Silver-Catalyzed Hydroamination: Synthesis of *N*-Bridgehead Pyrroles, Incorporating a Protection-Deprotection Strategy for Preparation of Cyclic Secondary Vinylogous Carbamates

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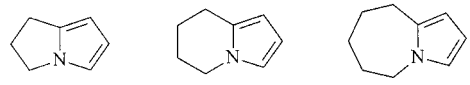
N-Bridgehead pyrroles are efficiently prepared from cyclic secondary vinylogous carbamates using a two-step sequence. This sequence involves *C*-propargylation followed by a silver-catalyzed intramolecular hydroamination. Hydroamination is brought about using microwave irradiation and affords the desired *N*-bridgehead pyrroles rapidly and in good yield. Cyclic secondary vinylogous carbamates are prepared using a mild, economical procedure.

Introduction

Pyrroles are amongst the most recognisable structures in organic chemistry; this being due to the enormous amount of research focussed on their synthesis and reactivity,[1] as well as their abundance in nature either as monopyrrolic compounds[2] or cyclic tetrapyrroles (porphyrins, chlorins etc.).[3]

We have recently reported a novel one-pot synthesis of pyrroles via the silver-mediated reaction of secondary vinylogous amides or carbamates with propargyl bromide.[4] This procedure has been improved upon by employing a two-step procedure which incorporates a silver-catalyzed hydroamination as its second step.[5] We have now extended this methodology to *N*-bridgehead pyrroles (Figure 1; **1**, **2**, and **3**), the pyrrole analogues of pyrrolizidines, indolizidines, and pyrroloazepines (the term "lehmizidine" has been suggested by Garraffo et al.[6] to describe the "5–7-izidines").



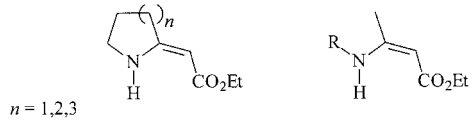
1 **2** **3**

Figure 1. *N*-Bridgehead pyrrole skeletons

It is interesting to note that the pyrrole analogues of pyrrolizidine alkaloids have been identified as the metabolites actually responsible for the hepatotoxicity of pyrrolizidine alkaloids in animals.[7] Subsequent to that finding, several syntheses of these types of compounds have appeared in the literature,[8] a list to which we now add our method.

Results and Discussion

In order to access the *N*-bridgehead pyrroles in question, it was necessary to prepare cyclic secondary vinylogous carbamates **4** and, although their acyclic analogues **5** can be readily obtained in high yield,[9] synthesis of the cyclic compounds can be problematic (Figure 2).



n = 1,2,3

4 **5**

Figure 2. Secondary yinylogous carbamates

They have been prepared from lactim ethers,[10] from azido dicarbonyl compounds,[11] from alkenyl-substituted β-enamino esters,[12] and by lithiation of ketimines[13] amongst others. However, the most common method used for preparation of these compounds is the Eschenmoser sulphide contraction (also known as the Eschenmoser coupling reaction).[14] A typical synthetic strategy (Scheme 1) would entail thionation of an appropriate lactam (**6**) to give the corresponding thiolactam (**7**), which would be treated, sequentially, with an activated alkyl halide ($BrCH_2CO_2Et$), a weak base (Et_3N) and a thiophile (Ph_3P) to give the vinylogous carbamate (**8**) at ambient temperature.

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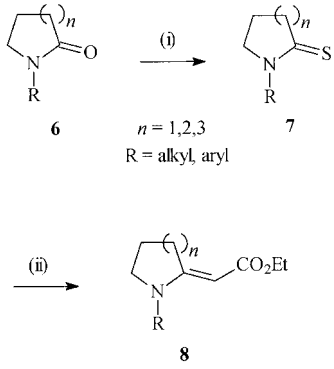


6 n = 1,2,3 7
R = alkyl, aryl
8

Scheme 1. (i) Lawesson's reagent, MW; (ii) $BrCH_2CO_2Et$, Et_3N, Ph_3P, MeCN

However, if a secondary thiolactam (**10**) is employed in the sulphide contraction, much harsher conditions are required.[14] Typical conditions for this form of the reaction are the use of potassium *tert*-butoxide, a large excess of thiophile (4 equivalents) and long reaction times at high temperature (72 hours in refluxing xylene).[15] This aside, the Eschenmoser sulphide contraction is an efficient reaction and it was deemed important to investigate ways of simplifying the reaction conditions in order to prepare the desired secondary vinylogous carbamates (Scheme 2).

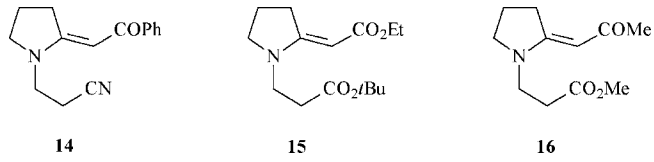
The conjugate addition of thiolactams to acrylates has been widely employed as a method of functionalising the nitrogen atom of these compounds.[16] It has also been demonstrated that this addition can be reversed by the addition of a strong base.[17] Both of these reactions are reported to give high yields (>90 %).

