EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201402336

Methanesulfonic Acid Mediated Cyclization and Meyer–Schuster Rearrangement of γ-Amino-ynones: Access to Enantiopure Pyrrolidine Exocyclic Vinylogous Amides

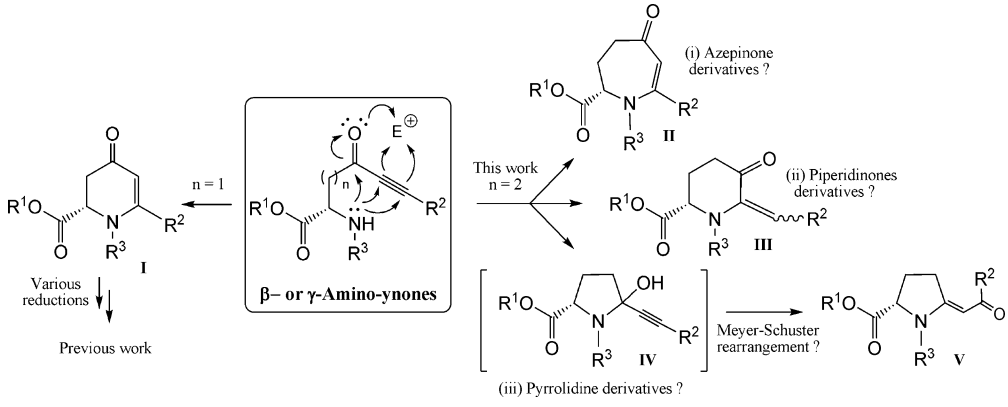
Huy-Dinh Vu,[a,b] Jacques Renault,*[a] Thierry Roisnel,[c] Nicolas Gouault,[a] and Philippe Uriac[a]

Keywords: Rearrangement / Nitrogen heterocycles / Alkynes / Amines / Cyclization / Regioselectivity

α- and β-Amino-ynones have been largely used to prepare heterocyclic rings in the presence of various electrophiles such as protic acids or gold(I). Herein we disclose the unprecedented formation of pyrrolidine exocyclic vinylogous amides, in place of the expected azepinones or piperidinones, starting from γ-amino-ynones derived from amino acids. The process involves a tandem 1,2-addition of the protected nitrogen to the carbonyl group followed by a Meyer–Schuster rearrangement, which efficiently afforded enantiopure pyrrolidine exocyclic vinylogous amides. The sequence is poorly catalyzed by gold salts, but proved to be very efficient in the presence of methanesulfonic acid.

Introduction

The use of ynones bearing a proximate nucleophile is a straightforward approach to the construction of small and medium-sized heterocyclic rings by intramolecular Michael additions,[1] and these substrates have been efficiently used for the synthesis of various natural products.[2] In general, the success of these methodologies largely depends upon the control of the cyclization mode: *exo*- versus *endo*-dig. Owing to electronic effects, *endo*-dig cyclization predominates over *exo*-dig cyclization and results in good regioselectivity. Although various types of heterocycles have been obtained from these starting materials, the above approach is not uniformly effective for the formation of seven-membered and larger rings[3] because these cyclization reactions are less favored, in accord with Baldwin's rules.[4]



Scheme 1. Intramolecular cyclizations of β- and γ-amino-ynones (n = 1 or 2).

In a recent report, we described the gold-catalyzed cyclization of β-amino-ynones to *N*-protected dihydropyridones **I** and their various reductions to diverse pipecolic acid derivatives (n = 1, Scheme 1).[5] We subsequently became interested in similar electrophilic gold- or acid-catalyzed cyclizations of γ-amino-ynones (n = 2) bearing two electrophilic

[a] Produits Naturels, Synthèse et Chimie Médicinale, UMR 6226, Sciences Chimiques de Rennes, Université de Rennes 1, 2, Avenue du Pr Léon Bernard, 35043 Rennes Cedex, France
E-mail: jacques.renault@univ-rennes1.fr
http://www.scienceschimiques.univ-rennes1.fr/equipes/pnscm
[b] Department of Chemistry, Vietnam Forestry University, Hanoi, Vietnam
[c] Institut des Sciences Chimiques de Rennes, Centre de diffraction X, UMR 6226 CNRS – Université de Rennes 1, 35042 Rennes Cedex, France
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402336.

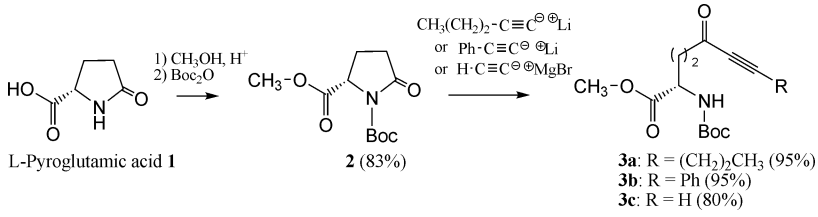
sites. We first considered the activation of the triple bond by the "alkynophilic" gold to form azepinone derivatives **II**. The required trajectory for nucleophilic attack does not seem to be in favor of such a 7-*endo*-dig cyclization according to Baldwin's rules. If 6-*exo*-dig is favored, however, alkyne polarity disfavored the formation of piperidone derivatives **III**. Faster alternative pathways, if available, may compete with these two routes. Thus, we also envisaged the formation of five-membered-ring compounds **IV** by intramolecular 1,2-addition and then, depending on the conditions, transformation of such hemi-aminal propargylic intermediates into pyrrolidines **V** by a Meyer–Schuster rearrangement.

Results and Discussion

The γ-amino-ynones were obtained from L-pyroglutamic acid **1**, which has been extensively used in organic synthesis as a cheap source of chirality. This amino acid derivative with two differentially activated carbonyls has been exploited in various asymmetric syntheses.[6] Its commercially available (*R*) enantiomer was subjected to the same reaction steps to assess the stereochemistry of the described compounds.

Initially, the esterification of the carboxylic acid of **1**[7] and Boc protection of the amine in the presence of DMAP[8] led to the protected compound **2** (83%; Scheme 2). The next step involved the addition of lithium propylacetylide, phenylacetylide, or ethynylmagnesium bromide, which furnished γ-amino-ynones **3a**–**c** in good yields.[9] We then attempted to optimize the conditions of the cyclization reaction and then analyzed the results of three different reactions.

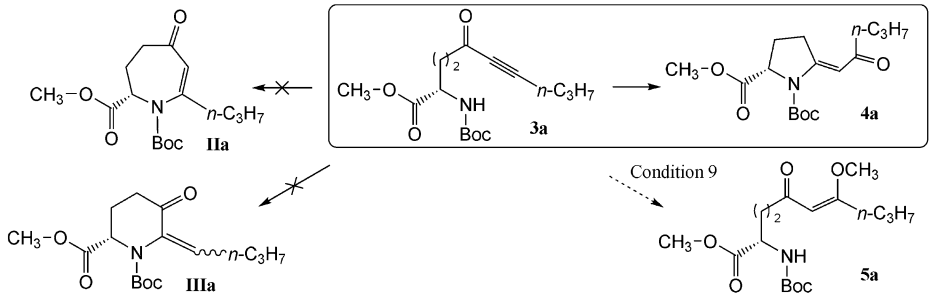
Our experiments were conducted on small batches of propyl ynone **3a** (1 mmol) dissolved in various solvents (1 mL). We first experimented with gold catalysis, which had been found in most cases to be efficient for the cyclization of β-amino-ynones,[5] by using (triphenylphosphine)-gold chloride (PPh_3AuCl) in the presence of an equimolar amount of silver hexafluoroantimonate ($AgSbF_6$) or silver triflate (AgOTf) as co-catalyst. We also tested gold(III) chloride ($AuCl_3$), (triphenylphosphine)gold(I) bis(trifluoromethanesulfonyl) imidate (PPh_3AuNTf_2), and chloro-[1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene]gold(I) ("AuCl-Imidazole") in the presence of $AgSbF_6$. The amount of catalyst, and co-catalyst when relevant, was chosen to be 0.2 equiv. The yields were estimated by ^1H NMR spectroscopy in the presence of an internal standard,



Scheme 2. Synthesis of ynones **3a**–**c**.

Table 1. Preliminary investigation of the gold-catalyzed cyclization from **3a**.

Entry	Conditions	**3a**/**4a** [%]
1	$PPh_3AuCl/AgOTf$ (0.2 equiv.), CH_2Cl_2, 12 h, r.t.	45:5
2	$PPh_3AuCl/AgSbF_6$ (0.2 equiv.), CH_2Cl_2, 12 h, r.t.	90:10
3	$AuCl_3$ (0.2 equiv.), CH_2Cl_2, 12 h, r.t.	100:0
4	PPh_3AuNTf_2 (0.2 equiv.), $C_2H_4Cl_2$, 12 h, r.t.	100:0
5	PPh_3AuNTf_2 (0.2 equiv.), $C_2H_4Cl_2$, 6 h, 80 °C	100:0
6	PPh_3AuNTf_2 (0.2 equiv.), toluene, 6 h, 110 °C	80:20
7	AuCl–Imidazole/$AgSbF_6$ (0.2 equiv.), CH_2Cl_2, 12 h, r.t.	60:25
8	AuCl–Imidazole/$AgSbF_6$ (0.2 equiv.), CH_2Cl_2, CH_3OH (10:1), 12 h, r.t.	0:60
9	AuCl–Imidazole/$AgSbF_6$ (0.2 equiv.), CH_3OH, 12 h, r.t.	40:0 (**5a**: 60)



which allowed for a global quantitative estimation of yields. In many experiments, CH_2Cl_2 was found equivalent to $C_2H_4Cl_2$ and was preferred due to its easier removal. The main results are reported in Table 1.

