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Gold Catalysis

# Gold-Catalyzed Cycloisomerization of Alkyne-Containing Amino Acids: Controlled Tuning of C–N vs. C–O Reactivity

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**Abstract:** Versatile alkyne-containing amino acids were used as ambident precursors in the divergent synthesis of alkylidenelactones and 1-pyrrolines. Two gold-catalyzed protocols were applied for selective intramolecular O- and N-cycloisomerization reactions.

## Introduction

Homogenous gold catalysis has emerged as a powerful tool by which to achieve a diverse range of chemical transformations.[1,2] Moreover, heteroatoms such as O, S or N can react as nucleophiles with gold-activated alkyne moieties.[1a,3] In the particular case of an intramolecular nucleophilic addition, cyclization can occur in an *endo* or *exo* manner (5-*endo-dig*, 5-*exo-dig*, 6-*endo-dig* and 6-*exo-dig*), thus generating five- or six-membered heterocyclic rings.[4]

Alkyne-containing amino acids are versatile structures readily available by a number of methods and are accessible using very few transformations from economical starting materials.[5] Some such amino acids are commercially attainable in enantiomerically pure form. A variety of heterocycles have been prepared from amino acid derivatives using gold-catalyzed reactions.[6] As can be seen from the structure, alkyne-containing amino acids are ambident nucleophiles.[7] These amino acids have two well-positioned nucleophilic atoms – N and O – for participation in gold-catalyzed intramolecular cycloisomerizations. With the appropriate use of protecting groups, the nucleophilicities of the O and the N in the amino acid can be modulated, and thus two different classes of heterocycles (O-containing heterocycles and N-containing heterocycles)[8] can be obtained from the same ambident intermediate (Figure 1). In the case where the nucleophile is the oxygen atom of an alkynoic acid, gold-catalyzed intramolecular cycloisomerization generates the alkylidenelactone (Figure 1, path a).

In 2006 Genet et al. reported the first use of AuCl in MeCN, without additives, for the intramolecular nucleophilic addition of a carboxylic acid to gold-activated alkynes leading to γ-lactones.[9] A few months later, Pale and co-workers[10] published a similar cycloisomerization catalyzed by AuCl employing different 4-pentynoic acids, but in this case adding catalytic amounts of $K_2CO_3$ in order to generate the more reactive carboxylate group. The same conditions were used by Marchal et al. to transform *o*-alkynylbenzoic acids and 2-(2-ethynylphenyl)acetic acids into the corresponding alkylidenelactones.[11] More recently, a water-soluble $Au^{III}$–NHC complex,[12] dispersed thiol-stabilized gold nanoparticles in the pores of siliceous mesocellular foam[13] and a gold catalyst in combination with deep eutectic solvents[14] were applied in the catalytic cycloisomerization of γ-alkynoic acids. Nevertheless, the gold-catalyzed cycloisomerization of alkyne-containing amino acids was scarcely explored.[5b,15]

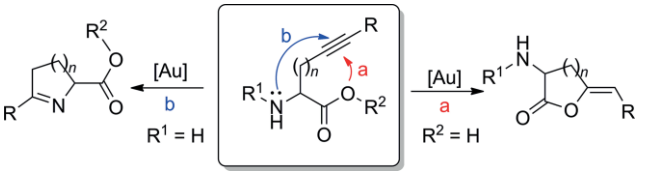


Figure 1. Possible modes of cycloisomerization of alkyne-containing amino acids.

In this regard, cycloisomerizations of alkyne-containing amino acids gave γ-alkylidenelactones, which proved to be enzyme-activated irreversible inhibitors of serine proteases.[16] In general, γ-alkylidenelactones display a variety of biological activities that are based on the susceptibility of the enol ester moiety to a nucleophilic attack, making this class of compounds "suicide" substrates.[15,17]

On the contrary, if the nucleophile of these alkyne-containing amino acids is the nitrogen atom, a gold-catalyzed intramolecular cycloisomerization produces the corresponding pyrrolines (Figure 1, path b).[18] The first example of gold-catalyzed intramolecular hydroamination was Utimoto's 1987 seminal report regarding the $Au^{III}$-catalyzed intramolecular hydroamination of 5-alkynylamines to form tetrahydropyridine derivatives.[19] It is worth noting that other transition metals like palladium and silver have been used to achieve C–N and C–O functionalization of alkynyl amino acids.[5b,18,20] Indeed, Rutjes has reported several studies detailing the intramolecular hydroamination of alkyne-containing amino acids (Scheme 1). The first is a detailed report of several types of Pd-catalyzed cyclo-