Thiolactams **10** can be easily prepared from the corresponding lactam[18] and subsequent treatment with methyl acrylate and a catalytic amount of sodium hydroxide gives the acrylate adducts **12** in good yield (Table 1) and short reaction time (2 h).[16] These adducts, being tertiary thiolactams, can be converted to tertiary vinylogous carbamates **13** using the mild Eschenmoser sulphide contraction conditions described above.[19] These two-step reactions are typically complete after 12–16 hours and in good yield (Table 1).

Table 1. Preparation of secondary vinylogous carbamates (Scheme 2)

Entry	Starting material	*n*	Yield (%)
10a	**9a**	1	97
10b	**9b**	2	92
10c	**9c**	3	89
12a	**10a**	1	70
12b	**10b**	2	58
12c	**10c**	3	90
13a	**12a**	1	83
13b	**12b**	2	84
13c	**12c**	3	23
11a	**13a**	1	63
11b	**13b**	2	86
11c	**13c**	3	83

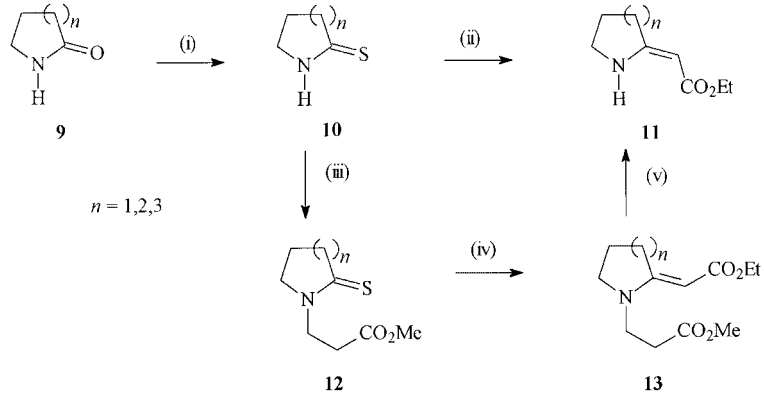
Michael and Parsons have shown that acrylonitrile can be successfully removed from a similar adduct **14** by treatment with excess potassium *tert*-butoxide.[17] However, when employing this method to remove methyl acrylate from adduct **13a**, the only product isolated was, rather surprisingly, the transesterification product **15** (Figure 3).



14 15 16

Figure 3. Related adducts

It was found that by using potassium hexamethyl disilazide (KHMDS), in a similar fashion to previous work in



9 10 11 12 13

Scheme 2. (i) Lawesson's reagent, MW; (ii) $BrCH_2CO_2Et$, *t*BuOK, Ph_3P, xylene; (iii) $CH_2{=}CHCO_2Me$, NaOH, THF; (iv) $BrCH_2CO_2Et$, Et_3N, Ph_3P, MeCN; (v) KHMDS, THF

our group involving a vinylogous amide adduct **16**,[17] that methyl acrylate was cleaved rapidly and efficiently to give secondary vinylogous carbamates **11** in good yields. The secondary compounds adopt the energetically more favourable *Z* configuration due to hydrogen bonding, a fact that is evident from the chemical shift of the amino proton of the prepared compounds.

These vinylogous carbamates **11** were treated with propargyl bromide and silver nitrate, in the one-pot manner originally reported,[4] to afford *N*-bridgehead pyrroles **20** albeit in low yield (Table 2). This reaction is believed to proceed via silver-mediated hydroamination of the triple bond of propargyl bromide (**17**, Scheme 3), followed by nucleophilic substitution via the enaminone functionality (**18**). Rearrangement of the cyclic enamine intermediate **19** would afford the thermodynamically more stable *N*-bridgehead pyrrole **20**. It is believed that the low yields observed for this reaction are due to the many potential reaction pathways subsequent to the initial hydroamination.

Table 2. Preparation of *N*-bridgehead pyrroles (Scheme 4)

Entry	Method[a]	Starting material	Yield, % (Overall)
20a	A	**11a**	13
20b	A	**11b**	19
20c	A	**11c**	14[b]
21a	–	**11a**	66
21b	–	**11b**	35[c]
21c	–	**11c**	24
20a	B	**21a**	75 (50)
20b	B	**21b**	75 (26)
20c	B	**21c**	71 (17)

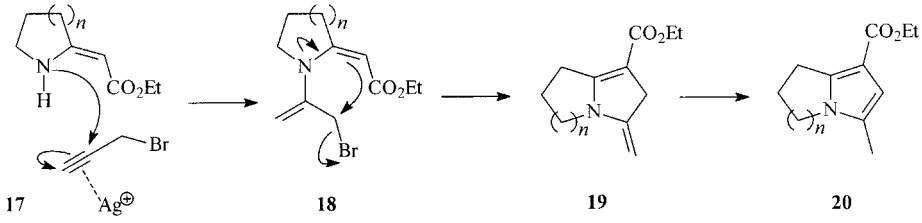
[a] Method A: One-pot procedure, Method B: Two-step procedure. [b] Isolated as a mixture of starting material and product. [c] Bisadduct also isolated as by-product (13 %).

