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# Total synthesis of 275A lehmizidine frog skin alkaloid (or of its enantiomer)

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ABSTRACT

A concise asymmetric total synthesis of the potentially bioactive 275A lehmizidine frog skin alkaloid (or of its enantiomer) is described. Key features of the protocol include an acyliminium butenyl Grignard addition and a seven-membered intramolecular reductive amination step. Both reactions ensure a high degree of diastereocontrol, with installation of the same relative configuration at the C3, C5 and C10 stereocentres as in the natural product 275A. Despite this total synthesis, the absolute configuration of the natural product remains unknown, due to the lack of specific rotation data for alkaloid 275A.

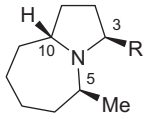


## 1. Introduction

Dendrobatid frogs of Central and South America have been a large source of synthetically interesting and biologically active compounds with over 800 alkaloids that encompass over 20 structural classes being detected in their skin extracts, probably deriving from dietary ants.[1]

Some of them are known to target nAChRs: epibatidine is a quite remarkable as a nicotinic agonist, while histrionicotoxins, pumiliotoxin and some indolizidines are potent blockers of nicotinic channels.[2] Recent studies show that frog alkaloids alter the function of nicotinic receptors in a subtype-selective manner, suggesting that an analysis of these compounds and analogues may aid in the development of selective drugs useful in degenerative CNS pathologies.[3]

The structural diversity and pharmacological activity associated with these alkaloids have stimulated research in numerous synthetic groups.[4] Alkaloid 275A **1** (Fig. 1), one of the major compounds isolated from skin extracts of the Colombian poison frog *Dendrobates lehmanni*, possesses an unusual 1-azabicyclo[5.3.0]decane ring system. At present, the same ring system, coupled with different substitutions at C3, was postulated for nine other alkaloids, assigned to the lehmizidine class, named after the frog species from which they were discovered. After that a gross structure was presented for alkaloid 275A in 1999,[5] the relative stereochemistry of which has been definitively established in 2001 from Garraffo et al.,[6] by comparison of tetrahydro-**1** with the four synthetic diastereoisomers. To the best of our knowledge, neither the asymmetric synthesis of the naturally occurring alkaloid, nor biological studies have been reported, presumably due to a lack of material.




Alkaloid 275A **1**

(R = $(CH_2)_7C{\equiv}CH$)

**Figure 1.** Lehmizidine alkaloids.

As a continuation of our focus on the development of new methodologies for the stereoselective synthesis of pharmacologically significant scaffolds, such as indolizidine, quinolizidine alkaloids and analogues,[7] we became intrigued by the chemical architecture of this compound and pursued its total synthesis.

## 2. Results and discussion

Figure 2 illustrates our retrosynthetic strategy. Keeping as the last step the introduction of the two carbon acetylene group, it was envisioned that the seven-membered ring of the natural product **1** could be accessed by an intramolecular reductive amination. Through a cross metathesis reaction, the required intermediate was thought to be formed from a suitable 2,5-*trans*-disubstituted pyrrolidine and methyl vinyl ketone. The properly functionalised pyrrolidine could be accessed by acyliminium chemistry in order to introduce the but-1-enyl side chain and by alkyl cuprate nucleophilic substitution to achieve the seven carbon side chain.

Starting from the known methyl lactamol **2**,[8] readily available from commercial L-pyroglutamic acid, butenylation was realised using butenylmagnesium bromide and the $CuBr{\cdot}SMe_2$ complex, following the protocol by Pedregal.[9] After Boc deprotection and

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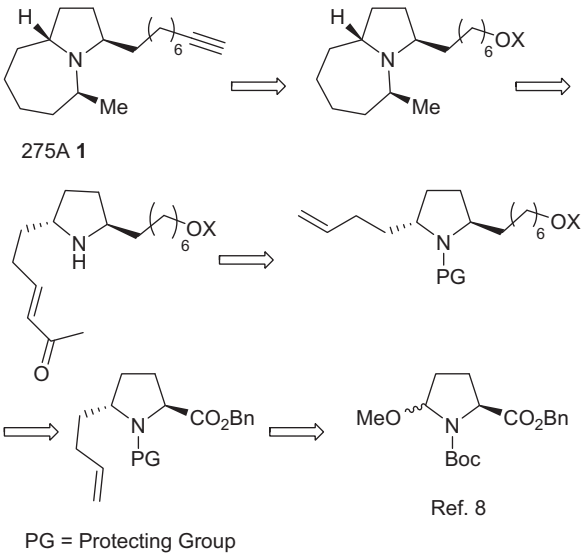
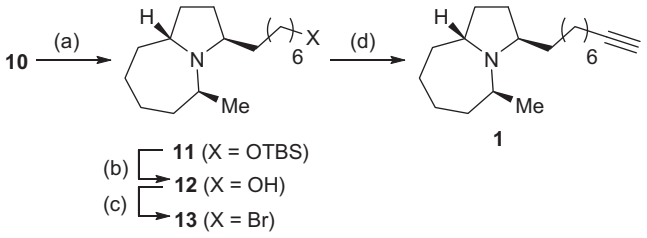