The preliminary experiments showed poor results. On the one hand, we never obtained azepinone **IIa** nor piperidinone derivative **IIIa**. On the other hand, the poorly oxophilic properties of gold(I) and gold(III) only resulted in low (Table 1, entries 1, 2, and 6) or even non-existent conversion of the starting material into **4a** (entries 3–5). The use of Au-Imidazole slightly improved the yield to 25% (entry 7), which was increased to 60% in the presence of a small portion of methanol (entry 8). However, in pure dry methanol (entry 9), only the product of addition, **5a**, was obtained in 60% yield; the (*Z*) geometry of **5a** was attested by NOESY experiments. A few attempts at AuCl-Imidazole catalysis starting from **3b**,**c**, aimed at preparing **4b**,**c**, analogues of **4a**, only resulted in **4c** in an acceptable yield of 60% under the conditions described in entry 7; **4b** was not found.

The formation of the five-membered ring **4a**, albeit in low yield, could only result from carbonyl attack by the poorly nucleophilic carbamate nitrogen lone pair to form a pyrrolidine (Scheme 1), which then underwent Meyer–Schuster rearrangement.[11] The X-ray structure[10] of **4a** is given in Figure 1.

Hence, we directed our efforts to obtaining a better yield of **4a**–**c**. We first attempted acidic removal of the Boc protecting group followed by treatment with K_2CO_3,[12] which we have previously used for similar cyclizations of β-aminoynones.[5] As observed for the gold-catalyzed reactions, these reactions starting from **3a**–**c** never yielded azepinones, but mainly gave a mixture of small amounts of **4a**–**c** together with the corresponding unprotected compounds. We also successfully tested a non-nucleophilic acid, methanesulfonic acid, under various conditions. The results, obtained by ^{1}H NMR analysis in the presence of an internal standard, are reported in Table 2.

First, as expected, the absence of sulfonic acid (entry 1) left the starting material unchanged. In other cases, as partially observed with hydrochloric acid, we mainly obtained

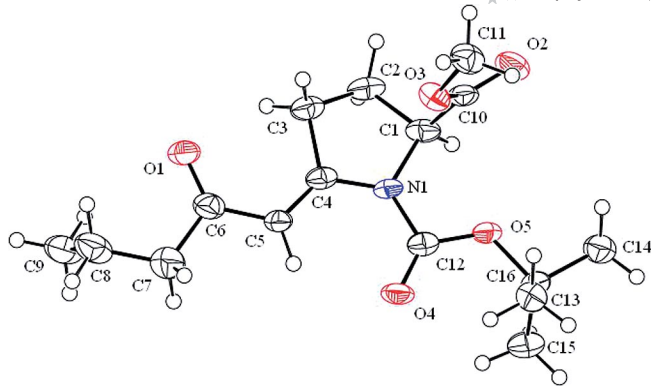
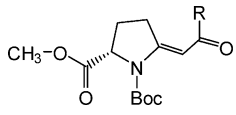


Figure 1. ORTEP drawing of the X-ray crystal structure of **4a**.

Boc-protected compounds **4a**–**c** in varying yields. Then the reactions were carried out at two different concentrations of methanesulfonic acid (entries 2 and 3); good results were obtained only with **3c** (90% in both cases). The favorable role of methanol in the gold-catalyzed Meyer–Schuster rearrangement[13] was again observed: Indeed, **3a** and **3b** were almost completely converted into pyrrolidine derivatives **4a** and **4b** in the presence of (or in) methanol (entries 4 and 5). In contrast, **3c** was converted almost entirely into the stable acetal **6c** (see Scheme 3), resulting in a very low yield of **4c**. Finally, the presence of water had a deleterious effect on the reactivity, whether in the absence (entry 6) or presence of a co-solvent (methanol, entry 7). Camphorsulfonic acid was found to be as efficient as anhydrous methanesulfonic acid in this reaction (entry 8).

If the results reported in Tables 1 and 2 are different in terms of yields, they are similar in terms of products. According to Baldwin's rules,[4] *endo*-dig cyclization (Scheme 1) is disfavored and the azepinone derivatives **II** were never observed, whereas the *exo*-dig cyclization, even if favored by Baldwin's rules, did not occur because of the electronic effect of the carbonyl group. The unique cyclization of **3a**–**c** to the pyrrolidine derivatives **4a**–**c** can be explained by the following considerations: 1) The electrophilic character of the carbonyl carbon atom (better for R = H

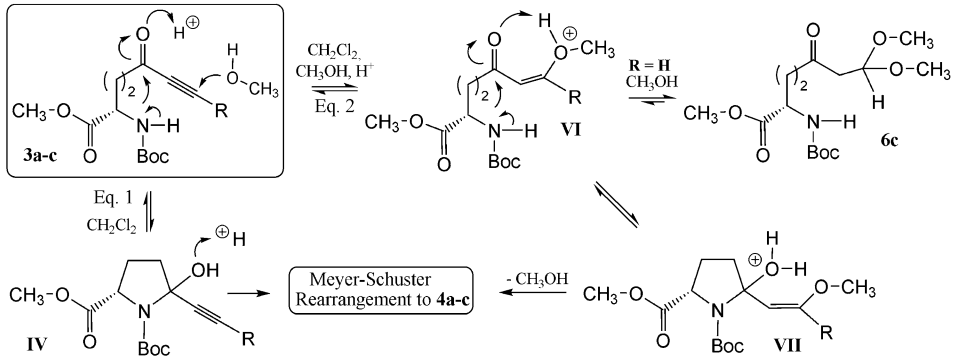
Table 2. Acid-mediated cyclization of **3a**–**c** to give **4a**–**c**.



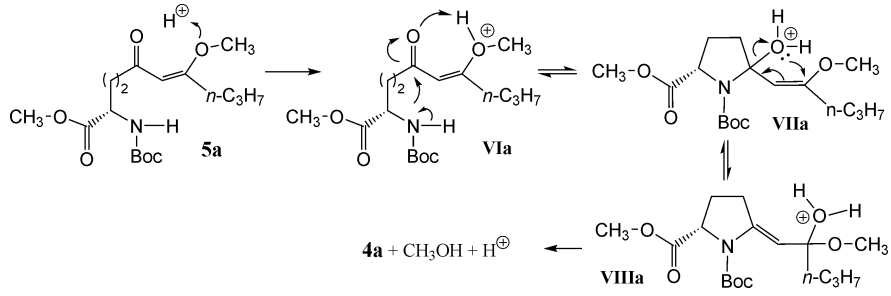
4a: R = $(CH_2)_2CH_3$
4b: R = Ph
4c: R = H

Entry	Conditions	3a/4a	3b/4b	3c/4c
1	CH_2Cl_2/CH_3OH 9:1, 12 h, r.t.	100:0	n.d.[a]	n.d.[a] .
2	CH_3SO_3H (0.2 equiv.), CH_2Cl_2, 4 h, r.t.	80:20	70:0	0:90[b]
3	CH_3SO_3H (0.8 equiv.), CH_2Cl_2, 4 h, r.t.	55:10	15:0	0:90[b]
4	CH_3SO_3H (0.8 equiv.), CH_2Cl_2/CH_3OH 9:1, 4 h, r.t.	0:90	0:85	0:50
5	CH_3SO_3H (0.8 equiv.), CH_3OH, 4 h, r.t.	0:90	0:90	0:5
6	CH_3SO_3H (0.8 equiv.), CH_2Cl_2, H_2O (50 μL), 4 h, r.t.	95:0	100:0	90:5
7	CH_3SO_3H (0.8 equiv.), CH_3OH/H_2O 20:1 (v/v), 4 h, r.t.	0:70	n.d.[a]	n.d.[a]
8	Camphorsulfonic acid (0.8 equiv.), CH_2Cl_2/CH_3OH 9:1, 4 h, r.t.	0:95	n.d.[a]	n.d.[a]

[a] n.d: not done. [b] Obtained in 30 min for **3c**.



Scheme 3. Possible pathways to pyrrolidine derivatives from **3a**–**c**.

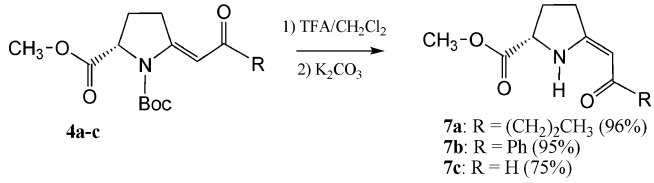


Scheme 4. Proposed mechanism for the formation of **4a** from **5a**.

than Pr or Ph), 2) the extremely favorable formation of a five-membered ring, and 3) the possible Meyer–Schuster rearrangement of the hemi-aminal **IV**.