As mentioned above, this one-pot method has been improved upon by carrying out the procedure in two discrete steps (Scheme 4). *C*-Propargylation of vinylogous carbamates **11** using n-butyllithium affords propargyl adducts **21**. A bisadduct (13 %), arising from addition of two equivalents of propargyl bromide to the carbamate, is noted during the preparation of **21b**. The *C*-propargyl adducts **21** undergo silver-catalyzed (0.2 equivalents) hydroamination to afford *N*-bridgehead pyrroles **20**. The mechanism proposed for this transformation is in keeping with the generally accepted mechanism of nucleophilic addition to metal-activated carbon-carbon multiple bonds.[20] Hydroamination is performed using a domestic microwave oven and, as such, is extremely rapid (1 minute).

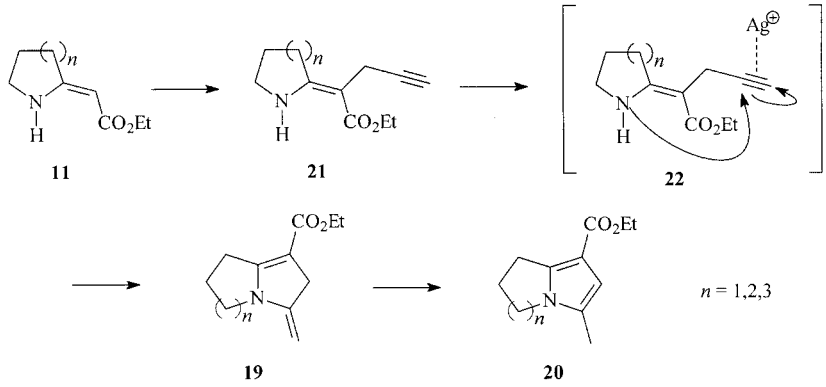
This two-step procedure shows an improvement in overall yields compared to the one-pot approach with the added bonus that the hydroamination is catalytic with respect to silver (I) whereas the one-pot procedure requires a full stoichiometric equivalent.

Conclusions

In conclusion, we have developed a mild and efficient means of preparing secondary cyclic vinylogous carbamates in a relatively short time compared to other common meth-



Scheme 3



Scheme 4

ods. We have also shown that these compounds can be rapidly converted into the corresponding *N*-bridgehead pyrroles utilizing readily available materials and an inexpensive catalyst system. We are currently attempting to optimize the *C*-propargylation reaction discussed above in order to achieve further overall improvement. We are also exploring the possibility of using this strategy in the total synthesis of bicyclic alkaloids.

Experimental Section

NMR spectra were recorded using a 500 MHz Varian Unity Inova spectrometer equipped with an Oxford magnet (11.744T) and a switchable 5 m probe. ^{1}H NMR spectra were recorded at 500 MHz in deuteriochloroform and referenced against the deuteriochloroform singlet at δ = 7.26 ppm. ^{13}C NMR spectra were recorded at 125 MHz in deuteriochloroform and referenced against the central line of the deuteriochloroform triplet at δ = 77.0 ppm. IR spectra were recorded as thin films (chloroform) using a Perkin–Elmer Spectrum One spectrometer. High resolution mass spectra were obtained by the Mass Spectrometry Unit of the University of the North West using an Autospec-TOF (Micromass) mass spectrometer and the Mass Spectrometry Service at the School of Chemistry at the University of the Witwatersrand using a Micromass VG 70 SEQ mass spectrometer. THF and acetonitrile were distilled before use from sodium benzophenone and calcium hydride respectively. Ethyl acetate and hexane, for chromatography, were distilled before use. Thin-layer chromatography was carried out using silica gel 60 F_{254} aluminium backed plates. The plates were viewed under UV light and developed in iodine thereafter. Silica gel 60 PF_{254} was used for radial chromatography. Microwave reactions were carried out using a National 700 W domestic microwave oven.

Thiolactams (**10**)[18] and their acrylate adducts (**12**)[16] were prepared using literature procedures.

Preparation of Vinylogous Carbamate Acrylate Adducts (13). General Procedure: [19] Ethyl bromoacetate (10 mmol) was added to a solution of **12** (5 mmol) in dry CH_3CN (10 mL) and stirred overnight at room temperature to ensure salt formation. A solution of NEt_3 (6 mmol) and PPh_3 (6 mmol) in dry CH_2Cl_2 (2 mL) was added to the reaction mixture and stirred until the reaction was complete according to TLC analysis (1–2 hours). The reaction was quenched with water (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo to afford **13** after chromatography.

