]. Removal of PMB group in compound **16** was performed using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in CH_2Cl_2-H_2O at rt for 18 h to afford the desired product **17** in 78% yield. The primary alcohol group of **17** was converted into the ester **2** in 65% yield by a sequence of Jones' oxidation and esterification using MeI/K_2CO_3 in *N*,*N*-dimethylformamide (DMF) (Scheme **5**).

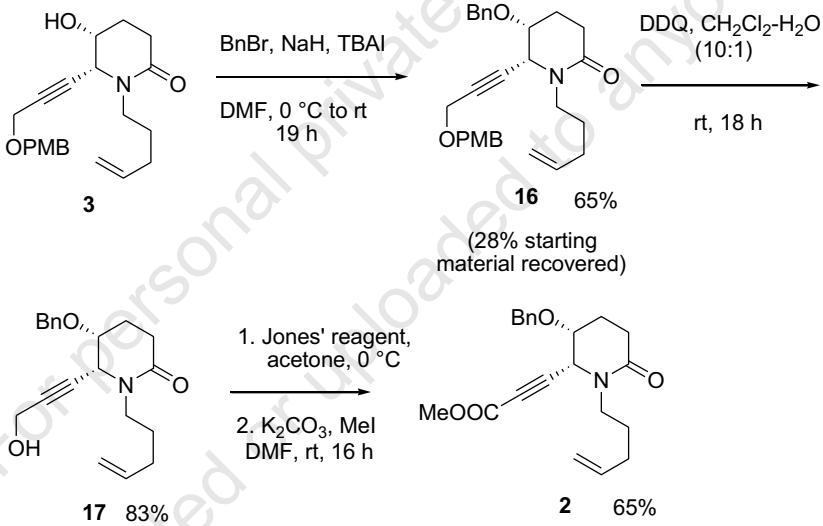
The bicyclic compound **18** was furnished in 80% yield *via* an ene-yne RCM reaction by treatment of the compound **2** with Grubbs' 1st generation Ru catalyst in CH_2Cl_2 for 8 h under a N_2 atmosphere (Scheme **3**) **14**. This compound was further reduced to the inseparable mixture of two diastereomers in 77% (dr =4:1, determined by 1H NMR) by treatment with $NaBH_4$/MeOH *via* a 1,4-"hydride" reduction reaction by Mori's procedure [16].

My next goal was to synthesize a mixture of the tricyclic **19** (Fig. **3**) from the bicyclic compound **1** (Seheme **6**). Mori, in his total synthesis of stemoamide [16], hydrolysed the ester **20**, which was synthesized from (-)-pyroglutamic acid in 12 steps, using NaOH/MeOH-H_2O at 0ºC for 7 h to furnish the corresponding acid. Then bromolactonization of this acid by treatment with $CuBr_2$ on alumina proceeded smoothly *via* a *5-endo-trig* cyclization, and two products **21** and **22** were obtained in 25% and 31% yields, respectively. Treatment of the bromide **21** with Et_3N in EtOAc converted it into compound **22** (total yield of **22** = 51%) (Scheme **7**). However, this bromolactonization reaction did not work with my compound **1**. The desired compound **19** did not form, and only the mixture of acid **23** was obtained (Scheme **7**).

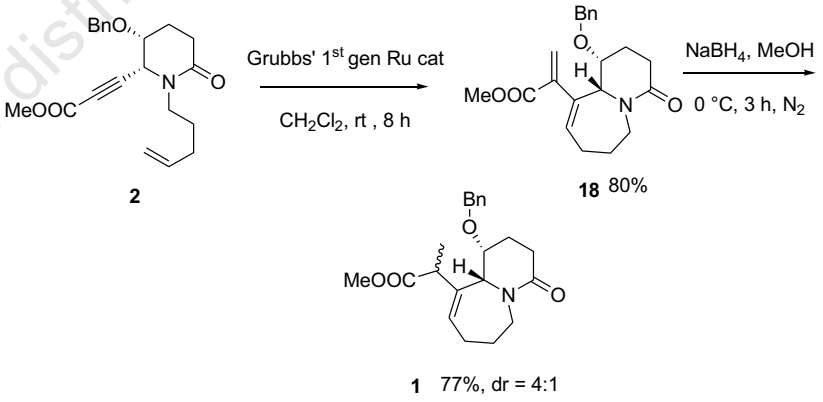
Swamy prepared the tricyclic lactone **25** from **24**, which was synthesized from L- malic acid in 10 steps, *via* a dihydroxylation process using K_2OsO_4/NMO [17]. Lactone **25**



Scheme 4. Synthesis of the lactam **3**.



Scheme 5. Synthesis of the compound **3**.



Scheme 6. Synthesis of the bicyclic compound **1**.