Depending on the substrates and experimental conditions, two pathways are possible, as shown in Scheme 3. First, the expected classical mechanism involving intermediate **IV** occurred in CH_2Cl_2 as the only solvent [Equation (1)]. Under these conditions, the efficiency of the cyclization increased with the electrophilicity of the carbonyl compounds **3a**–**c** (R = Ph < Pro < H). The resulting intermediate **IV** then underwent a Meyer–Schuster rearrangement to give **4a**–**c**. Secondly, in the presence of methanol [Equation (2)], we suggest that under acidic conditions methanol adds to the alkyne to yield intermediate **VI**. To support this pathway, as a control experiment, we performed the reaction with the (*Z*)-enol ether **5a**, prepared by gold catalysis (Table 1). Compound **5a** was activated by methanesulfonic acid (0.8 equiv.), which induced its complete and immediate conversion into **4a** (Scheme 4). It seems reasonable to assume that the attractive effect of the protonated methoxy group promotes the attack by nitrogen to give **VIIa**, which undergoes the migration of water to give **VIIIa**. The subsequent loss of a proton and methanol would then lead to **4a**.

The unprotected compounds **7a**–**c** were easily obtained from **4a**–**c** in the presence of trifluoroacetic acid followed by treatment in an alkaline medium (Scheme 5). In contrast to **4a**–**c**, which have an (*E*) configuration, **7a**–**c** possess a (*Z*) geometry, as confirmed by NOESY experiments. The X-ray crystal structures[10] of both conformations of **7b** confirmed the (*Z*) configuration (Figure 2).



Scheme 5. Synthesis of compounds **7a**–**c**.

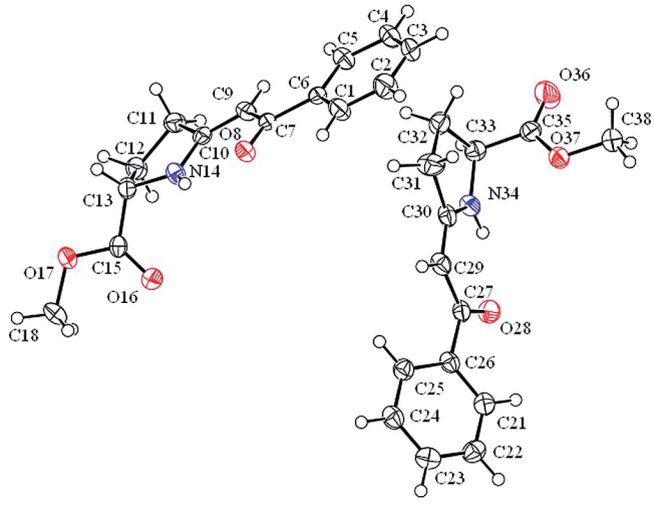
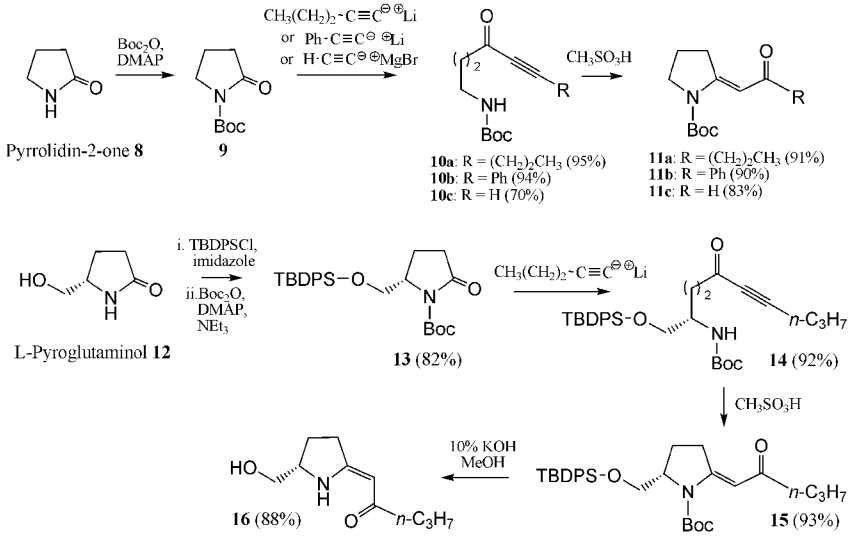


Figure 2. ORTEP drawing of the X-ray crystal structure of **7b** conformers.

The synthesis of further pyrrolidines starting from pyrrolidin-2-one (**8**) and L-pyroglutaminol (**12**; Scheme 6) proved the reliability of the method. In the first example,



Scheme 6. Synthesis of pyrrolidines from pyrrolidin-2-one (**8**) and L-pyroglutaminol (**12**).

pyrrolidin-2-one (**8**) was *N*-protected[14] and then treated with various alkyne salts to give **10a**–**c**. Subsequent cyclization and rearrangement furnished **11a**–**c** in good yields. In a similar manner, L-pyroglutaminol (**12**) was protected to yield **13**,[15] ring-opened with the pent-1-yne lithium salt **14**, cyclized to **15,** and finally deprotected to give **16**,[16] which was obtained in an overall yield of 60%.

Conclusions

The method presented herein provides a new rapid access to various enantiopure pyrrolidine vinylogous amides in good yields. Such compounds, which can be prepared by Eschenmoser coupling[17] or Knoevenagel-type reactions,[18] have been used as intermediates in the synthesis of many natural compounds,[19] such as anisomycin,[20a] apomitomycin,[20b] mesembrenone,[20c] desoxoprosophylline,[20d] cassine,[19c] pinidinone,[20e] deoxyfebrifugine,[20f] and sedacryptine.[20g] Optimised conditions have allowed the efficient production of **4a**–**c**. In the case of an alkyl or aromatic group (**3a** and **3b**), the use of methanol proved to be very efficient (90% yields), whereas it was necessary to use only dichloromethane with **3c** (R = H) to achieve a faster and as efficient transformation. The stereochemistry was analyzed and revealed no racemization of the nitrogen-protected **4a**–**c** or unprotected **7a**–**c**. The scope of this method was successfully extended to similar starting compounds **8** and **12**.

Experimental Section

General Methods: All reagents were of high quality and purchased from commercial suppliers. They were used without further purification or purified/dried according to literature procedures.[21] ^{1}H and ^{13}C NMR were recorded at 300 and 75 MHz, respectively, using TMS as an internal standard. Chemical shifts (δ) are given in ppm, coupling constants (J) are given in Hz, and the multiplicity of signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quadruplet), quint. (quintet), sext (sextet), m (multiplet), br. s (broad singlet), dt (doublet of triplets), and td (triplet of doublets). IR spectra were recorded with a Perkin–Elmer Spectrum 2 spectrometer by using a Universal ATR Sampling Accessory. HRMS analyses were performed with a Waters Q-TOF 2, a Micromass ZABSpec TOF, a Bruker MicrO-TOF QII, or a LTQ Orbitrap XL spectrometer for ESI MS. X-ray crystallographic data were collected with an APEXII crystal diffractometer. Optical rotations were recorded with a Perkin–Elmer Model 341 polarimeter. TLC was performed on precoated silica gel plates (0.2 mm thickness). Chiral HPLC was performed by using a Shimadzu (Prominence Evolutive) instrument equipped with a Chiralpak IA column (5 μm, 4.6 × 250 mm).

1-*tert*-Butyl 2-Methyl (*S*)-5-Oxopyrrolidine-1,2-dicarboxylate (2): Concentrated hydrochloric acid (50 μL) was added to a solution of pyrroglutamic acid (**1**; 5 g, 38.7 mmol) in dry methanol (30 mL). The solution was allowed to react at room temperature for 24 h and then concentrated under vacuum to yield methyl (*S*)-5-oxopyrrolidine-2-carboxylate (5.15 g) as a pale oil. This compound was used without purification (93%). R_f = 0.40 (dichloromethane/methanol, 90:10). $[\alpha]_D^{25}$ = +12.0 (c = 1, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09 (s, 1 H), 4.29 (dd, J = 5.1, J = 8.4 Hz, 1 H), 3.78 (s, 3 H), 2.43 (m, 3 H), 2.23 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.5, 172.6, 55.5, 52.6, 29.3, 24.8 ppm. IR (neat): $\tilde{\nu}$ = 3241, 1736, 1683, 1436, 1206 cm^{-1}. HRMS (ESI): calcd. for $C_6H_9NO_3Na$ $[M + Na]^+$ 166.04801; found 166.0479.

Di-*tert*-butyl dicarbonate (12.0 g, 52.2 mmol), triethylamine (3.62 g, 35.85 mmol), and 4-(dimethylamino)pyridine (DMAP; 0.426 g, 3.49 mmol) were added to a solution of methyl (*S*)-5-oxopyrrolidine-2-carboxylate (5 g, 34.9 mmol) in dichloromethane (25 mL). The mixture was allowed to react at room temperature for 24 h and then extracted with diethyl ether (3 × 100 mL). The organic layer was washed with an aqueous solution of $NaHSO_4$ (50 mL), then a 1 M aqueous solution of Na_2CO_3 (50 mL), then with brine (2 × 50 mL), dried with $MgSO_4$, and concentrated under vacuum. The residue was purified over silica gel (diethyl ether/petroleum ether, 80:20) to yield **2** as a white solid (7.6 g, 89%), m.p. 70–72 °C. R_f = 0.60 (diethyl ether). $[\alpha]_D^{25}$ = –48.7 (c = 1, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.62 (dd, J = 3.9, J = 9.3 Hz, 1 H), 2.64 (m, 1 H), 2.49 (ddd, J = 3.7, J = 9.3, J = 17.4 Hz, 1 H),

2.32 (m, 1 H), 2.04 (m, 1 H), 1.49 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3, 171.9, 149.3, 83.6, 58.8, 52.6, 31.2, 27.9, 21.5 ppm. IR (neat): $\tilde{\nu}$ = 2993, 1792, 1742, 1439, 1256, 1193 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{17}NO_5Na$ [M + Na]$^+$ 266.10044; found 266.1004.