Methyl 3-[(2*E*)-2-(2-Ethoxy-2-oxoethylidene)pyrrolidin-1-yl]propanoate (13a): 12a (0.50 g, 2.7 mmol) was treated with ethyl bromoacetate (0.60 mL, 0.90 g, 5.4 mmol), NEt_3 (0.45 mL, 0.32 g, 3.2 mmol), and PPh_3 (0.84 g, 3.2 mmol) to afford **13a** as a colourless oil (0.54 g, 2.2 mmol, 83 %) after radial chromatography (CH_2Cl_2/Hex, 1:1 → EtOAc/Hex, 1:3); R_f 0.31 (EtOAc/Hex, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.23 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.91 (m, 2 H, $NCH_2CH_2CH_2$), 2.57 (t, J = 6.9 Hz, 2 H, $CH_2CO_2CH_3$), 3.12 (t, J = 7.9 Hz, 2 H, CH_2C=CH), 3.38 (t, J = 7.2 Hz, 2 H, $NCH_2CH_2CH_2$), 3.48 (t, J = 7.1 Hz, 2 H, $NCH_2CH_2CO_2CH_3$), 3.68 (s, 3 H, OCH_3), 4.07 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.51 (s, 1 H, C=CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.7 (OCH_2CH_3), 21.1 ($NCH_2CH_2CH_2$), 30.7 (CH_2C=CH), 32.5 ($CH_2CO_2CH_3$), 41.9 ($NCH_2CH_2CO_2CH_3$), 51.8 (OCH_3), 52.8 ($NCH_2CH_2CH_2$), 58.3 (OCH_2CH_3), 78.3 (C=CH), 164.4 (C=CH), 169.2 ($CO_2CH_2CH_3$), 171.9 (CO_2CH_3). IR (thin film, $CHCl_3$): $\tilde{\nu}$ = 2934, 1736, 1682, 1594, 1130 cm^{-1}. MS (EIMS): m/z (%) = 241 [M$^+$] (78), 196 (77), 182 (77), 169 (79), 154 (40), 136 (50), 110 (100). HRMS: found m/z = 241.1314 [M$^+$], $C_{12}H_{19}NO_4$ requires 241.1314.

Methyl 3-[(2*E*)-2-(2-Ethoxy-2-oxoethylidene)piperidin-1-yl]propanoate (13b): 12b (1.32 g, 6.56 mmol) was treated with ethyl bromoacetate (1.46 mL, 2.19 g, 13.1 mmol), NEt_3 (1.10 mL, 0.80 g, 7.87 mmol), and PPh_3 (2.06 g, 7.87 mmol) to afford **13b** as a colourless oil (1.40 g, 5.48 mmol, 84 %) after radial chromatography (CH_2Cl_2/Hex, 1:1); R_f 0.43 (EtOAc/Hex, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.19 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.58 (m, 2 H, $NCH_2CH_2CH_2$), 1.71 (m, 2 H, $NCH_2CH_2CH_2$), 2.59 (t, J = 7.2 Hz, 2 H, $CH_2CO_2CH_3$), 3.04 (t, J = 6.8 Hz, 2 H, CH_2C=CH), 3.21 (t, J = 6.3 Hz, 2 H, $NCH_2CH_2CH_2$), 3.45 (t, J = 7.2 Hz, 2 H, $NCH_2CH_2CO_2CH_3$), 3.65 (s, 3 H, OCH_3), 4.01 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 4.49 (s, 1 H, C=CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.6 (OCH_2CH_3), 19.4 ($NCH_2CH_2CH_2$), 23.2 ($NCH_2CH_2CH_2$), 26.3 (CH_2C=CH), 30.1 ($CH_2CO_2CH_3$), 47.4 ($NCH_2CH_2CO_2CH_3$), 50.0 ($NCH_2CH_2CH_2$), 51.7 (OCH_3), 58.1 (OCH_2CH_3), 82.1 (C=CH), 161.3 (C=CH), 168.7 ($CO_2CH_2CH_3$), 172.0 (CO_2CH_3). IR (thin film, $CHCl_3$): $\tilde{\nu}$ = 2945, 1736, 1679, 1569, 1133, 1050 cm^{-1}. MS (EIMS): m/z (%) = 255 [M$^+$] (84), 210 (68), 196 (65), 182 (100), 150 (60), 122 (67), 97 (87). HRMS: found m/z = 255.1471 [M$^+$], $C_{13}H_{21}NO_4$ requires 255.1471.

Methyl 3-[(2*E*)-2-(2-Ethoxy-2-oxoethylidene)azepan-1-yl]propanoate (13c): 12c (1.40 g, 6.51 mmol) was treated with ethyl bromoacetate (1.49 mL, 2.25 g, 13.5 mmol), NEt_3 (1.13 mL, 0.82 g, 8.09 mmol), and PPh_3 (2.12 g, 8.09 mmol) to afford **13c** as a colourless oil (0.40 g, 1.5 mmol, 23 %) after radial chromatography (EtOAc/Hex, 1:3); R_f 0.52 (EtOAc/Hex, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.22 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.53 (br., 2 H, NCH_2CH_2), 1.61 (br., 4 H, $NCH_2CH_2CH_2CH_2$), 2.60 (t, J = 7.1 Hz, 2 H, $CH_2CO_2CH_3$), 3.21 (br., 2 H, CH_2C=CH), 3.40 (m, 2 H, $NCH_2CH_2CH_2$), 3.53 (t, J = 7.1 Hz, 2 H, $NCH_2CH_2CO_2CH_3$), 3.67 (s, 3 H, OCH_3), 4.04 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.46 (s, 1 H, C=CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.6 (OCH_2CH_3), 25.9 ($NCH_2CH_2CH_2$), 27.0 (CH_2C=CH), 28.7 ($NCH_2CH_2CH_2$), 29.3 (CH_2CH_2C=CH), 31.3 ($CH_2CO_2CH_3$), 48.5 ($NCH_2CH_2CO_2CH_3$), 51.7 (OCH_3), 53.0 ($NCH_2CH_2CH_2$), 58.2 (OCH_2CH_3), 82.9 (C=CH), 166.3 (C=CH), 169.0 ($CO_2CH_2CH_3$), 172.1 (CO_2CH_3). IR (thin film, $CHCl_3$): $\tilde{\nu}$ = 2923, 1733, 1681, 1572, 1443, 1135 cm^{-1}. HRMS: found m/z = 269.1628 [M$^+$], $C_{14}H_{23}NO_4$ requires 269.1627.