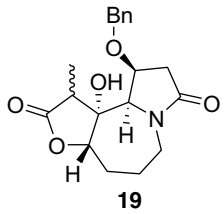


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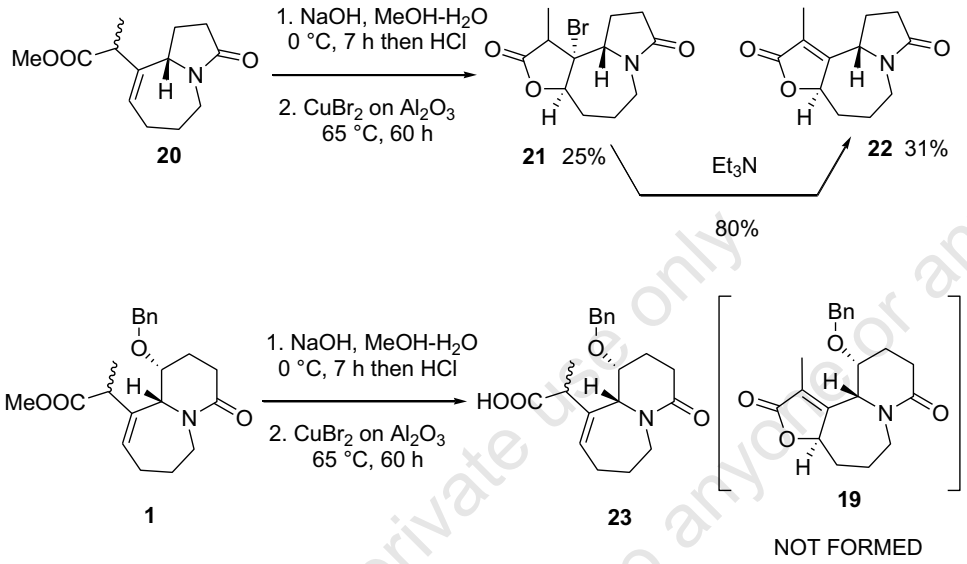
Fig. (3). Structure of compound **19**.



Scheme 7. Attempted bromolactonization of compounds 1 under Mori's procedure.

was obtained in moderate yield (56%) and relatively high diastereoselectivity (dr = 5:1) (Scheme **8**). Attempts at the dihydroxylation reactions of compounds **1** under Swamy's conditions were failed to form the desired product **19**. Our next attempt to dihydroxylate this compound using AD-mix-α and $MeSO_2NH_2$ using a co-solvent system of *t*-BuOH-H_2O was also unsuccessful. Only the starting materials were recovered (Scheme **8**). I am not sure why compound **1** was so unreactive towards these bromolactonization and dihydroxylation reaction conditions, when compared to the pyrrolidine analogues **20** and **24**.

3. EXPERIMENTAL SECTION

^1H and ^{13}C NMR spectra were recorded on a Varian Inova NMR Spectrometer (^1H NMR running at 500 MHz and ^{13}C NMR running at 125 MHz) instrument. $CDCl_3$ was used as the NMR solvent. ^1H NMR chemical shifts are quoted in δ values in ppm and are referenced relative to the chemical shift of $CDCl_3$ (7.26 ppm). Low-resolution mass spectra were obtained on a Shimadzu GC spectrometer (EI) or Water LCZ single quadrupole (ESI). High resolution spectra were obtained on a VG Autospec mass spectrometer (EI) or Waters QTOF (ESI). Infrared spectra were obtained as neat samples on a Smart Omni-Sampler Avator ESP Nicolet-Brand. 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.

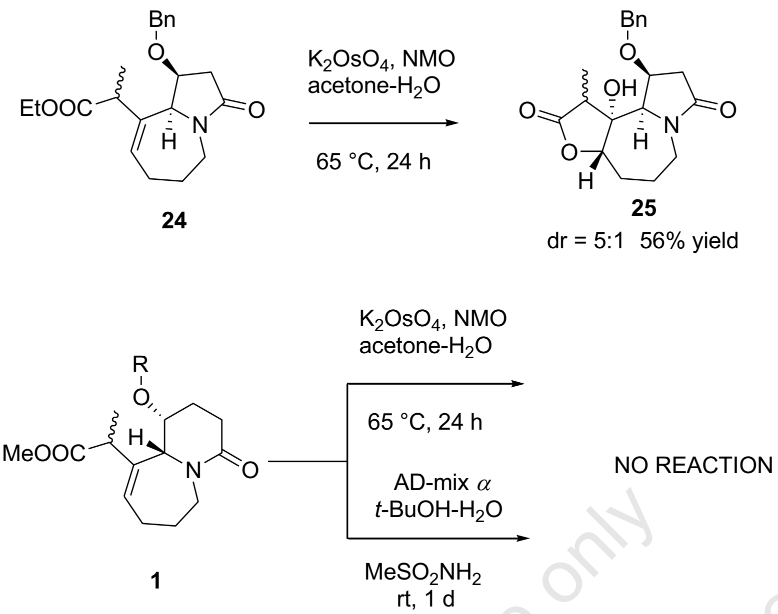
3.1. General Procedure for Preparation of all Compounds and their Spectroscopic Data

3.1.1. 5-Iodo-4-pentyn-1-ol (7)

A solution of KOH (8.40 g, 150 mmol, 2.5 equiv) in H_2O (12 mL) was added to a solution of 4-pentyn-1-ol (5.04 g, 60 mmol). Then I_2 (16.76 g, 66 mmol, 1.1 equiv) was added portion-wise to the resulting solution over a period of 30 min. After being stirred 3 h at rt, a saturated solution of $Na_2S_2O_3$ (60 mL) was added and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were concentrated by rotary evaporation to give a brown residue. The residue was dissolved in CH_2Cl_2 (100 mL), which was washed with brine (50 mL) and then was dried over Na_2SO_4 and filtered. The solvent was removed by rotary evaporation to give the crude product which was purified by column chromatography to afford the iodide **7** (9.69g, 75% yield) as a colourless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 3.74 (t, *J* = 6.0 Hz, 2H), 2.50 (t, *J* = 7.0 Hz, 2H), 1.80 – 1.74 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 94.2, 61.8, 31.4, 17.7, -5.9. NMR spectroscopic data matched with the published data [14].