Methyl (*S*)-2-(*tert*-Butoxycarbonylamino)-5-oxodec-6-ynoate (3a): A 2.5 M solution of *n*BuLi in hexane (10.7 mL, 26.7 mmol) was added dropwise to a solution of pent-1-yne (2.24 g, 32.9 mmol) in anhydrous THF (50 mL) cooled to –50 °C. The mixture was stirred for 30 min, added dropwise to a solution of oxopyrrolidine **2** (5.0 g, 20.55 mmol) in anhydrous THF (50 mL) at –50 °C, and stirred for 3 h. A 1 M aqueous solution of $NaHSO_4$ (30 mL) was then added and the mixture extracted with diethyl ether (3× 100 mL). The organic layer was washed with an aqueous saturated solution of Na_2SO_4 (2× 300 mL), dried with $MgSO_4$, and concentrated under vacuum. The crude residue was purified by silica gel chromatography (dichloromethane/diethyl ether, 9.5:0.5) to yield a clear yellow oil (6.1 g, 95%). R_f = 0.80 (diethyl ether/petroleum ether, 60:40). $[\alpha]_D^{25}$ = –12.1 (*c* = 1, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.11 (d, *J* = 7.7 Hz, 1 H), 4.31 (m, 1 H), 3.75 (s, 3 H), 2.66 (m, 2 H), 2.35 (t, *J* = 7.0 Hz, 2 H), 2.21 (m, 1 H), 1.99 (m, 1 H), 1.61 (sext, *J* = 7.2 Hz, 2 H), 1.44 (s, 9 H), 1.02 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.4, 172.7, 155.4, 95.0, 80.7, 80.1, 52.8, 52.4, 41.4, 28.3, 26.7, 21.2, 20.9, 13.5 ppm. IR (neat): $\tilde{\nu}$ = 3366, 2967, 2210, 1712, 1673, 1365, 1160 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{25}NO_5Na$ [M + Na]$^+$ 334.16304; found 334.1626.

Methyl (*S*)-2-(*tert*-Butoxycarbonylamino)-5-oxo-7-phenylhept-6-ynoate (3b): Compound **3b** was obtained from phenylacetylene (3.36 g, 32.9 mmol) following the procedure described above for the synthesis of **3a**. The residue was purified by silica gel chromatography (dichloromethane/diethyl ether, 9.5:0.5) to yield a brown oil (7.1 g, 95%). R_f = 0.55 (dichloromethane/diethyl ether, 95:5). $[\alpha]_D^{25}$ = +14.0 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (m, 2 H), 7.43 (m, 3 H), 5.21 (d, *J* = 8.1 Hz, 1 H), 4.37 (m, 1 H), 3.76 (s, 3 H), 2.80 (m, 2 H), 2.28 (m, 1 H), 2.06 (m, 1 H), 1.45 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.2, 172.6, 155.4, 133.1, 130.8, 128.6, 119.8, 91.3, 87.5, 80.1, 52.8, 52.5, 41.4, 28.3, 26.7 ppm. IR (neat): $\tilde{\nu}$ = 3363, 2977, 2201, 1711, 1668, 1490, 1158 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{23}NO_5Na$ [M + Na]$^+$ 368.14739; found 368.1473.

Methyl (*S*)-2-(*tert*-Butoxycarbonylamino)-5-oxohept-6-ynoate (3c): A 0.5 M solution of ethynylmagnesium bromide in THF (82.2 mL, 41.10 mmol) was added to oxopyrrolidine **2** (5.0 g, 20.55 mmol) at 0 °C, and the mixture was allowed to react for 2 h. A 1 M aqueous solution of $NaHSO_4$ (30 mL) was then added and the mixture was extracted with diethyl ether (3× 100 mL). The organic layer was washed with an aqueous saturated solution of Na_2SO_4 (3× 100 mL), dried with $MgSO_4$, and concentrated under vacuum. The crude residue was purified by silica gel chromatography (dichloromethane/diethyl ether, 9.5:0.5) to yield a clear yellow solid (4.43 g, 80%), m.p. 47–50 °C. R_f = 0.45 (dichloromethane/diethyl ether, 95:5). $[\alpha]_D^{25}$ = +16.9 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.22 (d, *J* = 7.5 Hz, 1 H), 4.32 (m, 1 H), 3.76 (s, 3 H), 3.34 (s, 1 H), 2.72 (m, 2 H), 2.23 (m, 1 H), 1.97 (m, 1 H), 1.44 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.6, 172.5, 155.4, 81.1, 80.1, 79.3, 52.6, 52.5, 41.4, 28.3, 26.4 ppm. IR (neat): $\tilde{\nu}$ = 3361, 3252, 2978, 2092, 1740, 1682, 1512, 1366, 1160 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{19}NO_5Na$ [M + Na]$^+$ 292.11609; found 292.1161.

1-*tert*-Butyl 2-Methyl (*S*,*E*)-5-(2-Oxopentylidene)pyrrolidine-1,2-dicarboxylate (4a): A 0.25 M solution of CH_3SO_3H in CH_2Cl_2 (10.3 mL) was added to a solution of ynone **3a** (1.00 g, 3.21 mmol) in dry methanol (10 mL) and the mixture was stirred at room temperature for 4 h. Diethyl ether (10 mL) and Na_2CO_3 (0.409 g) were then added to this solution and the mixture was stirred for 30 min, filtered, and the organic layer concentrated under vacuum. The residue was purified by silica gel chromatography (pentane/diethyl ether, 50:50) to yield a white solid (0.90 g, 90%), m.p. 64–66 °C. R_f = 0.60 (pentane/diethyl ether, 50:50). $[\alpha]_D^{25}$ = +27.6 (*c* = 1, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.02 (s, 1 H), 4.59 (dd, *J* = 3.5, *J* = 9.4 Hz, 1 H), 3.75 (s, 3 H), 3.41 (dddd, *J* = 1.5, *J* = 3.8, *J* = 9.0, *J* = 18.5 Hz, 1 H), 3.05 (m, 1 H), 2.44 (t, *J* = 7.4 Hz, 2 H), 2.21 (m, 1 H), 2.01 (m, 1 H), 1.63 (sext, *J* = 7.4 Hz, 2 H), 1.49 (s, 9 H), 0.92 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.2, 172.2, 155.9, 151.1, 104.5, 83.0, 61.8, 52.4, 46.7, 30.7, 28.0, 25.6, 18.2, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2961, 1728, 1575, 1314, 1273, 1042 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{25}NO_5Na$ [M + Na]$^+$ 334,16249; found 334,1625.

1-*tert*-Butyl 2-Methyl (*S*,*E*)-5-(2-Oxo-2-phenylethylidene)pyrrolidine-1,2-dicarboxylate (4b): A 0.25 M solution of CH_3SO_3H in CH_2Cl_2 (9.26 mL) was added to a solution of ynone **3b** (1.0 g, 2.90 mmol) in methanol (10 mL) and the mixture was stirred at room temperature for 4 h. Diethyl ether (10 mL) and Na_2CO_3 (0.368 g) were added to this solution and the mixture was stirred for 30 min, filtered, and the organic layer concentrated under vacuum. The residue was purified by silica gel chromatography (pentane/diethyl ether, 50:50) to yield a white solid (0.90 g, 90%), m.p. 110–112 °C. R_f = 0.50 (pentane/diethyl ether, 50:50). $[\alpha]_D^{25}$ = –5.3 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (m, 2 H), 7.82 (s, 1 H), 7.40 (m, 3 H), 4.66 (dd, *J* = 3.5, *J* = 9.4 Hz, 1 H), 3.77 (s, 3 H), 3.56 (dddd, *J* = 1.5, *J* = 3.8, *J* = 9.0, *J* = 18.5 Hz, 1 H), 3.22 (m, 1 H), 2.28 (m, 1 H), 2.07 (m, 1 H), 1.51 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.0, 172.2, 158.4, 151.1, 140.1, 131.7, 128.3, 127.9, 101.4, 83.2, 62.1, 52.4, 31.2, 28.0, 25.5 ppm. IR (neat): $\tilde{\nu}$ = 2976, 1732, 1644, 1561, 1320, 1243, 1147, 1039 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{23}NO_5Na$ [M + Na]$^+$ 368.14739; found 368.1472.