***tert*-Butyl 3-[(2*E*)-2-(2-Ethoxy-2-oxoethylidene)pyrrolidin-1-yl]propanoate (15):** *t*BuOK (1 M *solution* in *t*BuOH, 1.40 mL, 1.40 mmol) was added to a solution of **12a** (0.17 g, 0.70 mmol) in dry THF (5 mL) and stirred at room temperature for 30 minutes. The reaction was quenched with water (2 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated in vacuo to afford **15** as a colourless oil (20 mg, 0.071 mmol, 10 %) after radial chromatography (EtOAc/Hex, 1:4); R_f 0.60 (EtOAc/Hex, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.23 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.43 (s, 9 H, $C[CH_3]_3$), 1.90 (m, 2 H, $NCH_2CH_2CH_2$), 2.47 (t, J = 7.0 Hz, 2 H, $CH_2CO_2C[CH_3]_3$), 3.12 (t, J = 7.7 Hz, 2 H, CH_2C=CH), 3.37 (t, J = 7.0 Hz, 2 H, $NCH_2CH_2CH_2$), 3.43 (t, J = 7.1 Hz, 2 H, $NCH_2CH_2CO_2CCH_3$), 4.07 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 4.51 (s, 1 H, C=CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 15.0 (OCH_2CH_3), 21.4 ($NCH_2CH_2CH_2$), 28.3 ($C[CH_3]_3$), 32.5 (CH_2C=CH), 32.8 ($CH_2CO_2C[CH_3]_3$), 42.3 ($NCH_2CH_2CO_2C[CH_3]_3$), 53.0 ($NCH_2CH_2CH_2$), 58.5 (OCH_2CH_3),

78.4 (C=CH), 81.3 (*C* $[CH_3]_3$), 164.7 (*C*=*C*H), 169.6 ($CO_2CH_2CH_3$), 171.0 ($CO_2C[CH_3]_3$). IR (thin film, $CHCl_3$): $\tilde{\nu}$ = 2978, 1725, 1681, 1591, 1130 cm^{-1}. MS (EIMS): *m*/*z* (%) = 283 [M^+] (42), 182 (71), 154 (32), 110 (100).

Preparation of Secondary Vinylogous Carbamates (11). General Procedure: KHMDS (1.2 or 2.0 mmol) was added to a stirred solution of **13** (1 mmol) in dry THF (2 mL) and stirred for 15 minutes at room temperature. The reaction mixture was quenched with water (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo to afford, spectroscopically pure **11**.

Ethyl (2*Z*)-Pyrrolidin-2-ylideneacetate (11a): 13a (0.27 g, 1.1 mmol) was treated with KHMDS (0.47 g, 2.2 mmol) to afford **11a** as a white crystalline solid (m.p. 60–62 °C) (ref.[13] m.p. 61–62 °C) (0.11 g, 0.71 mmol, 63 %); R_f 0.57 (EtOAc/Hex, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.24 (t, *J* = 7.4 Hz, 2 H, OCH_2CH_3), 1.96 (m, 2 H, NCH_2CH_2), 2.57 (t, *J* = 7.5 Hz, 2 H, CH_2C=CH), 3.50 (t, *J* = 6.2 Hz, 2 H, NCH_2), 4.09 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 4.52 (s, 1 H, C=C*H*), 7.90 (br., 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.7 (OCH_2CH_3), 22.0 (NCH_2CH_2), 32.2 (CH_2C=CH), 47.0 (NCH_2), 58.4 (OCH_2CH_3), 76.6 (C=CH), 166.4 (*C*=*C*H), 170.8 (C=O). MS (EIMS): *m*/*z* (%) = 155 [M^+] (22), 110 (79), 83 (95), 82 (100), 80 (43), 54 (19).

Ethyl (2*Z*)-Piperidin-2-ylideneacetate (11b): 13b (0.70 g, 2.7 mmol) was treated with KHMDS (0.63 g, 3.0 mmol) to afford **11b** as a colourless oil (0.40 g, 2.4 mmol, 86 %); R_f 0.84 (EtOAc/Hex, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.21 (t, *J* = 6.8 Hz, 3 H, OCH_2CH_3), 1.66 (m, 2 H, $NCH_2CH_2CH_2$), 1.74 (m, 2 H, NCH_2CH_2), 2.32 (t, *J* = 6.2 Hz, 2 H, CH_2C=CH), 3.26 (dt, *J* = 5.8 and 2.4 Hz Hz, 2 H, NCH_2), 4.05 (q, *J* = 7.4 Hz, 2 H, OCH_2CH_3), 4.32 (s, 1 H, C=C*H*), 8.70 (br., 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.6 (OCH_2CH_3), 19.9 (NCH_2CH_2), 22.7 ($NCH_2CH_2CH_2$), 29.1 (CH_2C=CH), 41.2 (NCH_2), 58.1 (OCH_2CH_3), 80.1 (C=CH), 162.7 (*C*=*C*H), 170.7 (C=O). MS (EIMS): *m*/*z* (%) = 169 [M^+] (56), 124 (59), 97 (100), 82 (36).