3.1.2. (Z)-5-Iodo-4-penten-1-ol (5)

To a solution of alkyne **7** (9.69 g, 46 mmol) in MeOH (80 mL), pyridine (21,1 mL, 276 mmol, 6.0 equiv) and potassium azodicarboxylate were added (5.37 g, 27.7 mmol, 0.6 equiv) sequentially at rt. Acetic acid (16.7 mL, 292 mmol, 6.3 equiv) was then added slowly *via* a syringe pump



Scheme 8. Attempted bromolactonization of compounds **1** under Swamy's procedure.

over 10 h at rt. During the addition of acetic acid, additional potassium azodicarboxylate (0.6 equiv) was added at 2 h, 4 h, 6 h, and 8 h, respectively. After the complete addition of the acetic acid, the mixture was poured into a 1-L beaker together with Et_2O (150 mL) and aqueous HCl solution 1M (300 mL). The aqueous layer was extracted with Et_2O (3 x 150 mL) and the combined organic layers were concentrated by rotary evaporation to give a pale yellow residue. The residue was dissolved in Et_2O (150 mL), which was washed with aqueous 1M HCl solution (2 x 75 mL), saturated aqueous $NaHCO_3$ solution (100 mL) and brine (100 mL), then was dried over Na_2SO_4 and filtered. After removal of the solvent, the residue was treated with *n*-$BuNH_2$ (8 mL) and the solution was stirred at rt for 10 h to remove the over-reduced product. The mixture was dissolved in Et_2O (150 mL), which was washed with aqueous 1M HCl solution (2 x 100 mL), saturated aqueous $NaHCO_3$ (100 mL) solution, and brine (100 mL), then was dried over Na_2SO_4 and filtered. After removal of the solvent, the residue was purified by column chromatography to give the (*Z*)-vinyl iodide **5** (6.15 g, 58% yield) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.25-6.17 (m, 2H), 3.68 (t, *J* = 8.5 Hz, 2H), 2.25 (q, *J* = 7.0 Hz, 2H), 1.74 – 1.66 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.9, 83.4, 62.4, 31.5, 31.1. NMR spectroscopic data matched with the published data [14].

3.1.3. 1-(4-Methoxybenzyloxy)-2-propyne (8)

To a solution of propargyl alcohol (1.50 mL, 25.8 mmol) in anhydrous THF (70 mL), NaH (1.86 g, 60 wt% in oil, 46.4 mmol, 1.8 equiv) was added portionwise at 0ºC and the mixture was stirred for 15 min. Then *p*-methoxybenzyl chloride (5.20 mL, 38.7 mmol, 1.5 equiv) and TBAI (1.24 g, 3.35 mmol, 0.13 equiv) were added at 0ºC. The reaction mixture was warmed to rt and stirred for 16 h. Then the mixture was cooled to 0ºC and diluted with Et_2O (50 mL) and saturated aqueous NH_4Cl solution (50 mL) was added. The organic layer was separated and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography to give the alkyne **8** (3.33 g, 74% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 2H), 4.58 (s, 2H), 4.17 (d, *J* = 2.5 Hz, 2H), 3.84 (s, 3H), 2.49 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 130.1, 129, 114.2, 80.1, 74.8, 71.5, 57.0, 55.6. NMR spectroscopic data matched with the published data [18].

3.1.4. (Z)-8-(4-Methoxybenzyloxy)oct-4-en-6-yn-1-ol (9)

To a solution of the vinyl iodide **5** (1.484 g, 7 mmol) in Et_3N (50 mL), $PdCl_2(PPh_3)_2$ (112 mg, 0.154 mmol, 0.02 equiv) and CuI (267 mg, 1.54 mmol, 0.2 equiv) were added under a nitrogen atmosphere.The mixture was stirred for 15 min then a solution of alkyne **8** (1.48 g, 8.4 mmol, 1.2 equiv) 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 to give the ene-yne **9** (1.456 g, 80% yield) as a colourless oil. 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), 6.90 (d, *J* = 8.5 Hz, 2H), 5.97 (dt, *J* = 10.5, 7.5 Hz, 1H), 5.57 (d, *J* = 10.5 Hz, 1H), 4.56 (s, 2H), 4.30 (s, 2H), 3.82 (s, 3H), 3.67 (t, *J* = 6.5 Hz, 2H), 2.44 (q, *J* = 7.5 Hz, 2H), 1.73 – 1.67 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159., 143.9, 130.1, 129.8, 114.2, 109.7, 90.0, 83.4, 71.5, 62.4, 57.9, 55.6, 31.9, 26.9. ESIMS *m/z* 283 [(M+Na)$^+$ 100%]. HRESIMS calcd. for $C_{16}H_{20}O_3Na$, (M+Na)$^+$ 283.1316, found 283.1316.