1-*tert*-Butyl 2-Methyl (*S*,*E*)-5-(2-Oxoethylidene)pyrrolidine-1,2-dicarboxylate (4c): A 0.25 M solution of CH_3SO_3H in CH_2Cl_2 (2.97 mL) was added to a solution of ynone **3c** (1.0 g, 3.71 mmol) in dry CH_2Cl_2 (10 mL) and the mixture was stirred at room temperature for 30 min. Diethyl ether (10 mL) and Na_2CO_3 (0.118 g) were added to this solution and the mixture was stirred for 30 min, filtered, and the organic layer concentrated under vacuum. The residue was purified by silica gel chromatography (diethyl ether) to yield a white solid (0.85 g, 85%), m.p. 96–98 °C. R_f = 0.55 (diethyl ether). $[\alpha]_D^{25}$ = +20.0 (*c* = 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.73 (d, *J* = 7.3 Hz, 1 H), 6.74 (d, *J* = 7.3 Hz, 1 H), 4.66 (dd, *J* = 3.1, *J* = 9.2 Hz, 1 H), 3.76 (s, 3 H), 3.29 (dddd, *J* = 1.4, *J* = 3.5, *J* = 8.8, *J* = 16.9 Hz, 1 H), 3.06 (m, 1 H), 2.29 (m, 1 H), 2.09 (m, 1 H), 1.49 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.3, 171.8, 160.2, 150.7, 108.3, 83.9, 62.3, 52.6, 29.0, 28.0, 25.4 ppm. IR (neat): $\tilde{\nu}$ = 2977, 1731, 1369, 1133 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{19}NO_5Na$ [M + Na]$^+$ 292.11609; found 292.1160.

Methyl (*S*,*Z*)-2-(*tert*-Butoxycarbonylamino)-7-methoxy-5-oxodec-6-enoate (5a): Chloro[1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene]gold(I) (103 mg, 0.192 mmol) and silver hexafluoroantimonate ($AgSbF_6$, 66 mg, 0.192 mmol) were added to a solution of compound **3a** (300 mg, 0.96 mmol) in dry methanol (2 mL). The mixture was stirred for 12 h at room temperature, then filtered through Celite, concentrated under vacuum, and purified by chromatography over silica gel (diethyl ether/pentane, 6:4) to yield a colorless oil (182 mg, 55%). R_f = 0.70 (diethyl ether/pentane, 6:4). $[\alpha]_D^{25}$ = +10.3 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.39 (s, 1

H), 5.22 (d, J = 8.0 Hz, 1 H), 4.28 (m, 1 H), 3.74 (s, 3 H), 3.64 (s, 3 H), 2.68 (m, 2 H), 2.53 (m, 2 H), 2.14 (m, 1 H), 1.96 (m, 1 H), 1.54 (m, 2 H), 1.43 (s, 9 H), 0.93 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.3, 176.9, 173.1, 155.5, 98.3, 79.8, 55.4, 53.3, 52.3, 40.2, 34.5, 28.3, 26.9, 20.8, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 3356, 2965, 1743, 1712, 1579, 1436, 1161 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{29}NO_6Na$ [M + Na]$^+$ 336.18926; found 336.1891.

Methyl (*S*)-2-(*tert*-Butoxycarbonylamino)-7,7-dimethoxy-5-oxoheptanoate (6c): A 0.25 M solution of CH_3SO_3H in CH_2Cl_2 (3 mL) was added to a solution of ynone **3c** (0.500 g, 1.86 mmol) in dry CH_3OH (5 mL). The solution was stirred for 4 h at room temperature and then Na_2CO_3 (106 mg, 1 mmol) and diethyl ether (5 mL) were added. The mixture was stirred for 30 min, diethyl ether (10 mL) was added, and the precipitate was filtered. The solution was concentrated and the residue purified by chromatography over silica gel using diethyl ether as eluent to yield a colorless oil (46%). R_f = 0.66 (diethyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.20 (d, J = 8.0 Hz, 1 H), 4.78 (t, J = 5.6 Hz, 1 H), 4.27 (m, 1 H), 3.74 (s, 3 H), 3.35 (m, 6 H), 2.72 (d, J = 5.6 Hz, 2 H), 2.57 (m, 2 H), 2.13 (m, 1 H), 1.88 (m, 1 H), 1.44 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.2, 172.9, 155.5, 101.5, 79.9, 53.9, 53.8, 52.8, 52.4, 46.5, 39.6, 28.3, 26.1 ppm. IR (neat): $\tilde{\nu}$ = 3357, 2976, 1743, 1708, 1513, 1365, 1161, 1049 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{27}NO_7Na$ [M + Na]$^+$ 356.16852; found 356.1686.

Methyl (*S*,*Z*)-5-(2-Oxopentylidene)pyrrolidine-2-carboxylate (7a): TFA (1.5 mL) was added to a solution of **4a** (500 mg, 1.61 mmol) in CH_2Cl_2 (1.5 mL). The solution was allowed to react at room temperature for 2 h and then diethyl ether (10 mL) was added. Sodium carbonate (1.5 g) was added and the mixture was stirred for 30 min and then filtered. The organic layer was concentrated under vacuum and the residue purified by chromatography over silica gel using diethyl ether as eluent to yield a colorless oil (326 mg, 96%), m.p. 99–101 °C. R_f = 0.62 (diethyl ether). $[\alpha]_D^{25}$ = –191.3 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.92 (s, 1 H), 5.16 (s, 1 H), 4.44 (dd, J = 5.2, J = 8.5 Hz, 1 H), 3.75 (s, 3 H), 2.67 (m, 2 H), 2.31 (m, 1 H), 2.27 (t, J = 7.4 Hz, 2 H), 2.14 (m, 1 H), 1.62 (sext, J = 7.4 Hz, 2 H), 0.92 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.1, 172.1, 165.9, 90.6, 61.0, 52.6, 44.0, 31.4, 25.6, 19.4, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 3298, 2958, 1740, 1623, 1544, 1201, 1059 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{17}NO_3Na$ [M + Na]$^+$ 234.11061; found 234.1104.

Methyl (*S*,*Z*)-5-(2-Oxo-2-phenylethylidene)pyrrolidine-2-carboxylate (7b): Compound **7b** was obtained from **4b** (500 mg, 1.45 mmol) by following the procedure described above for the synthesis of **7a** and purified by chromatography over silica gel (CH_2Cl_2/diethyl ether, 85:15) to yield a pale-yellow solid (337 mg, 95%), m.p. 99–101 °C. R_f = 0.65 (CH_2Cl_2/diethyl ether, 75:25). $[\alpha]_D^{25}$ = –188.0 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.36 (s, 1 H), 7.89 (m, 2 H), 7.42 (m, 3 H), 5.87 (s, 1 H), 4.53 (dd, J = 5.3, J = 8.5 Hz, 1 H), 3.77 (s, 3 H), 2.80 (m, 2 H), 2.19 (m, 1 H), 2.36 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.8, 171.8, 167.7, 139.9, 130.8, 128.8, 127.1, 87.5, 61.1, 52.6, 31.8, 25.5 ppm. IR (neat): $\tilde{\nu}$ = 3289, 2956, 1740, 1608, 1578, 1505, 1322, 1210, 1178, 1058, 706 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{15}NO_3Na$ [M + Na]$^+$ 268.09496; found 268.0948.

Methyl (*S*,*Z*)-5-(2-Oxoethylidene)pyrrolidine-2-carboxylate (7c): Compound **7c** was obtained from **4c** (500 mg, 1.86 mmol) by following the procedure described above for the synthesis of **7a** and purified by chromatography over silica gel (CH_2Cl_2/diethyl ether, 50:50) to yield a pale-yellow oil (236 mg, 75%). R_f = 0.25 (CH_2Cl_2/diethyl ether, 50:50). $[\alpha]_D^{25}$ = –167.9 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.01 (s, 1 H), 9.07 (d, J = 2.0 Hz, 1 H), 5.15 (d, J = 1.4 Hz, 1 H), 4.49 (dd, J = 5.2, J = 8.6 Hz, 1 H), 3.77 (s, 3 H), 2.73 (m, 2 H), 2.34 (m, 1 H), 2.28 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.8, 171.6, 167.6, 91.8, 61.2, 52.7, 31.5, 25.4 ppm. IR (neat): $\tilde{\nu}$ = 3278, 2955, 1737, 1592, 1539, 1374, 1173 cm^{-1}. HRMS (ESI): calcd. for $C_8H_{11}NO_3Na$ [M + Na]$^+$ 192.06366; found 192.0637.

***tert*-Butyl 2-Oxopyrrolidine-1-carboxylate (9):** A solution of di-*tert*-butyl dicarbonate (14.10 g, 26.25 mmol) in acetonitrile (20 mL) was added dropwise to a 0 °C solution of pyrrolidin-2-one (**8**; 5 g, 58.75 mmol) in acetonitrile (50 mL). DMAP (718 mg, 5.88 mmol) was added portionwise and the mixture was stirred at room temperature for 3 h. It was then concentrated under vacuum and the residue dissolved in ethyl acetate (200 mL) and washed with a 1 M aqueous solution of HCl (10 mL). The organic layer was evaporated under vacuum and the crude residue purified over silica gel (EtOAc/petroleum ether, 9:1) to yield the desired compound as a pale oil (10.34 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (t, J = 7.2 Hz, 2 H), 2.52 (t, J = 8.1 Hz, 2 H), 2.01 (m, 2 H), 1.53 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.4, 150.2, 82.8, 46.5, 33.0, 28.0, 17.4 ppm. IR (neat): $\tilde{\nu}$ = 2979, 1780, 1749, 1709, 1366, 1297, 1145, 1015 cm^{-1}.