**Figure 2.** Basic strategy for the construction of the lehmizidine skeleton of alkaloid 275A **1**.

chromatographic separation, the major *trans*-diastereoisomer **3** (9:1 dr) was isolated in satisfactory yields (Scheme 1).

After protection of **3** as the Cbz derivative **4**, we pursued the exploitation of the ester group in order to set up the required seven carbon side chain. Reduction of **4** with $LiBH_4$ to give **5**, followed by treatment with tosyl chloride afforded tosylate **6** in high yield. With compound **6** in hand, we turned our attention to the Cu-catalysed alkylation chemistry. Reaction with CuI and the appropriate Grignard reagent, prepared from the 6-(*t*-butyldimethylsilyloxy)hexyl bromide **7**,[10] provided an unsatisfactory yield of **9** after 24 h, with the majority of the remaining material consisting of starting tosylate **6**. By using the cuprate reagent, prepared from the iodo derivative **8**,[11] *t*-BuLi and CuI, *trans*-pyrrolidine **9** could be obtained in satisfactory yield. Accurate temperature control proved to be necessary in order to preserve the stability of the cuprate reagent and to ensure a clean reaction. At this point, cross metathesis reaction was carried out with a stoichiometric amount of methyl vinyl ketone in a 0.05 M toluene solution, using the Grubbs–Hoveyda catalyst. The reaction proceeded smoothly at 40 °C in 6 h to afford **10** in 90% yield.

Pyrrolidine **10** was subjected to the removal of the Cbz group by treatment with catalytic Pd/C (10%) under a hydrogen atmosphere, resulting in a concomitant intramolecular reductive amination and cyclisation (Scheme 2). This type of reaction is well documented starting from the appropriate ketopyrrolidines to afford indolizidine[12] and pyrrolizidine[13] ring systems. Since to the best of our knowledge, there are only a few examples, of seven-membered intramolecular reductive amination steps, the stereochemical outcome was difficult to predict.




**Scheme 2.** Reagents and conditions: (a) (i) $H_2$, Pd/C 10%, MeOH, rt, (ii) chromatographic separation, 76% (overall); (b) TBAF, THF, 0 °C to rt, 62%; (c) $CBr_4$, $PPh_3$, $CH_2Cl_2$, 0 °C to rt, 93%; (d) lithium acetylide ethylenediamine complex, DMSO, rt, 45%.

We were pleased to observe that the indicated 5*S* diastereoisomer **11** was mainly obtained (5:1 dr, after chromatographic separation), as the result of a stereoselective palladium-catalysed reduction from the less hindered face of the rigid cyclic iminium intermediate. Steric hindrance of the nine carbon side chain at C3 proved to play a key role in this transformation. The combination of 2D NMR NOESY experiments with computational[14] evaluation of interatomic distances on the minimum conformer for both diastereoisomers at C5 (Fig. 3) allowed us to establish the configuration of the newly formed stereocentre of **11**. Installation of the