*3.1.5. (Z)-tert-Butyl(8-(4-*methoxybenzyloxy*)oct-4-en-6-ynyloxy)diphenylsilane (10)*

Imidazole (0.957 g, 13.95 mmol, 2.5 equiv) and TBDPSCl (1.75 mL, 6.69 mmol, 1.2 equiv) were added to a solution of alcohol **9** (1.456 g, 5.58 mmol) in DMF (30 mL) at rt

under a N_2 atmosphere and the mixture was stirred under the same conditions for 6 h. The reaction mixture then was poured into a beaker containing water (60 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 to give the TBS ether **10** (2.422 g, 87% yield) as a colourless oil. IR (neat, ν_{max}/cm^{-1}): 2931, 2856, 1513, 1426, 1248, 1107, 821, 739. ^{1}H NMR (500 MHz, CDCl3) δ 7.69-7.63 (m, 4H), 7.46 – 7.33 (m, 6H), 7.26 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 5.92 (dt, *J* = 10.7, 7.4 Hz, 1H), 5.50 (d, *J* = 10.7 Hz, 1H), 4.52 (s, 2H), 4.26 (s, 2H), 3.79 (s, 3H), 3.69 (t, *J* = 6.3 Hz, 2H), 2.45 – 2.41 (m, 2H), 1.72 – 1.64 (m, 2H), 1.04 (s, 9H). ^{13}C NMR (125 MHz, CDCl3) δ 159.7, 144.4, 135.9, 134.3, 130.2, 130.1, 130.0, 129.9, 128.0, 127.9, 109.1, 89.8, 83.5, 71.4, 63.7, 57.9, 55.6, 32.2, 27.3, 27.2, 19.6. ESIMS *m/z* 521 [(M+Na)$^+$ 100%]. HRESIMS calcd. for $C_{32}H_{38}O_3SiNa$, (M+Na)$^+$ 521.2488, found 521.2478.

3.1.6. tert-Butyl(3-((2R,3S*)-3-(3-(4-methoxybenzyloxy) prop-1-ynyl)oxiran-2-yl)propoxy)diphenylsilane (4)*

Purified *m*-chloroperbenzoic acid (1.080 g, 6.26 mmol, 1.3 equiv) was added to solution of the alkene **10** (2.4 g, 4.82 mmol) in CH_2Cl_2 (100 mL) and the mixture was stirred at rt for 14 h. The reaction was quenched with saturated $NaHCO_3$ (60 mL) and the aqueous phase was extracted with Et_2O (3x 100 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 to give the epoxide **4** (2.055 g, 64% yield) as a colourless oil and the starting alkene (576 mg, 24% yield). IR (neat, ν_{max}/cm^{-1}): 3282, 2957, 2308, 1428, 1107, 818, 668. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72-7.64 (m, 4H), 7.43 – 7.34 (m, 6H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.49 (s, 2H), 4.14 (s, 2H), 3.79 (s, 3H), 3.73 (t, *J* = 5.6 Hz, 2H), 3.50 (d, *J* = 3.5 Hz, 1H), 3.09 (dd, *J* = 6.0, 3.5 Hz, 1H), 1.86 – 1.75 (m, 4H), 1.04 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 135.9, 135.1, 134.2, 130.1, 130.0, 129.9, 129.6, 128.1, 128.0, 114.2, 82.0, 81.8, 71.6, 63.8, 58.3, 57.3, 55.6, 45.6, 29.3, 27.2, 26.9, 19.6. ESIMS *m/z* 537 [(M+Na)$^+$ 100%]. HRESIMS calcd. for $C_{32}H_{38}O_4SiNa$, (M+Na)$^+$ 537.2439, found: 537.2437.

3.1.7. (4R,5R)-1-((tert-butyldiphenylsilyl)oxy)-8-((4-methoxybenzyl)oxy)-5-(pent-4-en-1-ylamino)oct-6-yn-4-ol (11)

Lithium triflate (0.63 g, 3.89 mmol, 1 equiv) and pent-4-en-1-amine (0.661 g, 7.78 mmol, 2 equiv) were added to solution of the epoxide **4** (2.0 g, 3.89 mmol) in CH_3CN (2 mL) in a microwave reactor vial. The mixture was heated in a microwave reactor at 110ºC, 200 W for 1.5 h. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography to give the amine **11** (1.723 mg, 74% yield) as a pale yellow oil. IR (neat, ν_{max}/cm^{-1}): 3346, 2928, 1623, 1518, 1256, 1113, 1013, 847, 709. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.0 Hz, 4H), 7.42-7.35 (m, 6H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 5.82 (ddt, *J* = 17; 10.0; 6.5, Hz 1H), 5.04 (d, *J* = 17.0 Hz, 1H), 4.97 (d, *J* = 10.0 Hz, 1H), 4.50 (s, 2H), 4.15 (s, 2H), 3.80 (s, 3H), 3.44 (td, *J* = 8.5; 2.0 Hz, 2H), 3.14 (d, *J* = 9.0 Hz, 2H), 2.96-2.87 (m, 1H), 2.67-2.60 (m, 1H), 2.13 (q, *J* = 7.0 Hz, 1H), 2.00 – 1.92 (m, 1H), 1.84 (qd, *J* = 12.0; 6.0 Hz, 1H) 1.76 – 1.67 (m, 1H), 1.61 (dq, *J* = 13.5; 7.0 Hz, 1H), 1.55-146 (m, 1 H), 1.05 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 138.5, 135.8, 135.7, 134.2, 130.0, 129.8, 127.8, 115.1, 111.1, 85.5, 81.3, 72.8, 71.5, 64.2, 57.4, 56.2, 55.5, 46.9, 31.7, 30.3, 29.5, 28.9, 27.1, 19.4. ESIMS *m/z* 572 [(M+Na)$^+$ 100%]. HRESIMS calcd, for $C_{35}H_{46}O_4NSiNa$, (M+Na)$^+$ 572.3224, found: 572.3196.