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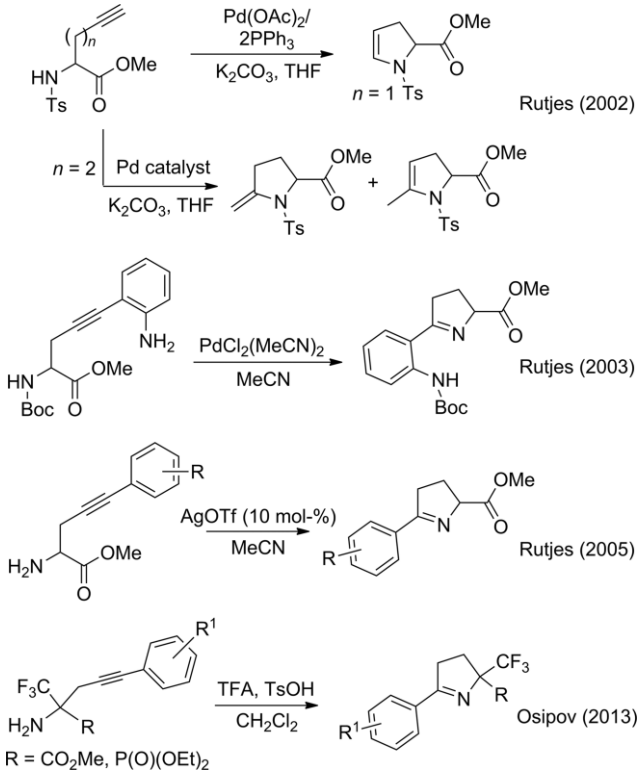
isomerization reactions of acetylene-containing amino acids using, in all cases, *N*-tosyl- or *N*-nosyl-protected amino acids to provide the corresponding cyclic enamides. The second report details the Pd-catalyzed cyclization of aniline containing acetylenic *N*-Boc-protected amino acids.[20a] This procedure is limited in that the pyrrolines are obtained only in the presence of an *ortho*-aniline nitrogen atom in the precursor. Without the *ortho*-aniline group, the reaction does not proceed. The third report involves an efficient AgOTf-catalyzed cyclization of aryl-substituted acetylene-containing amino acids.[18] In this case, the amino groups need to be unprotected to afford the pyrrolines. Finally, Osipov and co-workers used Brønsted acid catalysis to cycloisomerize $CF_3$-containing or phosphonate propargyl-containing amines; this procedure works specifically for these substrates.[21]

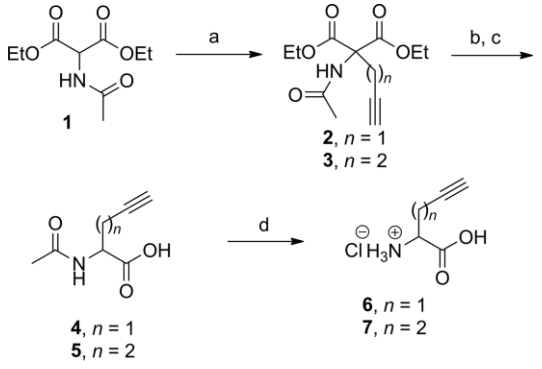



Scheme 1. Other C–N functionalization reactions of alkyne-containing amino acids.

In this context and as part of our research program concerning the application of gold chemistry to the synthesis of heterocycles,[22] we decided to explore the syntheses of γ-lactones and 1-pyrrolines from alkyne-containing amino acids by means of gold catalysis.

## Results and Discussion

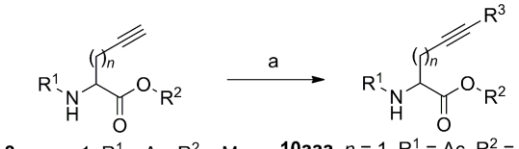
We prepared the cycloisomerization precursors, the alkyne-containing amino acids, from commercially available diethyl acetamidomalonate (**1**) (Scheme 2). Alkylation of **1** employing propargyl bromide ($n$ = 1) in the presence of $Cs_2CO_3$ afforded intermediate **2** in excellent yield.[23] In contrast, alkylation of **1** using homopropargyl derivatives ($n$ = 2, using both bromide and tosylate as the leaving groups) turned out to be quite difficult. Our best result, after extensive optimization efforts, used *t*BuOK and the homopropargyl tosylate in rigorously dried dioxane under refluxing conditions.[5a] Unfortunately, the best yield attained by these efforts was only 30 %.[24]




Scheme 2. (a) Base, solvent, X–$(CH_2)_n$–C≡CH ($n$ = 1: X = Br, $Cs_2CO_3$, MeCN, room temp., 99 %; $n$ = 2: X = OTs, *t*BuOK, dioxane, 100 °C, 30 %); (b) KOH, MeOH/$H_2O$, reflux, 4 h; (c) HCl (2 N) ($n$ = 1, 77 %, two steps); (d) HCl (2 N), reflux, 2 h ($n$ = 1, 98 %).