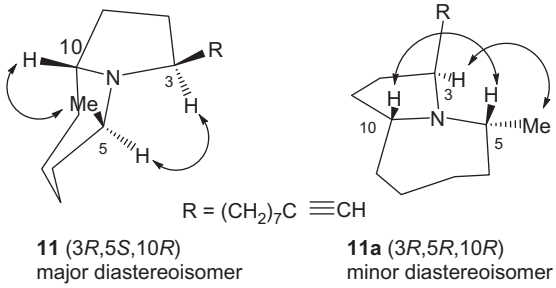
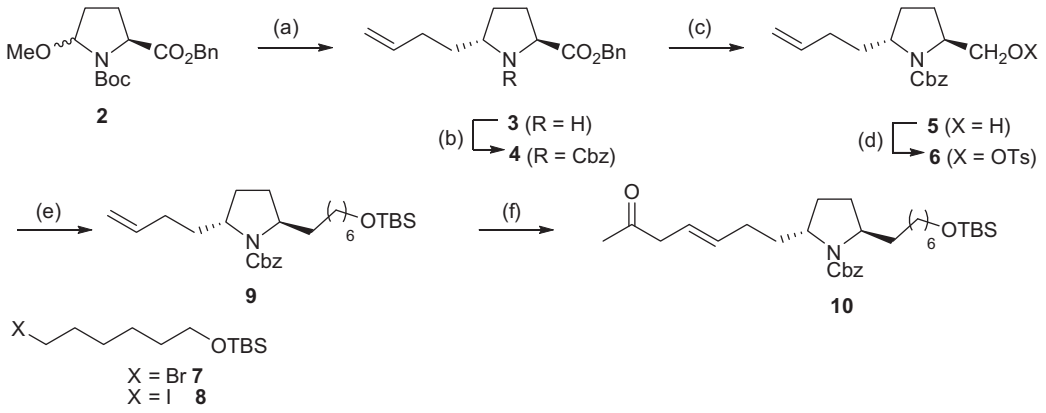



**Figure 3.** Diagnostic NOE contacts for **11** and **11a**.




**Scheme 1.** Reagents and conditions: (a) (i) but-3-enylmagnesium bromide, CuBr·$Me_2S$, $BF_3$·$Et_2O$, THF dry, −78 °C to rt, 84%, (ii) 30% TFA in $CH_2Cl_2$, (iii) chromatographic separation, 74% (overall); (b) Cbz-Cl, TEA, $CH_2Cl_2$, 96%; (c) $LiBH_4$ 2 M in THF, 0 °C, 84%; (d) *p*-TsCl, TEA, DMAP, $CH_2Cl_2$, 0 °C to rt, 97%; (e) **8**, *t*-BuLi 1.7 M in pentane, CuI, $Et_2O$/hexane, −78 to −5 °C, 81%; (f) methyl vinyl ketone, Ru-cat. Hoveyda–Grubbs, toluene, 40 °C, 90%.

same relative configuration at the C3, C5 and C10 stereocentres, as in the natural product 275A, was thus completed.

Conversion of **11** into the final target compound **1** was performed in a few steps. The exposure of **11** to TBAF led to the desilylated product **12**, which was converted into the corresponding bromide **13**, by the reaction with $CBr_4$ and $PPh_3$. The alkyl bromide underwent displacement with lithium acetylide–ethylendiamine complex in DMSO[15] and produced the desired alkyne **1** in satisfactory yield.[16] The specific rotation of our synthetic **1** had a negative value {$[\alpha]_D^{25} = -19.2$ (*c* 0.5, $CHCl_3$)}. Since the $[\alpha]_D$ value or an authentic sample of the alkaloid 275A is not at present available, the absolute configuration of the natural product remains unknown.

## 3. Conclusions

In conclusion, we have accomplished a concise, asymmetric synthesis of the 275A lehmizidine frog skin alkaloid (or of its enantiomer). Starting from L-pyroglutamic acid as the source of chirality, key features of this protocol are an acyliminium butenyl Grignard addition and a seven-membered intramolecular reductive amination step, both ensuring a high degree of diastereocontrol. It should be noted that the described sequence is adaptable to the generation of a variety of natural analogues, above all other natural lehmizidines, bearing different substituents at C3.

## 4. Experimental

### 4.1. General information

All solvents were distilled and properly dried, when necessary, prior to use. All chemicals were purchased from commercial sources and used directly, unless otherwise indicated. All reactions were run under $N_2$, unless otherwise indicated. All reactions were monitored by thin layer chromatography (TLC) on precoated Silica Gel 60 F254; spots were visualised with UV light or by treatment with 1% aqueous $KMnO_4$ solution. Products were purified by flash chromatography on Silica Gel 60 (230–400 mesh). $^1H$ and $^{13}C$ NMR spectra were recorded using 300 and 400 MHz spectrometers. Chemical shifts ($\delta$) are expressed in ppm relative to TMS at $\delta = 0$ ppm for $^1H$ NMR and to $CDCl_3$ at $\delta = 77.16$ ppm for $^{13}C$ NMR. High-resolution MS spectra were recorded using a FT-ICR (Fourier Transform Ion Ciclotron Resonance) instrument, equipped with ESI source, or a standard MS instrument, equipped with EI source. IR spectra were recorded using a FTIR instrument.