3.1.8. (4R,5R*)-8-(4-Methoxybenzyloxy)-5-(pent-4-enylamino) oct-6-yne-1,4-diol (12)*

1M tetrabutylamonium fluoride solution in THF (3.8 mL, 3.8 mmol, 1.5 equiv) was added dropwise to a solution of the TBS ether **11** (1.19 g, 2.5 mmol) in THF (30 mL) at 0ºC and the mixture was warmed to rt and stirred for 4 h. Saturated $NaHCO_3$ solution (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 to give the diol **12** (890 mg, 91% yield) as a colourless oil. 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), 6.90 (d, *J* = 8.5 Hz, 2H), 5.82 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H), 5.04 (d, *J* = 17.0, 1H), 4.98 (d, *J* = 10.0 Hz, 1H), 4.52 (s, 2H), 4.17 (s, 2H), 3.82 (s, 3H), 3.74-3.64 (m, 2H), 3.48 – 3.43 (m, 1H), 3.15 (d, *J* = 9.0 Hz, 1H), 2.90 (dt, *J* = 11.5, 7.0 Hz, 1H), 2.63 (dt, *J* = 11.5, 7.0 Hz, 1H), 2.14 (q, *J* = 7.0 Hz, 2H), 2.04 – 1.95 (m, 1H), 1.83 – 1.74 (m, 2H), 1.63-1.59 (m, 2H), 1.58 – 1.48 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 138.5, 130.1, 129.7, 115.3, 114.2, 85.2, 81.7, 73.0, 71.6, 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'). ESIMS *m/z* 362 [(M+H)$^+$ 100%]. HRESIMS calcd. for $C_{21}H_{32}O_4N$, (M+H)$^+$ 362.2321, found: 362.2331.

3.1.9. (9H)-Fluoren-9-yl)methyl (4R,5R*)-5,8-dihydroxy-1-(4-methoxybenzyloxy)oct-2-yn-4-yl(pent-4-enyl)carbamate (13)*

To a solution of the amine **12** (975 mg, 2.7 mmol) in THF (40 mL), a saturated solution of Na_2CO_3 (20 mL) was added and the mixture was allowed to cool to 0ºC. FmocCl (768 mg. 2.97 mmol, 1.1 equiv) was added portionwise at 0ºC 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 to give the Fmoc-diol **13** (1.511 g, 96% yield) as a waxy solid. IR (neat, ν_{max}/cm^{-1}): 3436, 2927, 1687, 1611, 1458, 1248, 1066, 1032, 739. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (*J* = 8.5 Hz, 2H), 7.59 (*J* = 8.5 Hz, 2H), 7.39 (t, *J* = 8.5 Hz, 2H), 7.31 (t, *J* = 8.5 Hz, 2H), 7.23 (*J* = 9.0 Hz, 2H), 6.87 (*J* = 9.0 Hz, 2H), 5.72-5.62 (bm, 1H), 5.01-4.90 (bm, 2H), 4.77-4.72 (bm, 1H), 4.67-4.57 (bm, 2H), 4.47 (s, 2H), 4.23 (t, *J* = 6.0 Hz. 1H), 4.12 (s, 2H), 3.80 (s, 3H), 3.67-3.58 (bm, 3H), 3.12-2.97 (bm, 2H), 1.90-1.80 (bm, 2H), 1.75-1.65 (bm, 2H), 1.55-1.40 (bm, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 144.1, 141.6, 138.0, 129.9, 129.5, 127.9, 127.3, 124.9, 120.2, 115.2, 114.1, 82.5, 82.2, 73.0 , 71.5, 67.2, 63.0, 57.2, 55.5, 54.9, 47.7, 45.6, 31.4, 31.2, 29.4, 28.8. ESIMS *m/z* 606 [(M+Na)$^+$ 100%]. HRESIMS calcd. for $C_{36}H_{41}O_6NNa$, (M+Na)$^+$ 606.2832, found: 606.2822.