***tert*-Butyl 4-Oxonon-5-ynylcarbamate (10a):** A 2.5 M solution of *n*-butyllithium (35.10 mmol) in hexanes (14.0 mL) was added to a solution of pent-1-yne (2.76 g, 40.49 mmol) in anhydrous THF (100 mL) at –50 °C under nitrogen. This mixture was stirred at –50 °C for 30 min and added to a solution of *tert*-butyl 2-oxopyrrolidine-1-carboxylate (**9**; 5 g, 26.99 mmol) in THF (20 mL) cooled to –50 °C amd then stirred at room temperature for 3 h. The solution was diluted with diethyl ether (100 mL), washed with a 1 M aqueous solution of $NaHSO_4$ (36 mL) and then aqueous saturated solution of Na_2SO_4 (3× 50 mL), dried with $MgSO_4$, and concentrated under vacuum. The crude mixture was purified by chromatography over silica gel (CH_2Cl_2/diethyl ether, 95:5) to yield a yellow oil (6.50 g, 95%). R_f = 0.54 (CH_2Cl_2/diethyl ether, 95:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.74 (br. s, 1 H), 3.15 (m, 2 H), 2.60 (t, J = 7.3 Hz, 2 H), 2.35 (t, J = 7.1 Hz, 2 H), 1.84 (quint., J = 7.1 Hz, 2 H), 1.61 (sext, J = 7.2 Hz, 2 H), 1.44 (s, 9 H), 1.02 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.5, 156.0, 94.6, 80.9, 79.2, 42.8, 39.8, 28.4, 24.4, 21.2, 20.9, 13.5 ppm. IR (neat): $\tilde{\nu}$ = 3356, 2968, 2935, 2211, 1671, 1514, 1365, 1248, 1162 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{23}NO_3Na$ [M + Na]$^+$ 276.15756; found 276.1577.

***tert*-Butyl 4-Oxo-6-phenylhex-5-ynylcarbamate (10b):** Compound **10b** was obtained from phenylacetylene (4.13 g, 40.49 mmol) following the procedure described above for the synthesis of **10a** to yield, after chromatography (CH_2Cl_2/diethyl ether, 95:5), a yellow solid (7.29 g, 94%), m.p. 64 °C. R_f = 0.51 (CH_2Cl_2/diethyl ether, 95:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (m, 2 H), 7.47 (m, 1 H), 7.39 (m, 2 H), 4.65 (br. s, 1 H), 3.20 (m, 2 H), 2.74 (t, J = 7.2 Hz, 2 H), 1.92 (quint., J = 7.0 Hz, 2 H), 1.44 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.3, 156.0, 133.1, 130.8, 128.6, 119.8, 91.1, 87.7, 79.3, 42.7, 39.8, 28.4, 24.4 ppm. IR (neat): $\tilde{\nu}$ = 3368, 2978, 2868, 2203, 1663, 1516, 1247, 759 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{21}NO_3Na$ [M + Na]$^+$ 310.14191; found 310.1418.

***tert*-Butyl 4-Oxohex-5-ynylcarbamate (10c):** *tert*-Butyl 2-oxopyrrolidine-1-carboxylate (**9**; 5 g, 26.99 mmol) was added at 0 °C under nitrogen to a 0.5 M solution of ethynylmagnesium bromide (53.98 mmol) in THF (108 mL) and stirred for 3 h at room temperature. The solution was diluted with diethyl ether (100 mL), washed with a 1 M aqueous solution of $NaHSO_4$ (81 mL) and then an aqueous saturated solution of Na_2SO_4 (2× 50 mL), dried with $MgSO_4$, and concentrated under vacuum. The crude mixture was

purified by chromatography over silica gel (pentane/diethyl ether, 60:40) to yield a yellow solid (3.99 g, 70%), m.p. 68–70 °C. R_f = 0.53 (pentane/diethyl ether, 60:40). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.73 (br. s, 1 H), 3.29 (s, 1 H), 3.16 (m, 2 H), 2.66 (t, J = 7.2 Hz, 2 H), 1.86 (quint., J = 7.0 Hz, 2 H), 1.44 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.7, 156.0, 81.3, 79.3, 79.0, 42.7, 39.6, 28.4, 24.1 ppm. IR (neat): $\tilde{\nu}$ = 3379, 3186, 2974, 2950, 2086, 1703, 1678, 1366, 1273, 1160, 1003, 778 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{17}NO_3Na$ [M + Na]$^+$ 234.11061; found 234.1105.

***tert*-Butyl (*E*)-2-(2-Oxopentylidene)pyrrolidine-1-carboxylate (11a):** A 0.25 M solution of CH_3SO_3H in CH_2Cl_2 (12.6 mL) was added to a solution of ynone **10a** (1 g, 3.95 mmol) in anhydrous methanol (10 mL). The mixture was stirred at room temperature for 3 h, neutralized with Na_2CO_3 (0.5 g), and diethyl ether (10 mL) was added. The mixture was filtered and the organic layer concentrated under vacuum. The residue was purified by chromatography over silica gel (pentane/diethyl ether, 5:5) to yield a white solid (0.91 g, 91%), m.p. 68–70 °C. R_f = 0.55 (pentane/diethyl ether, 5:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.96 (t, J = 1.7 Hz, 1 H), 3.66 (t, J = 7.2 Hz, 2 H), 3.19 (td, J = 7.8, J = 1.7 Hz, 2 H), 2.41 (t, J = 7.4 Hz, 2 H), 1.87 (quint., J = 7.5 Hz, 2 H), 1.63 (sext, J = 7.4 Hz, 2 H), 1.54 (s, 9 H), 0.92 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.2, 157.1, 151.9, 103.9, 82.1, 49.5, 46.7, 32.5, 28.2, 21.0, 18.4, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 2958, 1708, 1578, 1375, 1314, 1237, 1142 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{23}NO_3Na$ [M + Na]$^+$ 276.15756; found 276.1577.

***tert*-Butyl (*E*)-2-(2-Oxo-2-phenylethylidene)pyrrolidine-1-carboxylate (11b):** Ynone **10b** (1 g, 3.48 mmol) was treated with a 0.25 M solution of CH_3SO_3H in CH_2Cl_2 (11.1 mL) under the conditions described above for the synthesis of **11a**. The residue was purified by chromatography over silica gel (pentane/diethyl ether, 5:5) to yield a white solid (0.90 g, 90%), m.p. 138–139 °C. R_f = 0.48 (pentane/diethyl ether, 6:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (m, 2 H), 7.75 (t, J = 1.7 Hz, 1 H), 7.45 (m, 3 H), 3.73 (t, J = 7.3 Hz, 2 H), 3.66 (td, J = 7.7, J = 1.7 Hz, 2 H), 1.94 (quint., J = 7.5 Hz, 2 H), 1.56 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.0, 159.6, 152.0, 140.4, 131.6, 128.3, 127.8, 100.8, 83.2, 49.8, 33.0, 28.2, 21.0 ppm. IR (neat): $\tilde{\nu}$ = 2983, 1716, 1641, 1561, 1369, 1307, 1141, 836, 705 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{21}NO_3Na$ [M + Na]$^+$ 310.14191; found 141.1418.

***tert*-Butyl (*E*)-2-(2-Oxoethylidene)pyrrolidine-1-carboxylate (11c):** Ynone **10c** (1 g, 4.73 mmol) was treated with a 0.25 M solution of CH_3SO_3H in CH_2Cl_2 (7.57 mL) under the conditions described above for the synthesis of **4c**. The residue was purified by chromatography over silica gel (diethyl ether) to yield a white solid (0.83 g, 83%), m.p. 70–72 °C. R_f = 0.45 (diethyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.74 (d, J = 7.6 Hz, 1 H), 6.65 (td, J = 7.6, J = 1.7 Hz, 1 H), 3.75 (t, J = 7.1 Hz, 2 H), 3.16 (td, J = 7.7, J = 1.7 Hz, 2 H), 1.98 (quint., J = 7.4 Hz, 1 H), 1.54 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.4, 161.1, 151.5, 108.0, 83.0, 50.0, 30.5, 28.1, 20.9 ppm. IR (neat): $\tilde{\nu}$ = 2978, 1720, 1650, 1603, 1369, 1308, 1122, 847 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{17}NO_3Na$ [M + Na]$^+$ 234.11061; found 234.1107.