Ethyl (2*Z*)-Azepan-2-ylideneacetate (11c): 13c (0.32 g, 1.2 mmol) was treated with KHMDS (0.30 g, 1.4 mmol) to afford **11c** as a white crystalline solid (m.p. 47–50 °C) (ref.[13] m.p. 55–56 °C) (0.18 g, 0.98 mmol, 83 %); R_f 0.68 (EtOAc/Hex, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.16 (t, *J* = 6.9 Hz, 3 H, OCH_2CH_3), 1.63–1.49 (m, 6 H, $NCH_2CH_2CH_2CH_2$), 2.21 (br., 2 H, CH_2C=CH), 3.22 (br., 2 H, NCH_2), 4.00 (q, *J* = 6.8 Hz, 2 H, OCH_2CH_3), 4.35 (s, 1 H, C=C*H*), 8.76 (br., 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.3 (OCH_2CH_3), 26.3 ($NCH_2CH_2CH_2$), 29.9 (NCH_2CH_2), 30.2 (CH_2CH_2C=CH), 34.9 (CH_2C=CH), 43.9 (NCH_2), 58.0 (OCH_2CH_3), 80.4 (C=CH), 168.2 (*C*=*C*H), 170.6 (C=O). MS (EIMS): *m*/*z* (%) = 184 [M^+ + 1] (100), 183 [M^+] (68), 138 (55), 111 (83), 96 (28).

Preparation of *N*-Bridgehead Pyrroles (20). General One-Pot Procedure: $AgNO_3$ (1.2 mmol) was added to a stirred solution of **11** (1 mmol) and propargyl bromide (1.2 mmol) in dry CH_3CN (2 mL) and stirred overnight. The organic layer was washed with $NaI_{(aq)}$, dried ($MgSO_4$), and concentrated in vacuo to afford **20** after radial chromatography.

Ethyl 5-Methyl-2,3-dihydro-1*H*-pyrrolizine-7-carboxylate (20a): 11a (0.10 g, 0.64 mmol) was treated with $AgNO_3$ (0.13 g, 0.77 mmol) and propargyl bromide (80 % w/w solution in toluene, 0.09 mL, 0.09 g, 0.8 mmol) to afford **20a** as a colourless crystalline solid (m.p. 54–56 °C) (ref.[8a] m.p. 58 °C) (16 mg, 0.083 mmol, 13 %) after radial chromatography (EtOAc/Hex, 1:3); R_f 0.57 (EtOAc/Hex, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.30 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 2.17 (s, 3 H, $NCCH_3$), 2.51 (m, 2 H, NCH_2CH_2), 3.05 (t, *J* = 7.4 Hz, 2 H, $NCH_2CH_2CH_2$), 3.83 (t, *J* = 7.1 Hz, 2 H, NCH_2CH_2), 4.22 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 6.26 (s, 1 H, C=C*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 11.7 ($NCCH_3$), 14.6 (OCH_2CH_3), 25.9 ($NCH_2CH_2CH_2$), 26.9 (NCH_2CH_2), 44.9 (NCH_2), 59.1 (OCH_2CH_3), 106.3 ($CCO_2CH_2CH_3$), 110.0 (NC=CH), 124.0 (N*C*=*C*H), 142.6 (N*C*=*C*$CO_2CH_2CH_3$), 165.4 (C=O). IR (thin film, $CHCl_3$): $\tilde{\nu}$ = 2978, 1698, 1209, 1078 cm^{-1}. MS (EIMS): *m*/*z* (%) = 193 [M^+] (44), 164 (100), 148 (41), 120 (33). HRMS: found *m*/*z* = 193.1103 [M^+], $C_{11}H_{15}NO_2$ requires 193.1103.

Ethyl 3-Methyl-5,6,7,8-tetrahydro-1-indolizinecarboxylate (20b): 11b (75 mg, 0.44 mmol) was treated with $AgNO_3$ (90 mg, 0.53 mmol) and propargyl bromide (80 % w/w solution in toluene, 0.06 mL, 0.06 g, 0.5 mmol) to afford **20b** as a colourless oil (16 mg, 0.077 mmol, 19 %) after radial chromatography (EtOAc/Hex, 1:3); R_f 0.56 (EtOAc/Hex, 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.31 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 1.80 (m, 2 H, $NCH_2CH_2CH_2$), 1.96 (m, 2 H, NCH_2CH_2), 2.15 (s, 3 H, $NCCH_3$), 3.06 (t, *J* = 6.6 Hz, 2 H, CH_2C=C), 3.75 (t, *J* = 6.0 Hz, 2 H, NCH_2CH_2), 4.23 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 6.26 (s, 1 H, C=C*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 11.6 ($NCCH_3$), 14.6 (OCH_2CH_3), 19.9 ($NCH_2CH_2CH_2$), 23.0 (CH_2C=C), 23.9 (NCH_2CH_2), 42.9 (NCH_2), 59.0 (OCH_2CH_3), 107.0 (NC=CH), 109.4 ($CCO_2CH_2CH_3$), 127.1 (N*C*=*C*H), 136.2 (N*C*=*C*$CO_2CH_2CH_3$), 165.5 (C=O). IR (thin film, $CHCl_3$): $\tilde{\nu}$ = 2923, 1692, 1218, 1185 cm^{-1}. MS (EIMS): *m*/*z* (%) = 207 [M^+] (40), 178 (100), 134 (79). HRMS: found *m*/*z* = 207.1257 [M^+], $C_{12}H_{17}NO_2$ requires 207.1259.