3.1.10. (R)-5-((R*)-4-(4-Methoxybenzyloxy)-1-(pent-4-enylamino)but-2-ynyl)dihydrofuran-2(3H)-one (15)*

Triethylamine (5 mL) was added to a solution of the Fmoc-lactone **14** (1.080 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 to give the lactone **15** (0.597 g, 89% yield) as a pale yellow oil. 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), 6.89 (d, *J* = 8.5 Hz, 2H), 5.82 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H), 5.03 (d, *J* = 17.0 Hz, 1H), 4.97 (d, *J* = 10.0 Hz, 1H), 4.60 (dd, *J* = 7.0, 5.5 Hz, 1H), 4.52 (s, 2H), 4.17 (s, 2H), 3.81 (s, 3H), 3.59 (d, *J* = 5.5 Hz, 1H,), 2.92 (dt, *J* = 11.5, 7.0 Hz), 2.67 – 2.59 (m, 2H), 2.54 (m, 1H), 2.39 – 2.31 (m, 1H), 2.27 – 2.19 (m, 1H), 2.12 (q, *J* = 7.0 Hz, 2H), 1.64 – 1.55 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 159.7, 138.5, 130.0, 129.6, 115.1, 114.2, 83.7, 81.7, 81.4, 71.6, 57.3, 55.6, 54.7, 47.6, 31.7, 29.4, 28.7, 24.5. ESIMS *m/z* 380 [(M+Na)$^+$ 100%]. HRESIMS calcd. for $C_{21}H_{27}O_4NSiNa$, (M+Na)$^+$ 380.1838, found: 380.1842.

3.1.11. (5R,6R*)-5-Hydroxy-6-(3-(4-methoxybenzyloxy)prop-1-ynyl)-1-(pent-4-enyl)piperidin-2-one (3)*

To solution of the amino-lactone **15** (580 g, 1.62 mmol) in MeOH (7 mL), Et_3N (1.6 mL) was added and the mixture was stirred at reflux temperature for 3 days. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography to afford the lactam **3** (503 mg, 86% yield) as a pale yellow oil. 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), 6.87 (d, *J* = 7.5 Hz, 2H), 5.79 (ddt, *J* = 17.0, 10.0, 4.5 Hz, 1H), 5.01 (d, *J* = 17.0 Hz, 1H), 4.95 (d, *J* = 10.0 Hz, 1H), 4.49 (s, 2H), 4.32 (s, 1H), 4.17 (s, 2H), 4.01 – 3.95 (m, 1H), 3.79 (s, 3H), 3.81 – 3.71 (m, 1H), 3.12 (dt, *J* = 14.0, 7.0 Hz 1H), 2.59-2.53 (m, 1H), 2.38 (dt, *J* = 11.5, 7.0 Hz, 1H), 2.14 – 2.02 (m, 3H), 1.95-1.88 (m, 1H), 1.76 – 1.62 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 159.8, 138.0, 130.2, 129.3, 115.4, 114.2, 83.2, 81.8, 71.9, 66.8, 57.3, 55.6, 55.2, 46.2, 31.4, 29.8, 29.5, 26.7. ESIMS *m/z* 380 [(M+Na)$^+$ 100%]. HRESIMS calcd. for $C_{21}H_{27}O_4NSiNa$, (M+Na)$^+$ 380.1838, found: 380.1839.

3.1.12. (5R,6R*)-5-(Benzyloxy)-6-(3-(4-methoxybenzyloxy) prop-1-ynyl)-1-(pent-4-enyl)piperidin-2-one (16)*

Sodium hydride in mineral oil (60%, 60 mg, 1.5 mmol, 1.5 equiv), BnBr (300 µL, 2.5 mmol, 2.5 equiv) and Bu_4NI (37 mg, 0.1 mmol, 0.1 equiv) were added to a solution of the alcohol **3** (358 mg, 1 mmol) in DMF (15 mL) at 0ºC and the resultant mixture was warmed to rt and stirred for 19 h. The reaction mixture was diluted with EtOAc (15 mL), quenched with water (5 mL) and the aqueous layer extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with water (2 x 20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. This was purified by column chromatography to give the benzyl ether **16** (291 mg, 65%) as a colourless oil and the starting alcohol **3** (100 mg, 28%). IR (neat, ν_{max}/cm^{-1}): 2947, 2317, 1639, 1513, 1249, 1168, 1098, 1070, 1028, 698. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 7.24 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.2 Hz, 2H), 5.80 (ddt, *J* = 17.1, 10.2, 6.5 Hz, 1H), 5.02 (d, *J* = 17.1 Hz, 1H), 4.97 (d, *J* = 10.2 Hz, 1H), 4.67 (d, *J* = 11.8 Hz, 1H), 4.63 (d, *J* = 11.8 Hz, 1H), 4.52 (s, 2H), 4.39 (d, *J* = 2.7 Hz, 1H), 4.18 (s, 2H), 3.80 (s, 3H), 3.76 (dd, *J* = 14.8, 5.4 Hz, 2H), 3.16 – 3.09 (m, 1H), 2.63 – 2.56 (m, 1H), 2.42-2.34 (m, 1H), 2.26 – 2.16 (m, 1H), 2.07 – 2.00 (m, 3H), 1.69-1.63 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 159.6, 142.0, 137.8, 130.5, 129.6, 129.1, 128.5, 128.1, 115.5, 114.1, 85.2, 79.0, 73.5, 73.4, 71.5, 57.1, 55.7, 51.7, 46.2, 31.4, 29.5, 26.7, 23.7. ESIMS *m/z* 470 [(M+H)$^+$ 100%]. HRESIMS calcd. for $C_{28}H_{33}O_4NNa$, (M+Na)$^+$ 470.2034, found 470.2032.