### 4.2. (2*S*,5*R*)-Benzyl 5-(but-3-enyl)pyrrolidine-2-carboxylate (3)

To a stirred suspension of $CuBr{\cdot}Me_2S$ (4.90 g, 23.8 mmol, 4 equiv) in dry THF (30 mL) at −50 °C under a nitrogen atmosphere, but-3-enylmagnesium bromide (29.8 mL, 1.0 M in THF, 29.8 mmol, 5 equiv) was added dropwise and stirring was continued at −50 °C for 30 min. The mixture was cooled to −78 °C and $BF_3{\cdot}Et_2O$ (3.02 mL, 23.8 mmol, 4 equiv) was added dropwise. After 30 min, a solution of **2** (2.00 g, 5.9 mmol) in dry THF (6 mL) was added slowly and the reaction mixture was further stirred at −78 °C for 30 min, then allowed to warm to rt over 1 h. After completion of the reaction, a 2:1:1 mixture of $H_2O$/concd $NH_3$/$NH_4Cl$-saturated aqueous solution was added. The resulting mixture was vigorously stirred and then repeatedly extracted with EtOAc. The combined organic fractions were washed with $H_2O$ and brine, and dried over $Na_2SO_4$. Filtration and evaporation of the solvent under reduced pressure, followed by purification by flash chromatography on silica gel (*n*-hexane/EtOAc 9:1), afforded 1.80 g of (2*S*)-2-benzyl 1-*tert*-butyl-5-(but-3-enyl)pyrrolidine-1,2-dicarboxylate, as a light yellow oil (9:1 mixture of C5 diastereoisomers). $^1H$ NMR (400 MHz, $CDCl_3$, major *trans* diastereoisomer description, two conformers) $\delta$ = 7.41–7.31 (m, 5H), 5.91–5.77 (m, 1H), 5.29–4.94 (m, 4H), 4.40 (d, *J* = 8.4 Hz, 0.4H, minor conformer), 4.30 (d, J. = 8.4 Hz, 0.6H, major conformer), 4.05 (dt, *J* = 8.8, 3.2 Hz, 0.6H, major conformer), 3.94 (dt, *J* = 8.9, 2.8 Hz, 0.4H, minor conformer), 2.32–2.16 (m, 1H), 2.14–1.88 (m, 4H), 1.87–1.76 (m, 1H), 1.73–1.61 (m, 1H), 1.48 (s, 3.6H, minor conformer), 1.45–1.37 (m, 1H), 1.36 (s, 5.4H, major conformer). $^{13}C$ NMR (100 MHz, $CDCl_3$, major *trans* diastereoisomer description, two conformers) $\delta$ = 173.0 (major) and 172.7 (minor), 153.7, 138.2 (major) and 138.0 (minor), 135.9 (minor) and 135.7 (major), 128.6–128.1 (5C), 114.8 (minor) and 114.6 (major), 79.9 (minor) and 79.8 (major), 66.6, 59.8 (major) and 59.6 (minor), 57.9 (major) and 57.5 (minor), 33.8 (minor) and 33.1 (major), 30.9, 28.5 (minor) and 28.3 (major) (3C), 27.6, 27.4.

To a stirred solution of (2*S*)-2-benzyl 1-*tert*-butyl 5-(but-3-enyl)pyrrolidine-1,2-dicarboxylate (5.12 g, 14.2 mmol) in dry $CH_2Cl_2$ (100 mL) under a nitrogen atmosphere, trifluoroacetic acid (50 mL) was added and the reaction mixture was stirred at rt for 2 h. To this mixture a $NaHCO_3$-saturated aqueous solution was slowly added until pH 10. The phases were separated and the aqueous layer was repeatedly extracted with $CH_2Cl_2$. The combined organic phases were then washed with a $NaHCO_3$-saturated aqueous solution, dried over $Na_2SO_4$, filtered and evaporated to dryness. The residue was finally purified by flash chromatography on silica gel (*n*-hexane/EtOAc 55:45) to afford 1.13 g (74% overall) of **3** (major *trans* diastereoisomer) as a light yellow oil. $[\alpha]_D^{25} = -39.2$ (*c* 1.0, $CHCl_3$). $^1H$ NMR (400 MHZ, $CDCl_3$) $\delta$ = 7.42–7.32 (m, 5H), 5.90–5.78 (m, 1H), 5.18 (s, 2H), 5.05 (dd, *J* = 17.0, 1.6 Hz, 1H), 4.97 (dd, *J* = 10.0, 0.8 Hz, 1H), 3.93 (dd, *J*. = 6.0, 5.6 Hz, 1H), 3.30–3.22 (m, 1H), 2.45–2.30 (s, br, 1H), 2.32–2.20 (m, 1H), 2.19–2.04 (m, 2H), 1.99–1.84 (m, 2H), 1.65–1.35 (m, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ = 175.5, 138.5, 135.8, 128.6–128.2 (5C), 114.6, 66.7, 59.4, 58.1, 35.8, 31.5, 31.4, 29.6. HRMS (ESI) calcd for $C_{16}H_{21}NO_2$ 259,1572, found 259,1564.