Acetylenic malonate derivatives **2** and **3** were readily converted into *N*-acetyl-protected alkynyl amino acids **4** and **5**, respectively, by base-promoted hydrolysis and subsequent decarboxylation. Removal of the acetyl group under acidic conditions generated alkynyl amino acids **6** and **7**, respectively.

The primary amine was protected using acetyl, Boc and tosyl groups, whereas the acid was converted into the corresponding methyl ester derivative. The terminal alkyne-containing protected amino acids **8** were subjected to Sonogashira coupling[25] in order to increase the diversity of the final heterocycles (Scheme 3).




**8aa**, $n$ = 1, $R^1$ = Ac, $R^2$ = Me
**8ba**, $n$ = 1, $R^1$ = Boc, $R^2$ = Me
**8ca**, $n$ = 1, $R^1$ = Ts, $R^2$ = Me
**9aa**, $n$ = 2, $R^1$ = Ac, $R^2$ = Me

**10aaa**, $n$ = 1, $R^1$ = Ac, $R^2$ = Me, $R^3$ = Ph
**10aab**, $n$ = 1, $R^1$ = Ac, $R^2$ = Me, $R^3$ = *p*-tolyl
**10aac**, $n$ = 1, $R^1$ = Ac, $R^2$ = Me, $R^3$ = naphthyl
**10baa**, $n$ = 1, $R^1$ = Boc, $R^2$ = Me, $R^3$ = Ph
**10bab**, $n$ = 1, $R^1$ = Boc, $R^2$ = Me, $R^3$ = *p*-tolyl
**10bac**, $n$ = 1, $R^1$ = Boc, $R^2$ = Me, $R^3$ = naphthyl
**10bad**, $n$ = 1, $R^1$ = Boc, $R^2$ = Me, $R^3$ = *p*-methoxyphenyl
**10bae**, $n$ = 1, $R^1$ = Boc, $R^2$ = Me, $R^3$ = *p*-nitrophenyl
**10baf**, $n$ = 1, $R^1$ = Boc, $R^2$ = Me, $R^3$ = *p*-(methoxycarbonyl)phenyl
**10caa**, $n$ =1, $R^1$ = Ts, $R^2$ = Me, $R^3$ = Ph

Scheme 3. (a) $R^3X$, CuI, $PPh_3$, $Pd(PPh_3)_4$, $Et_3N$, DMF.

With derivatives **8**, **9** and **10** in hand, several gold-catalyzed conditions were evaluated with the aim of forming cyclic enam-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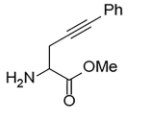
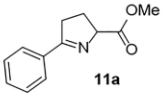
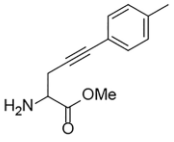
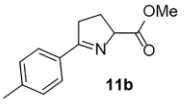
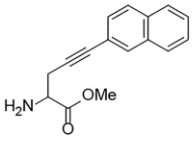
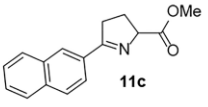
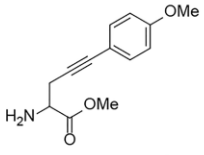
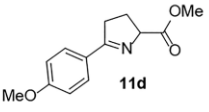
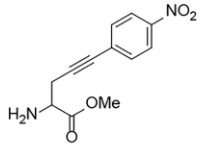
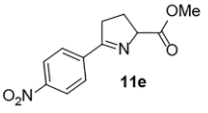
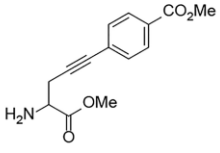
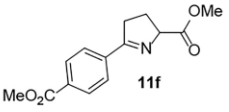
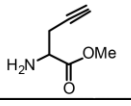
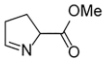
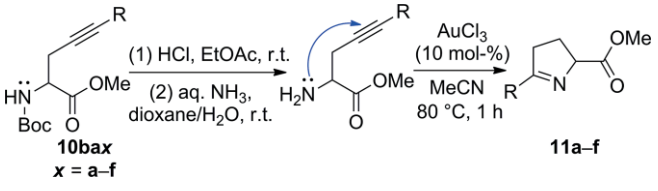
ides through C–N functionalization (Supporting Information; Table 1). Even though there are numerous examples of gold-catalyzed cyclizations of *N*-protected species in the literature,[26] no C–N functionalization was observed in our system under any of the conditions tested. However, *N*-deprotection afforded free amine species that readily participated in gold-catalyzed cycloisomerizations to produce the 1-pyrroline scaffold (Scheme 4). Of the gold catalysts examined, the most effective for this transformation was $AuCl_3$.[1h,1i,27]