3.1.13. (5R,6R*)-5-(Benzyloxy)-6-(3-hydroxyprop-1-ynyl)-1-(pent-4-enyl)piperidin-2-one (17)*

To a mixture of the PMB ether **16** (270 mg, 0.6 mmol) in CH_2Cl_2 (10 mL) and water (1 Ml,) DDQ (246 mg, 1.08 mmol, 1.8 equiv) was added portionwise at 0ºC and the mixture was allowed to stirr at rt for 18 h. Then the mixture was diluted with CH_2Cl_2 (80 mL) and washed with water (2 x 4mL). The organic layer was dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography to give the primary alcohol **17** (166 mg, 83% yield) as a pale yellow oil. IR (neat, ν_{max}/cm^{-1}): 3320, 2926, 2313, 1697, 1620, 1453, 1411, 1270, 1163, 1095, 1070, 914, 740. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.26 (m, 5H), 5.78 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H), 5.02 (d, *J* = 17.0 Hz, 1H), 4.97 (d, *J* = 10.5 Hz, 1H), 4.64 (d, *J* = 17.0 Hz, 1H), 4.61 (d, *J* = 17.0 Hz, 1H), 4.33 (s, 1H), 4.27 (s, 2H), 3.77 – 3.68 (m, 2H), 3.14 – 3.06 (m, 1H), 2.61-2.55 (m, 1H), 2.42 – 2.32 (m, 1H), 2.23 – 2.12 (m, H), 2.06 – 1.99 (m, 2H), 1.99-1.93 (m, 1H), 1.68 – 1.59 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 138.0, 137.6, 128.9, 128.4, 128.1, 115.4, 84.8, 80.7, 73.5, 71.5, 52.5, 51.1, 46.5, 31.3, 29.5, 26.6, 23.9. ESIMS *m/z* 350 [(M+Na)$^+$ 100%]. HRESIMS calcd. for $C_{20}H_{25}O_3NNa$, (M+Na)$^+$ 350.1732, found: 350.1718.

3.1.14. Methyl 3-((2R,3R*)-3-(benzyloxy)-6-oxo-1-(pent-4-enyl)piperidin-2-yl)propiolate (2)*

To a solution of the primary alcohol **17** (152 mg, 0.46 mmol) in acetone (3 mL), Jones' reagent (480 µL) was added dropwise at 0ºC. After stirring for 30 min at 0ºC, CH_3OH (0.1 mL) was added at the same temperature and the reaction mixture was stirred for additional 10 min. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 20 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* to give the crude acid (152 mg, 91% yield) as a yellow solid which was used in the next step without further purification. This acid was dissolved into anhydrous DMF (2 mL). Then K_2CO_3 (123 mg, 0.90 mmol, 2 equiv) was added at rt and the mixture was stirred for 15 min under a N_2 atmosphere. MeI (160 µL, 2.56 mmol, 6 equiv) was then added and the mixture was stirred at rt for 14 h. Water (10 mL) was added and the mixture was extracted with EtOAc (3 x 20 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 to give the methyl ester **2** (110 mg, 71% yield) as a pale yellow oil. IR (neat, ν_{max}/cm^{-1}): 2916, 2376, 2313, 1718, 1620, 1272, 1099, 698. H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.26 (m, 5H), 5.72 (ddt,

J = 17.0, 10.0, 6.5 Hz, 1H), 4.95 (d, *J* = 17.0 Hz, 1H), 4.91 (d, *J* = 10.0 Hz, 1H), 4.58 (s, 2H), 4.33 (d, *J* = 3.5 Hz, 1H), 3.73 (s, 3H), 3.73-3.63 (m, 2H), 3.03 (dt, *J* = 13.5, 7.5 Hz, 1H), 2.57-2.51 (m, 1H), 2.35-2.25 (m, 1H), 2.15-2.06 (m, 1H), 2.03-1.92 (m, 3H), 1.61-1.54 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 153.7, 138.0, 137.6, 129, 128.9, 128.1, 115.5, 83.3, 77.2, 73.4, 71.7, 53.2, 52.8, 46.6, 31.3, 29.7, 26.7, 24.5. ESIMS *m/z* 378 [$(M+Na)^+$ 100%]. HRESIMS calcd. for $C_{21}H_{25}O_4NNa$, $(M+Na)^+$, 378.1681, found; 378.1674.