***tert*-Butyl (*S*)-2-[(*tert*-Butyldiphenylsilyloxy)methyl]-5-oxopyrrolidine-1-carboxylate (13):** L-Pyroglutaminol (**12**; 5 g, 43.4 mmol), *tert*-butyldiphenylsilyl chloride (14.32 g, 52.11 mmol), and imidazole (7.39 g, 108.57 mmol) were dissolved in DMF (50 mL) and the mixture stirred at 0 °C for 12 h. AcOEt (300 mL) and toluene (200 mL) were then added. The organic layer was washed with water and dried with $MgSO_4$. The solution was concentrated under vacuum and di-*tert*-butyl dicarbonate (14.22 g, 65.14 mmol), triethylamine (4.39 g, 43.43 mmol), and DMAP (2.65 g, 21.71 mmol) were added to the crude residue dissolved in CH_2Cl_2 (100 mL). The mixture was stirred at room temperature for 5 h, washed with a saturated aqueous solution of Na_2SO_4, and concentrated under vacuum. The crude residue was purified by chromatography over silica gel (diethyl ether/pentane, 50:50) to yield a yellow solid (8.56 g, 82%), m.p. 112–113 °C. R_f = 0.43 (diethyl ether/pentane, 50:50). $[\alpha]_D^{25}$ = –37.6 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (m, 4 H), 7.40 (m, 6 H), 4.21 (m, 1 H), 3.90 (dd, J = 10.4, J = 4.1 Hz, 1 H), 3.71 (dd, J = 10.4, J = 2.4 Hz, 1 H), 2.80 (dt, J = 17.5, J = 10.4 Hz, 1 H), 2.42 (m, 1 H), 2.15 (m, 2 H), 1.43 (s, 9 H), 1.05 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.0, 149.7, 135.5, 133.0, 132.6, 129.9, 127.8, 82.6, 65.0, 58.8, 32.3, 28.0, 26.8, 21.1, 19.1 ppm. IR (neat): $\tilde{\nu}$ = 2930, 1746, 1706, 1307, 1105, 704, 503 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{35}NO_4NaSi$ [M + Na]$^+$ 476.22331; found 476.2235.

***tert*-Butyl (*S*)-1-(*tert*-Butyldiphenylsilyloxy)-5-oxodec-6-yn-2-ylcarbamate (14):** A 2.5 M solution of *n*-butyllithium (5.73 mL, 14.33 mmol) in hexanes was added dropwise to a solution of pent-1-yne (1.12 g, 16.53 mmol) in anhydrous THF (25 mL) at –50 °C. The mixture was stirred for 30 min and slowly added at –50 °C to a solution of *tert*-butyl (*S*)-2-[(*tert*-butyldiphenylsilyloxy)methyl]-5-oxopyrrolidine-1-carboxylate (**13**; 5.00 g, 11.02 mmol) in anhydrous THF (50 mL). The mixture was allowed to react at –50 °C for 3 h and a 1 M aqueous solution of $NaHSO_4$ (12 mL) was then added. The organic layer was extracted with diethyl ether (300 mL), washed with an aqueous saturated solution of Na_2SO_4 (2 × 30 mL), and dried with $MgSO_4$. After filtration, the organic layer was concentrated under vacuum and the crude residue was purified by chromatography over silica gel (diethyl ether/pentane, 50:50) to yield a pale oil (5.29 g, 92%). R_f = 0.64 (diethyl ether/pentane, 50:50). $[\alpha]_D^{25}$ = –12.8 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (m, 4 H), 7.41 (m, 6 H), 4.67 (d, J = 8.6 Hz, 1 H), 3.64 (m, 3 H), 2.59 (td, J = 7.6, J = 1.9 Hz, 2 H), 2.33 (t, J = 7.1 Hz, 2 H), 1.90 (m, 2 H), 1.60 (sext, J = 7.2 Hz, 2 H), 1.44 (s, 9 H), 1.07 (s, 9 H), 1.01 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.5, 155.6, 136.5, 135.5, 133.2, 133.1, 129.8, 127.8, 94.4, 80.9, 79.3, 65.8, 51.4, 42.3, 28.4, 26.9, 26.2, 21.2, 20.9, 19.3, 13.5 ppm. IR (neat): $\tilde{\nu}$ = 3356, 2963, 2932, 2212, 1712, 1673, 1498, 1365, 1166, 1111, 701, 503 cm^{-1}. HRMS (ESI): calcd. for $C_{31}H_{43}NO_4NaSi$ [M + Na]$^+$ 544.28591; found 544.2858.

***tert*-Butyl (*S*,*E*)-2-[(*tert*-Butyldiphenylsilyloxy)methyl]-5-(2-oxopentylidene)pyrrolidine-1-carboxylate (15):** A 0.25 M CH_3SO_3H in CH_2Cl_2 (6.1 mL) was added to a solution of ynone **14** (1 g, 1.92 mmol) in CH_3OH (10 mL). The solution was stirred for 4 h at room temperature and then Na_2CO_3 (250 mg) and diethyl ether (10 mL) were added. The mixture was stirred for 30 min, concentrated under vacuum, and the residue was purified by chromatography over silica gel (pentane/diethyl ether, 60:40) to yield colorless oil (0.93 g, 93%). R_f = 0.83 (pentane/diethyl ether, 60:40). $[\alpha]_D^{25}$ = +21.3 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (m, 4 H), 7.40 (m, 6 H), 4.26 (m, 1 H), 3.69 (m, 2 H), 3.48 (m, 1 H), 3.10 (m, 1 H), 2.41 (t, J = 7.4 Hz, 2 H), 2.13 (m, 1 H), 1.99 (m, 1 H), 1.62 (sext, J = 7.4 Hz, 2 H), 1.39 (s, 9 H), 1.00 (s, 9 H), 0.91 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.2, 158.0, 151.4, 135.5, 133.2, 132.9, 129.8, 127.8, 127.7, 104.0, 82.1, 64.6, 61.8, 46.7, 31.8, 28.1, 26.6, 24.0, 19.1, 18.4, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2959, 2859, 1721, 1578, 1383, 1367, 1290, 1111, 700, 503 cm^{-1}. HRMS (ESI): calcd. for $C_{31}H_{43}NO_4NaSi$ [M + Na]$^+$ 544.28591; found 544.2859.

(*S*,*Z*)-1-[5-(Hydroxymethyl)pyrrolidin-2-ylidene]pentan-2-one (16): Compound **15** (1 g, 1.92 mmol) was dissolved in a 10% KOH methanolic solution (10 mL) and stirred for 5 h at 50 °C. The mixture

was concentrated under vacuum and the residue purified by chromatography over silica gel (diethyl ether/MeOH, 9:1) to yield a colorless oil (0.31 g, 88%). R_f = 0.61 (diethyl ether/MeOH, 9:1). $[a]_D^{25}$ = –14.6 (c = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.89 (s, 1 H), 5.06 (s, 1 H), 4.17 (s, 1 H), 4.01 (m, 1 H), 3.73 (dd, J = 11.5, J = 3.7 Hz, 1 H), 3.53 (dd, J = 11.5, J = 3.7 Hz, 1 H), 2.62 (m, 2 H), 2.20 (t, J = 7.6 Hz, 2 H), 2.05 (m, 1 H), 1.78 (m, 1 H), 1.59 (sext, J = 7.5 Hz, 2 H), 0.91 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.4, 167.7, 89.4, 65.1, 62.1, 43.9, 32.2, 23.4, 19.8, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 3293, 2958, 2930, 2871, 1609, 1521, 1300, 1057 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{17}NO_2Na$ $[M + Na]^+$ 206.1157; found 206.1160.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of all compounds; chiral HPLC of compounds **3a**–**c**, **4a**–**c**, **5a**–**b**, and **7a**–**c**.

Acknowledgments

The authors are deeply grateful to M. Le Roch for technical assistance with the chiral HPLC, Claudia Lalli for manuscript preparation, P. Jéhan (CRMPO, Université de Rennes 1) for the mass spectra, L. Toupet (IPR, Rennes) and the Ministry of Education and Training of Vietnam for its financial support.

[1] a) Y. Liu, M. Liu, S. Guo, H. Tu, Y. Zhou, H. Gao, *Org. Lett.* **2006**, *8*, 3345–3448; b) K. Stevens, A. J. Tyrrell, S. Skerrat, J. Robertson, *Org. Lett.* **2011**, *13*, 5964–5967; c) N. Gouault, M. Le Roch, C. Cornée, M. David, P. Uriac, *J. Org. Chem.* **2009**, *74*, 5614–5617; d) R. Spina, E. Colacino, B. Gabriele, G. Salerno, J. Martinez, F. Lamaty, *Org. Biomol. Chem.* **2012**, *10*, 9085–9089; e) M. Ostovar, C. M. Marson, *Tetrahedron* **2013**, *69*, 6639–6647; f) M. Yoshida, Y. Fujino, T. Doi, *Org. Lett.* **2011**, *13*, 4526–4529; g) H. Harkat, A. Blanc, J.-M. Weibel, P. Pale, *J. Org. Chem.* **2008**, *73*, 1620–1623; h) N. Gouault, M. Le Roch, A. Cheignon, P. Uriac, M. David, *Org. Lett.* **2011**, *13*, 4371–4373; i) H. Fuwa, K. Mizunuma, S. Matsukida, M. Sasaki, *Tetrahedron* **2011**, *67*, 4995–5010; j) B. J. Turunen, G. I. Georg, *J. Am. Chem. Soc.* **2006**, *128*, 8702–8703; k) J. Renault, Z. Qian, P. Uriac, N. Gouault, *Tetrahedron Lett.* **2011**, *52*, 2476–2479; l) F. Silva, M. Reiter, R. Mills-Webb, M. Sawicki, D. Klär, N. Bensel, A. Wagner, V. Gouverneur, *J. Org. Chem.* **2006**, *71*, 8390–8394; m) T. Kataoka, H. Kinoshita, S. Kinoshita, T. Iwamura, *Tetrahedron Lett.* **2002**, *43*, 7039–7041; n) S. Dreessen, S. Schabbert, E. Schaumann, *Eur. J. Org. Chem.* **2001**, 245–251; o) K. H. Nguyen, S. Tomasi, M. Le Roch, L. Toupet, J. Renault, P. Uriac, N. Gouault, *J. Org. Chem.* **2013**, *78*, 7809–7815; p) D.-W. Chuang, M. El-Shazly, B. D. Balaji, Y.-M. Chung, F.-R. Chang, Y.-C. Wu, *Eur. J. Org. Chem.* **2012**, 4533–4540; q) S.-L. Shi, M. Kanai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2012**, *51*, 3932–3935; *Angew. Chem.* **2012**, *124*, 3998; r) C. Zhou, A. V. Dubrovsky, R. C. Larock, *J. Org. Chem.* **2006**, *71*, 1626–1632; s) M. Schuler, F. Silva, C. Bobbio, A. Tessier, V. Gouverneur, *Angew. Chem. Int. Ed.* **2008**, *47*, 7927–7930; *Angew. Chem.* **2008**, *120*, 8045.