### 4.3. (2*S*,5*R*)-Benzyl-1-benzyloxycarbonyl-5-(but-3-enyl)pyrrolidine-1,2-dicarboxylate (4)

To a stirred solution of **3** (2.84 g, 10.9 mmol) in dry THF (20 mL) under a nitrogen atmosphere, triethylamine (1.52 mL, 10.9 mmol, 1 equiv) and benzyloxycarbonylchloride (3.12 mL, 21.8 mmol, 2 equiv) were added. The mixture was left to stir at rt for 4 h, then diluted with EtOAc and washed with a saturated aqueous $NH_4Cl$ solution until the aqueous phase had a neutral pH. The organic layer was then dried over $Na_2SO_4$, filtered and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (*n*-hexane/EtOAc 8:2) provided 4.12 g (96%) of **4** as a colourless oil. $[\alpha]_D^{25} = -64.8$ (*c* 1.0, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$, two conformers) $\delta$ = 7.40–7.22 (m, 10H), 5.90–5.80 (m, 0.6H, major conformer), 5.78–5.68 (m, 0.4H, minor conformer), 5.26–4.91 (m, 6H), 4.47 (d, *J* = 8.4 Hz, 0.4H, minor conformer), 4.42 (d, *J* = 8.4 Hz, 0.6H, major conformer), 4.12 (dt, *J* = 8.4, 3.2 Hz, 0.6H, major conformer), 4.06 (dt, *J* = 8.4, 3.2 Hz, 0.4H, minor conformer), 2.34–2.19 (m, 1H), 2.14–1.92 (m, 5H), 1.87–1.68 (m, 1H), 1.49–1.37 (m, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$, two conformers) $\delta$ = 173.2, 154.9, 138.6 (major) and 138.4 (minor), 137.3, 136.3, 129.4–128.5 (10 C), 115.4 (minor) and 115.3 (major), 67.8, 67.4 (major) and 67.3 (minor), 60.6 (minor) and 60.3 (major), 59.2 (major) and 58.3 (minor), 34.3 (minor) and 33.6 (major), 31.3, 29.3 (major) and 28.9 (minor), 28.2 (minor) and 28.1 (major). HRMS (ESI) calcd for $C_{24}H_{27}NO_4$ 393,1940, found 393,1949.

### 4.4. (2*R*,5*S*)-Benzyl 2-(but-3-enyl)-5-(hydroxymethyl) pyrrolidine-1-carboxylate (5)

Lithium borohydride (5.5 mL, 2.0 M in THF, 11.0 mmol, 1.5 equiv) was added portionwise to a vigorously stirred solution

of **4** (2.90 g, 7.4 mmol) in dry THF (24 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to stir overnight at 0 °C and at this temperature was diluted with $H_2O$ and acidified by the dropwise addition of an HCl 2 M aqueous solution. The resulting mixture was extracted with EtOAc and the combined organic phase was washed with $H_2O$. The aqueous fractions were back-extracted with EtOAc and the combined organic phases were washed with brine, dried over $Na_2SO_4$, filtered and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (*n*-hexane/EtOAc from 8:2 to 6:4) yielding 1.80 g (84%) of **5** as a colourless oil. $[\alpha]_D^{25} = -45.4$ (*c* 1.0, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$, two conformers) $\delta$ = 7.37–7.32 (m, 5H), 5.90–5.76 (m, 0.3H, minor conformer), 5.75–5.60 (m, 0.7H, major conformer), 5.18 (d, *J* = 12.3 Hz, 1H), 5.10 (d, *J* = 12.3 Hz, 1H), 5.01–4.86 (m, 2H), 4.09–3.99 (m, 1H), 3.92–3.82 (m, 1H), 3.77–3.58 (m, 2H), 2.45–2.20 (s, br, 1H), 2.14–1.22 (m, 8H). $^{13}$C NMR (75 MHz, $CDCl_3$, two conformers) $\delta$ = 156.5, 138.0 (minor) and 137.7 (major), 136.4, 128.5–128.0 (5C), 114.9, 67.2 (major) and 67.0 (minor), 64.0, 60.4, 58.7 (minor) and 58.4 (major), 32.7, 30.7, 28.1, 26.6. HRMS (ESI) calcd for $C_{17}H_{23}NO_3$ 289,1678, found 289,1660.