Ethyl 3-Methyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-1-carboxylate (20c): 11c (0.18 g, 0.98 mmol) was treated with $AgNO_3$ (0.20 g, 1.18 mmol) and propargyl bromide (80 % w/w solution in toluene, 0.13 mL, 0.14 g, 1.18 mmol) to afford **20c** as an inseparable mixture of starting material and product (SM/prod, 2:1) (14 % from ^{1}H NMR integral values) after radial chromatography (EtOAc/Hex, 1:3); R_f 0.67 (EtOAc/Hex, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.29 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 1.64 (m, 2 H, $NCH_2CH_2CH_2CH_2$), 1.80 (m, 2 H, NCH_2CH_2), 2.15 (s, 3 H, $NCCH_3$), 3.20 (br., 2 H, CH_2C=C), 3.84 (m, 2 H, NCH_2CH_2), 4.20 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 6.15 (s, 1 H, C=C*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 12.2 ($NCCH_3$), 14.4 (OCH_2CH_3), 25.2 (CH_2C=C), 26.8 ($NCH_2CH_2CH_2$), 28.6 ($NCH_2CH_2CH_2CH_2$), 31.1 (NCH_2CH_2), 45.3 (NCH_2), 58.9 (OCH_2CH_3), 106.8 (NC=CH), 109.3 ($CCO_2CH_2CH_3$), 126.9 (N*C*=*C*H), 141.7 (N*C*=*C*$CO_2CH_2CH_3$), 165.7 (C=O). IR (thin film, $CHCl_3$): $\tilde{\nu}$ = 2928, 1695, 1651, 1602, 1253, 1168, 1116, 1053 cm^{-1}. MS (EIMS): *m*/*z* (%) = 221 [M^+] (54), 191 (77), 148 (100). HRMS: found *m*/*z* = 221.1416 [M^+], $C_{13}H_{19}NO_2$ requires 221.1416.

Preparation of *C*-Propargyl Vinylogous Amides and Carbamates (21). General Procedure: *n*BuLi (2.2 mmol) was added to a solution of **11** (2 mmol) in dry THF (10 mL) at 0 °C and allowed to warm to room temperature over 30 minutes. Propargyl bromide (3 mmol) was added thereafter and the reaction mixture was stirred overnight. The reaction was quenched by addition of $NH_4Cl_{(aq)}$ (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo to afford **21** after chromatography.

Ethyl (2*Z*)-2-Pyrrolidin-2-ylidenepent-4-ynoate (21a): 11a (0.35 g, 2.3 mmol) was treated with *n*BuLi (1.6 M solution in hexane,

1.55 mL, 2.48 mmol) and propargyl bromide (80 % w/w solution in toluene, 0.38 mL, 0.40 g, 3.4 mmol) to afford **21a** as a colourless oil (0.29 g, 1.5 mmol, 66 %) after radial chromatography (EtOAc/Hex, 1:3); R_f 0.61 (EtOAc/Hex, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.26 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.90 (t, J = 2.6 Hz, 1 H, C≡C*H*), 2.00 (m, 2 H, NCH_2CH_2), 2.72 (t, J = 7.8 Hz, 2 H, $NCH_2CH_2CH_2$), 3.08 (d, J = 2.6 Hz, 2 H, $CH_2C{\equiv}CH$), 3.51 (t, J = 7.0 Hz, 2 H, NCH_2), 4.14 (q, J = 7.3 Hz, 2 H, OCH_2CH_3), 8.14 (br., 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.6 (OCH_2CH_3), 17.0 ($CH_2C{\equiv}CH$), 21.8 (NCH_2CH_2), 30.8 ($CH_2CH_2C{=}C$), 47.2 (NCH_2), 58.9 (OCH_2CH_3), 66.4 (C≡*C*H), 84.2 (*C*≡CH), 84.5 (NC=C), 165.2 (N*C*=*C*), 169.4 (C=O). IR (thin film, $CHCl_3$): $\tilde{\nu}$ = 3362, 3307, 2972, 2104, 1654, 1596, 1248, 1212 cm^{-1}. MS (EIMS): *m*/*z* (%) = 193 [M$^+$] (35), 164 (100), 120 (74), 118 (46), 91 (22). HRMS: found *m*/*z* = 193.1091 [M$^+$], $C_{11}H_{23}NO_2$ requires 193.1103.