[2] a) M. J. Niphakis, G. I. Georg, *J. Org. Chem.* **2010**, *75*, 6019–6022; b) N. Gouault, M. Le Roch, G. de Campos Pinto, M. David, *Org. Biomol. Chem.* **2012**, *10*, 5541–5546; c) D. Liu, H. P. Acharya, M. Yu, J. Wang, V. S. C. Yeh, S. Kang, C. Chiruta, S. M. Jachak, D. L. J. Clive, *J. Org. Chem.* **2009**, *74*, 7417–7428; d) T. T. H. Trinh, K. H. Nguyen, P. de Aguiar Amaral, N. Gouault, *Beilstein J. Org. Chem.* **2013**, *9*, 2042–2047; e) M. J. Niphakis, G. I. Georg, *Org. Lett.* **2011**, *13*, 196–199.

[3] a) M. J. Niphakis, B. J. Turunen, G. I. Georg, *Org. Lett.* **2011**, *13*, 196–199; b) T. N. Grant, C. L. Benson, F. G. West, *Org. Lett.* **2008**, *10*, 3985–3988; c) A. R. Ranade, G. I. Georg, *J. Org. Chem.* **2014**, *79*, 984–992; d) J.-I. Matsuo, S. Sasaki, T. Hoshikawa, H. Ishibashi, *Tetrahedron* **2008**, *64*, 11224–11229; e) K. Sakamoto, E. Honda, N. Ono, H. Uno, *Tetrahedron Lett.* **2000**, *41*, 1819–1823.

[4] a) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.* **1976**, 734–736; b) K. Gilmore, V. Alabugin, *Chem. Rev.* **2011**, *111*, 6513–6556.

[5] H.-D. Vu, J. Renault, L. Toupet, P. Uriac, N. Gouault, *Eur. J. Org. Chem.* **2013**, 6677–6686.

[6] S. K. Panday, J. Prasad, D. K. Dikshit, *Tetrahedron: Asymmetry* **2009**, *20*, 1581–1632.

[7] T. Kawabata, W. Muramatsu, T. Nishio, T. Shibata, H. Schedel, *J. Am. Chem. Soc.* **2007**, *129*, 12890–12895.

[8] a) V. S. Kubyshkin, P. K. Mykhailiuk, S. Afonin, A. S. Ulrich, I. V. Komarov, *Org. Lett.* **2012**, *14*, 5254–5257; b) J. Yu, V. Truc, P. Riebel, E. Hierl, B. Mudryk, *Tetrahedron Lett.* **2005**, *46*, 4011–4013.

[9] a) P. K. Mandal, K. K. Kaluarachchi, D. Ogrin, S. G. Bott, J. S. McMurray, *J. Org. Chem.* **2005**, *70*, 10128–10131; b) V. J. Colandrea, I. E. Legiec, P. Huo, L. Yan, J. J. Hale, S. G. Mills, J. Bergstrom, D. Card, G. Chebret, R. Hajdu, C. A. Keohane, J. A. Milligan, M. J. Rosenbach, G.-J. Shei, S. M. Mandala, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2905–2908.

[10] CCDC-932590 (for **4a**) and -992751 (for **7b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

[11] a) L. Kürti, B. Czako (Ed.), *Strategic Applications of Named Reactions in Organic Synthesis* Elsevier, London, **2005**, p. 284–285; b) for a recent review, see: D. A. Engel, G. B. Dudley, *Org. Biomol. Chem.* **2009**, *7*, 4149–4158.

[12] M. J. Niphakis, B. J. Turunen, G. I. Georg, *J. Org. Chem.* **2010**, *75*, 6793–6805.

[13] M. N. Pennell, M. G. Unthank, P. Turner, T. D. Sheppard, *J. Org. Chem.* **2011**, *76*, 1479–1482.

[14] L. Banfi, A. Basso, V. Cerulli, G. Guanti, R. Riva, *J. Org. Chem.* **2008**, *73*, 1608–1611.

[15] N. Ikota, *Chem. Pharm. Bull.* **1992**, *40*, 1925–1927.

[16] A. A. Malik, R. J. Cormier, C. M. Sharts, *Org. Prep. Proced. Int.* **1986**, *18*, 345–352.

[17] a) M. Roth, P. Dubs, E. Götschi, A. Eschenmoser, *Helv. Chim. Acta* **1971**, *54*, 710–734; b) B. A. D. Neto, A. A. M. Lapis, A. B. Bernd, D. Russowsky, *Tetrahedron* **2009**, *65*, 2484–2496.

[18] a) M. M. Gugelshuk, D. J. Hart, Y. M. Tsaï, *J. Org. Chem.* **1981**, *46*, 3671–3675; b) J.-P. Célérier, E. Deloisy, G. Lhommet, P. Maitte, *J. Org. Chem.* **1979**, *44*, 3089–3089.

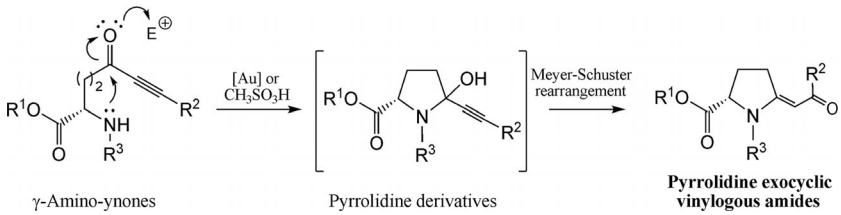
[19] a) A. Oppedisano, C. Prandi, P. Venturello, A. Deagostino, G. Goti, D. Scarpi, E. G. Occhiato, *J. Org. Chem.* **2013**, *78*, 11007–11016; b) R. J. Carra, M. T. Epperson, D. Y. Gin, *Tetrahedron* **2008**, *64*, 3629–3641; c) C. Herdeis, P. Küpper, S. Plé, *Org. Biomol. Chem.* **2006**, *4*, 524–529; d) M. T. Epperson, D. Y. Gin, *Angew. Chem. Int. Ed.* **2002**, *41*, 1778–1780; *Angew. Chem.* **2002**, *114*, 1856; e) T. Honda, M. Kimura, *Org. Lett.* **2000**, *2*, 3925–3927.

[20] a) L. Felner, K. Shenker, *Helv. Chim. Acta* **1970**, *53*, 754–763; b) T. Kametani, Y. Kigawa, H. Nemoto, M. Ihara, K. Fukumoto, *J. Chem. Soc. Perkin Trans. 1* **1980**, 1607–1613; c) A. S. Howard, R. B. Katz, J. P. Michael, *Tetrahedron Lett.* **1983**, *24*, 829–830; d) C. Herdeis, J. Tesler, *Eur. J. Org. Chem.* **1999**, 1407–1414; e) S. Fréville, P. Delbecq, V. M. Thuy, H. Petit, J.-P. Célérier, G. Lhommet, *Tetrahedron Lett.* **2001**, *42*, 4609–4611; f) J. P. Michael, C. B. de Koning, D. P. Pienaar, *Synlett* **2006**, 383–386; g) A. G. H. Wee, G.-H. Fan, *Org. Lett.* **2008**, *10*, 3869–3872.

[21] W. L. F. Armarego, C. L. L. Chai, *Purification of Laboratory Chemicals*, 6th ed., Elsevier, Oxford, UK, **2009**.

Received: March 31, 2014
Published Online: ■

Exocyclic Vinylogous Amides



Starting from γ-amino-ynones, the 1,2-addition of the protected nitrogen to the carbonyl group followed by a Meyer–Schuster rearrangement leads to pyrrolidine exocyclic vinylogous amides. This tandem reaction proved to be very efficient in the presence of methanesulfonic acid, leading to various enantiopure products.

H.-D. Vu, J. Renault,* T. Roisnel, N. Gouault, P. Uriac **1–11**

Methanesulfonic Acid Mediated Cyclization and Meyer–Schuster Rearrangement of γ-Amino-ynones: Access to Enantiopure Pyrrolidine Exocyclic Vinylogous Amides

Keywords: Rearrangement / Nitrogen heterocycles / Alkynes / Amines / Cyclization / Regioselectivity