### 4.5. (2*R*,5*S*)-Benzyl 2-(but-3-enyl)-5-(tosyloxymethyl) pyrrolidine-1-carboxylate (6)

To an ice-cooled solution of **5** (1.45 g, 5.0 mmol) in dry $CH_2Cl_2$ (30 mL) under a nitrogen atmosphere, triethylamine (1.40 mL, 10.1 mmol, 2 equiv), then *p*-toluenesulfonyl chloride (1.39 g, 7.3 mmol, 1.5 equiv) portionwise and dimethylaminopyridine (61 mg, 0.5 mmol, 0.1 equiv) were added. The reaction mixture was stirred at rt for 5 h, then diluted with $CH_2Cl_2$ and washed with 1 M HCl aq solution, $NaHCO_3$-saturated aqueous solution and brine. The organic phase was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (*n*-hexane/EtOAc 8:2) afforded 2.15 g (97%) of **6** as a colourless oil. $[\alpha]_D^{25} = -43.4$ (*c* 1.0, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$, two conformers) $\delta$ = 7.75 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.39–7.23 (m, 7H), 5.84–5.71 (m, 0.5H, conformer A), 5.70–5.58 (m, 0.5H, conformer B), 5.15–4.86 (m, 4H), 4.24–3.73 (m, 4H), 2.42 (s, 1.5H, conformer A), 2.41 (s, 1.5H, conformer B), 2.10–1.22 (m, 8H). $^{13}$C NMR (75 MHz, $CDCl_3$, two conformers) $\delta$ = 154.2, 144.8, 137.8 and 137.6, 136.4, 132.9, 129.9–127.8 (9C), 114.8, 69.3 and 69.0, 66.8, 58.3 and 57.7, 56.1 and 55.5, 32.9–25.5 (4C), 21.6. HRMS (EI) calcd for $C_{24}H_{29}SNO_5$ 443,1766, found 443,1735.

### 4.6. (2*R*,5*R*)-Benzyl 2-(but-3-enyl)-5-(7-(*tert*-butyldimethylsilyloxy)heptyl)pyrrolidine-1-carboxylate (9)

Under a nitrogen atmosphere, a 1.7 M solution of *tert*-butyllithium in pentane (9.2 mL, 15.6 mmol, 8 equiv) was added dropwise to a solution of **8** (2.68 g, 7.8 mmol, 4 equiv) in a 1:1 mixture of dry hexane and dry $Et_2O$ (20 mL) at −78 °C. Stirring was continued at −78 °C for 15 min before warming to rt over 1 h. The solution was re-cooled to −78 °C and added to a slurry of copper(I) iodide (746 mg, 3.9 mmol, 2 equiv) in dry $Et_2O$ (20 mL) via cannula. The mixture was then warmed to −10 °C over 1 h and stirred for a further 20 min between −10 °C and −5 °C. The resultant cuprate reagent was re-cooled to −60 °C before a solution of **6** (868 mg, 1.9 mmol) in dry $Et_2O$ (10 mL) was added dropwise. The mixture was further stirred and allowed to warm to −5 °C for 1 h. The reaction was quenched by addition of $NH_4Cl$-saturated aqueous solution and the pH was adjusted to 7 with concentrated $NH_3$. The resultant mixture was repeatedly extracted with EtOAc and the combined organic extracts were dried over $Na_2SO_4$. Filtration, followed by solvent removal and purification by flash chromatography on silica gel (*n*-hexane/EtOAc 95:5), afforded 751 mg (81%) of **9** as a light yellow oil. $[\alpha]_D^{25} = -41.8$ (*c* 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$, two conformers) $\delta$ = 7.41–7.31 (m, 5H), 5.92–5.79 (m, 0.5H, conformer A), 5.78–5.65 (m, 0.5H, conformer B), 5.21 (d, *J* = 12.4 Hz, 1H), 5.09 (d, *J* = 12.4 Hz, 1H), 5.05–4.90 (m, 2H), 3.88–3.74 (m, 2H), 3.61 (t, *J* = 6.4 Hz, 2H), 2.11–1.12 (m, 20H), 0.92 (s, 9H), 0.07 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$, two conformers) $\delta$ = 154.3, 138.2 and 138.0, 137.1, 128.4–127.8 (5C), 114.6, 66.4, 63.3, 58.3 and 57.7, 57.7 and 57.2, 34.0–26.6 (9C), 26.0 (3C), 25.8, 18.4, −5.2 (2C). HRMS (ESI) calcd for $C_{29}H_{49}NO_3Si$ 487,3482, found 487,3468.