3.1.15. Methyl 2-((1R,10aR*)-1-(benzyloxy)-4-oxo-1,2,3,4,6,7,8,10a-octahydropyrido[1,2-a]azepin-10-yl)acrylate (18)*

To a solution of the ene-yne **2** (100 mg, 0.28 mmol) in anhydrous CH_2Cl_2 (40 mL), Grubb's 1st generation Ru catalyst (23,2 mg, 0.028 mmol, 0.1 equiv) was added 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 to give the bicyclic compound **18** (79 mg, 80% yield) as a pale yellow oil. IR (neat, ν_{max}/cm^{-1}): 2937, 1740, 1635, 1623, 1451, 1250, 1171, 1050, 726. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 5H), 6.10 (s, 1H), 5.88 (dd, *J* = 8.5, 6.5 Hz, 1H), 5.54 (s, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.36 (d, *J* = 12.5 Hz, 2H), 4.24 (dd, *J* = 12.7, 7.3 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 1H), 3.20 (td, *J* = 12.7, 6.8 Hz, 1H), 2.72 – 2.61 (m, 1H), 2.39-2.33 (m, 1H), 2.24 – 2.14 (m, 1H), 1.94 – 1.86 (m, 1H), 1.77-1.69 (m, 1H), 1.63 – 1.53 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 167.3, 142.1, 138.6, 136.4, 132.2, 128.6, 128.4, 127.6, 127.3, 71.9, 70.9, 66.7, 52.5 , 42.7, 27.2, 24.0, 23.5, 21.8. ESIMS *m/z* 378 [$(M+Na)^+$ 100%]. HRESIMS calcd. for $C_{21}H_{25}O_4NNa$, $(M+Na)^+$, 378.1697, found; 378.1681.

3.1.16. Methyl 2-((1R,10aR*)-1-(benzyloxy)-4-oxo-1,2,3,4,6,7,8,10a-octahydropyrido[1,2-a]azepin-10-yl)propanoate (1)*

Sodiumborohydride (68 mg, 1.8 mmol, 9 equiv) was added portionwise to a solution of the enone **8** (72 mg, 0.2 mmol) in anhydrous MeOH (4 mL) at 0ºC under a N_2 atmosphere and the mixture was stirred at 0ºC for 3 h. Saturated aqueous $NaHCO_3$ solution (10 mL) was added at 0ºC and the mixture was extracted with EtOAc (3 x 20 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 to give **1** (56 mg, 77% yield) as a pale yellow oil as an inseparable mixture of diastereomers. IR (neat, ν_{max}/cm^{-1}): 2940, 1730, 1626, 1454, 1276, 1246, 1173, 1108, 1098, 736, 717. ^{1}H NMR (500 MHz, $CDCl_3$) *major diastereomer* δ 7.34 – 7.24 (m, 5H), 5.88 (t, *J* = 7.0 Hz, 1H), 4.60 (d, *J* = 11.0 Hz, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 4.20 (dd, *J* = 13.2, 7.3 Hz, 1H), 4.04 (s, 1H), 3.99 (s, 1H), 3.67 (s, 3H), 2.95 (q, *J* = 7.0 Hz, 1H), 2.86-2.76 (m, 1H), 2.74-2.64 (m, 1H), 2.64-2.56 (m, 1H), 2.37 (dd, *J* = 17.5, 5.5 Hz, 1H), 2.27-2.20 (m, 1H), 2.17-2.09 (m, 1H), 1.91-1.73 (m, 2H), 1.52-1.43 (m, 1H), 1.32 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) *major diastereomer* δ 174.8, 169.6, 138.8, 136.8, 128.6, 127.7, 127.6, 127., 72.4, 71.2, 69.2, 52.3, 44.3, 43.0, 27.2, 24.0, 23.9, 21.2, 19.1 . ^{1}H NMR (500 MHz, $CDCl_3$) *minor diastereomer* δ 7.34 – 7.24 (m, 5H), 5.88 (t, *J* = 7 Hz, 1H), 4.60 (d, *J* = 11.0 Hz, 1H), 4.40 (d, *J* = 11.0 Hz, 1H), 4.18 (dd, *J* = 13.2, 7.3 Hz, 1H), 4.11 (s, 1H), 3.86 (s, 1H), 3.56 (s, 3H), 2.92-2.87 (m, 1H), 2.86-2.76 (m, 1H), 2.74-2.64 (m, 1H), 2.64-2.56 (m, 1H), 2.37 (dd, *J* = 17.5, 5.5 Hz, 1H), 2.27-2.20 (m, 1H), 2.17-2.09 (m, 1H), 1.91-1.73 (m, 2H), 1.52-1.43 (m, 1H), 1.29 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *minor diastereomer* δ 175.3, 169.5, 138.4, 134.4, 128.6, 127.9, 127.7, 127.2, 72.4, 71.0, 69.1, 52.4, 44.3, 42.8, 27.2, 24.0, 23.9, 21.3, 16.5. ESIMS *m/z* 358 [$(M+H)^+$ 100%]. HRESIMS calcd. for $C_{21}H_{28}O_4N$, $(M+H)^+$ 358.2018, found: 358.2001.

CONCLUSION

This study demonstrated the synthesis of pyrido[1,2-*a*]azepine alkaloids by constructing the bicyclic structure **1**. This compound was synthesized in 17 steps from the commercially available 4-pentyn-1-ol in 1.7% overall yield. The key steps involve oxidation of 1,4 diol to lactone and an ene-yne ring-closing metathesis reaction. Unfortunately, all attempts to prepare the tricyclic compound **19** from the bicyclic **1** were unsuccessful. In the future, other methods for halolactonization of **1** will be examined. Another direction will be the preparation of all products from compound **4** as single enantiomers by using asymmetric epoxidation. Compared to the previous study [11], this synthetic route required more steps and a lower overall yield. However, if the synthesis of the tricyclic compound **19** was successful, the synthesis of pyrido[1,2-*a*]azepine alkaloids such as stemocurtisine could be accomplished in several synthetic steps.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

All data generated or analysed during this study are included in this published article [and its supplementary information files].

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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