Ethyl (2*Z*)-2-Piperidin-2-ylidenepent-4-ynoate (21b): 11b (0.38 g, 2.25 mmol) was treated with *n*BuLi (1.6 M solution in hexane, 1.54 mL, 2.47 mmol) and propargyl bromide (80 % w/w solution in toluene, 0.38 mL, 0.40 g, 3.37 mmol) to afford **21b** as a colourless oil (0.16 g, 0.79 mmol, 35 %) and ethyl 2-prop-2-ynyl-2-(3,4,5,6-tetrahydropyridin-2-yl)pent-4-ynoate as a colourless oil (70 mg, 0.29 mmol, 13 %) after radial chromatography (EtOAc/Hex, 1:9); R_f 0.37 and 0.30 (EtOAc/Hex, 1:4) respectively. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.27 (t, J = 7.4 Hz, 3 H, OCH_2CH_3), 1.78–1.72 (m, 4 H, $NCH_2CH_2CH_2$), 1.91 (t, J = 2.5 Hz, 1 H, C≡C*H*), 2.58 (t, J = 6.2 Hz, 2 H, $CH_2CH_2C{=}C$), 3.12 (d, J = 2.4 Hz, 2 H, $CH_2C{\equiv}CH$), 3.31 (m, 2 H, NCH_2), 4.13 (q, J = 7.4 Hz, 2 H, OCH_2CH_3), 9.65 (br., 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.6 (OCH_2CH_3), 15.6 ($CH_2C{\equiv}CH$), 19.8 (NCH_2CH_2), 22.0 ($NCH_2CH_2CH_2$), 25.9 ($CH_2CH_2C{=}C$), 41.3 (NCH_2), 58.7 (OCH_2CH_3), 66.3 (C≡*C*H), 84.8 (*C*≡CH), 85.3 (NC=C), 161.2 (N*C*=*C*), 169.7 (C=O). IR (thin film, $CHCl_3$): $\tilde{\nu}$ = 3280, 2939, 2857, 2109, 1690, 1637, 1591, 1207 cm^{-1}. MS (EIMS): *m*/*z* (%) = 207 [M$^+$] (44), 178 (100), 162 (23), 134 (60), 132 (33). HRMS: found *m*/*z* = 207.1245 [M$^+$], $C_{12}H_{17}NO_2$ requires 207.1259.

Ethyl (2*Z*)-2-Azepan-2-ylidenepent-4-ynoate (21c): 11c (0.34 g, 1.9 mmol) was treated with *n*BuLi (1.6 M solution in hexane, 1.28 mL, 2.04 mmol) and propargyl bromide (80 % w/w solution in toluene, 0.31 mL, 0.33 g, 2.8 mmol) to afford **21c** as a colourless oil (0.10 g, 0.45 mmol, 24 %) after radial chromatography (EtOAc/Hex, 1:9); R_f 0.69 (EtOAc/Hex, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.27 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.61–1.56 (m, 2 H, NCH_2CH_2), 1.73–1.66 (m, 4 H, $NCH_2CH_2CH_2CH_2$), 1.92 (t, J = 2.6 Hz, 1 H, C≡C*H*), 2.59 (m, 2 H, $CH_2CH_2C{=}C$), 3.21 (d, J = 2.8 Hz, 2 H, $CH_2C{\equiv}CH$), 3.32 (m, 2 H, NCH_2), 4.13 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 9.67 (br., 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.6 (OCH_2CH_3), 16.6 ($CH_2C{\equiv}CH$), 25.3 ($NCH_2CH_2CH_2$), 29.1 ($CH_2CH_2C{=}C$), 30.0 (NCH_2CH_2), 30.4 ($CH_2CH_2C{=}C$), 44.0 (NCH_2), 59.0 (OCH_2CH_3), 66.5 (C≡*C*H), 85.6 (*C*≡CH), 86.2 (NC=C), 167.8 (N*C*=*C*), 170.2 (C=O). IR (thin film, $CHCl_3$): $\tilde{\nu}$ = 3291, 2928, 2109, 1643, 1591, 1248, 1196 cm^{-1}. MS (EIMS): *m*/*z* (%) = 221 [M$^+$] (42), 192 (100), 148 (84), 146 (41), 120 (32). HRMS: found *m*/*z* = 221.1401 [M$^+$], $C_{13}H_{19}NO_2$ requires 221.1416.

Preparation of *N*-Bridgehead Pyrroles (20). General Two-Step Procedure: $AgNO_3$ (0.2 mmol) was added to a Pyrex test tube containing a solution of **21** (1 mmol) in dry CH_3CN (1 mL). The test tube was sealed and subjected to microwave irradiation (700 W, low) for 60 seconds (30, 30). The organic layer was washed with $NaI_{(aq)}$, dried ($MgSO_4$), and concentrated in vacuo. The crude material was filtered (MeOH) through a short plug of silica gel to afford **20**.

Note: Spectral and physical data for the compounds shown below matched those acquired for the same compounds in prior reactions.

Ethyl 5-Methyl-2,3-dihydro-1*H*-pyrrolizine-7-carboxylate (20a): 21a (0.25 g, 1.29 mmol) was treated with $AgNO_3$ (44 mg, 0.26 mmol) and irradiated to afford **20a** as a colourless crystalline solid (0.19 g, 0.97 mmol, 75 %).

Ethyl 3-Methyl-5,6,7,8-tetrahydro-1-indolizinecarboxylate (20b): 21b (48 mg, 0.23 mmol) was treated with $AgNO_3$ (8 mg, 0.05 mmol) and irradiated to afford **20b** as a colourless oil (36 mg, 0.17 mmol, 75 %).

Ethyl 3-Methyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-1-carboxylate (20c): 21c (98 mg, 0.44 mmol) was treated with $AgNO_3$ (15 mg, 0.09 mmol) and irradiated to afford **20c** as a colourless oil (70 mg, 0.32 mmol, 71 %).

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