### 4.7. (2*R*,5*R*)-Benzyl 2-(7-(*tert*-butyldimethylsilyloxy)heptyl)-5-((*E*)-5-oxohex-3-enyl)pyrrolidine-1-carboxylate (10)

To a stirred solution of **9** (965 mg, 2.0 mmol) and methyl vinyl ketone (165 μL, 2.0 mmol, 1 equiv) in dry toluene (40 mL) under a nitrogen atmosphere, Ru-catalyst (Hoveyda–Grubbs second generation) (62 mg, 5 mol %) was added. The solution was stirred at 40 °C for 6 h. The solvent was then evaporated and the residue was purified by flash chromatography on silica gel (*n*-hexane to *n*-hexane/EtOAc 8:2) yielding 952 mg (90%) of **10** as a light yellow oil. $[\alpha]_D^{25} = -38.2$ (*c* 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$, two conformers) $\delta$ = 7.39–7.31 (m, 5H), 6.82 (dt, *J* = 16.0, 7.0 Hz, 0.6H, major conformer), 6.64 (dt, *J* = 16.0, 7.0 Hz, 0.4H, minor conformer), 6.12 (d, *J* = 16.0 Hz, 0.6H, major conformer), 6.01 (d, *J* = 16.0 Hz, 0.4H, minor conformer), 5.26–5.05 (m, 2H), 3.90–3.74 (m, 2H), 3.61 (t, *J* = 6.4 Hz, 2H), 2.25 (s, 1.8H, major conformer), 2.16 (s, 1.2H, minor conformer), 2.27–1.18 (m, 20H), 0.92 (s, 9H), 0.07 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$, two conformers) $\delta$ = 198.4, 154.4, 147.6 (major) and 147.1 (minor), 136.9, 131.6, 128.4–127.9 (5C), 66.6, 63.3, 58.4 (minor) and 57.9 (major), 57.5 (major) and 56.8 (minor), 33.9–26.6 (9C), 26.6, 26.0 (3C), 25.8, 18.4, -5.2 (2C). HRMS (ESI) calcd for $C_{31}H_{51}NO_4Si$ 529,3587, found 529,3562.

### 4.8. (3*R*,5*S*,10*R*)-3-(7-(*tert*-Butyldimethylsilyloxy)heptyl)-5-methyloctahydro-1*H*-pyrrolo[1,2-*a*]azepine (11)

To a solution of **10** (500 mg, 0.94 mmol) in dry MeOH (25 mL) Pd/C 10% (100 mg) was added. The resultant mixture was stirred under a hydrogen atmosphere for 72 h at rt. The mixture was filtered over a Celite pad and rinsed with MeOH. The solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel (EtOAc/MeOH/$NH_{3\ aqueous}$ 97:2.5:0.5) yielding 273 mg (76%) of **11** [major (5*S*)-diastereoisomer] as a light brown oil. $[\alpha]_D^{25} = -27.9$ (*c* 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CD_3CN$) $\delta$ = 3.63 (t, *J* = 6.4 Hz, 2H), 3.29–3.20 (m, 1H), 3.12–3.00 (m, 2H), 2.12–1.26 (m, 24H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H). $^{13}$C NMR (100 MHz, $CD_3CN$) $\delta$ = 64.3, 62.6, 60.2, 52.5, 39.2–27.0 (12C), 26.8 (3C), 24.1, 22.2, −4.6 (2C). HRMS (EI) calcd for $C_{23}H_{46}NOSi$ ($M^+-1$) 380.3349, found 380.3338.

### 4.9. 7-((3*R*,5*S*,10*R*)-5-Methyloctahydro-1*H*-pyrrolo[1,2-*a*]azepin-3-yl)heptan-1-ol (12)

Tetrabutylammonium fluoride (1.17 mL, 1.0 M in THF, 1.17 mmol, 1.9 equiv) was added at 0 °C under a nitrogen atmosphere to a solution of **11** (235 mg, 0.62 mmol) in dry THF (14 mL) and the reaction mixture was stirred at 0 °C for 2 h. The temperature was then raised to rt for 2 h. The reaction mixture was diluted with EtOAc and washed with $NaHCO_3$-saturated aqueous solution. The organic layer was dried over $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (EtOAc/MeOH/$NH_{3\ aqueous}$ 97:2.5:0.5) to afford 103 mg (62%) of **12** as a yellow oil. $[\alpha]_D^{25} = -38.9$ (*c* 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$ + $CF_3CO_2D$) $\delta$ = 4.26–4.10 (m, 1H), 3.83–3.70 (m, 1H), 3.76 (t, *J* = 6.4 Hz, 2H), 3.54–3.36 (m,

1H), 2.42–1.24 (m, 25H), 1.44 (d, $J$ = 6.7 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 67.2, 66.2, 63.7, 58.3, 33.6–25.1 (12C), 19.7. HRMS (EI) calcd for $C_{17}H_{33}NO$ 267.2562, found 267.2568.

### 4.10. (3*R*,5*S*,10*R*)-3-(7-Bromoheptyl)-5-methyloctahydro-1*H*-pyrrolo[1,2-a]azepine (13)

To a stirred solution of **12** (110 mg, 0.4 mmol) in dry $CH_2Cl_2$ (4 mL) under a nitrogen atmosphere, tetrabromomethane (172 mg, 0.5 mmol) was added. The solution was cooled to 0 °C and triphenylphosphine (157 mg, 0.6 mmol) was added. The reaction mixture was stirred for 2 h at 0 °C and for 12 h at rt. Removal of the solvent under reduced pressure gave the crude product, which was purified by flash chromatography on silica gel (EtOAc to EtOAc/MeOH/$NH_{3\ aq}$ 98:1:1) to afford 123 mg (93%) of **13** as a yellow oil. $[\alpha]_D^{25} = -33.6$ ($c$ 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$ + $CF_3CO_2D$) $\delta$ = 4.22–4.16 (m, 1H), 3.94–3.85 (m, 1H), 3.54–3.40 (m, 1H), 3.43 (t, $J$ = 6.4 Hz, 2H), 2.42–1.29 (m, 24H), 1.44 (d, $J$ = 6.4 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 66.6, 65.6, 57.5, 33.8, 33.0–25.6 (12C), 19.1. HRMS (ESI) calcd for $C_{17}H_{32}BrN$ 329,1718, found 329,1726.

### 4.11. (3*R*,5*S*,10*R*)-5-Methyl-3-(non-8-ynyl)octahydro-1*H*-pyrrolo[1,2-*a*]azepine (1)

Under a nitrogen atmosphere, lithium acetylide–ethylenediamine complex (90%) (82 mg, 0.8 mmol) was suspended in dry DMSO (2 mL) and cooled to 15 °C with stirring. Compound **13** (88 mg, 0.3 mmol) was dissolved in dry DMSO (2 mL) and added dropwise to the acetylide suspension. The reaction mixture was allowed to warm to rt and was stirred for 2 h. The mixture was then poured over an ice/brine solution and the product was extracted with $CH_2Cl_2$. The combined extracts were washed with brine, dried over $Na_2SO_4$, filtered and concentrated. Purification of the residue by flash chromatography on silica gel (EtOAc/MeOH/$NH_{3\ aqueous}$ 97:2.5:0.5) yielded 37 mg (45%) of **1** as a yellow oil. $[\alpha]_D^{25} = -19.2$ ($c$ 0.5, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 3.92–3.85 (m, 1H), 3.34–3.25 (m, 1H), 3.20–3.12 (m, 1H), 2.22–2.14 (m, 2H), 1.97 (t, $J$ = 2.6 Hz, 1H), 1.80–1.29 (m, 24H), 1.25 (d, $J$ = 6.4 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 85.6, 68.2, 66.4, 65.2, 57.4, 33.0–25.6 (12C), 25.0, 23.1. HRMS (ESI) calcd for $C_{19}H_{33}N$ 275,2613, found 275,2595.

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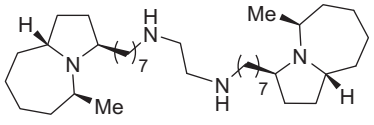
16. Some trace of a dimeric compound, tentatively ascribed to the competitive double substitution of ethylenediamine on bromide **13**, was also detected.




HRMS (ESI) calcd for $C_{36}H_{70}N_4$ 558, 5600, found 558, 5632.