Table 1. Gold-catalyzed C–N functionalization of alkynyl amino acids derivatives.

| Entry | Alkynyl amino acid | Pyrroline | Yield [%][a] |
|---|---|---|---|
| 1 |  |  **11a** | 75 |
| 2 |  |  **11b** | 55 |
| 3 |  |  **11c** | 71 |
| 4 |  |  **11d** | 41 |
| 5 |  |  **11e** | 90 |
| 6 |  |  **11f** | 87 |
| 7 |  |  | n.r. |

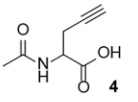
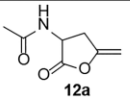
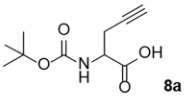
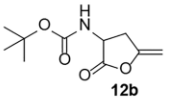
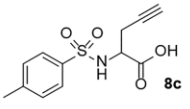
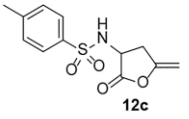
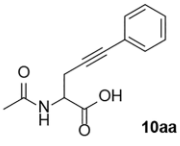
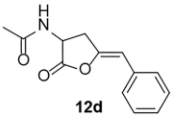
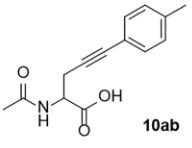
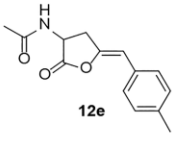
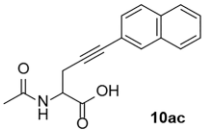
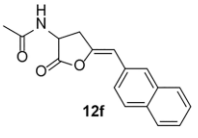
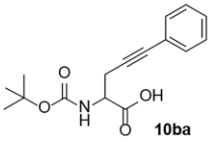
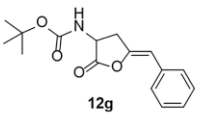
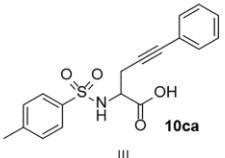
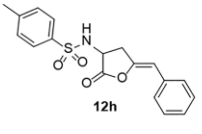
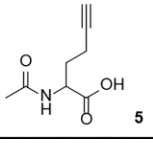
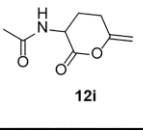
[a] Overall isolated yield after flash column chromatography from the Boc-protected compound (three steps: Boc removal, neutralization and gold-catalyzed cycloisomerization).




Scheme 4. Gold-catalyzed C–N functionalization.

Despite the fact that this transformation can be performed using other transition metals[18,20a] and Brønsted acids,[21] these methodologies have some limitations. The use of $AuCl_3$ provides a broader scope and good yields for the cycloisomerization of aryl-substituted alkynyl-containing amino acids en route to 1-pyrrolines (Table 1). This conversion proceeds exclusively by an $Au^{III}$-catalyzed 5-*endo-dig* N-cyclization. As can be seen from Table 1, aryl-substituted alkynyl amino acids bearing electron-withdrawing groups provide excellent yields of the C–N-functionalized product (Table 1, Entries 5 and 6). Reference compounds such as phenyl- and naphthyl-modified derivatives (Table 1, Entries 1 and 3) provide good yields of the desired pyrrolines **11a** and **11c** (75 % and 71 %, respectively). Lower yields were obtained with derivatives carrying electron-donat-

Table 2. Gold-catalyzed C–O functionalization of alkynyl amino acids derivatives.

| Entry | Alkynyl amino acid | Lactone | Yield [%] |
|---|---|---|---|
| 1 |  **4** |  **12a** | 95 |
| 2 |  **8a** |  **12b** | 94 |
| 3 |  **8c** |  **12c** | 97 |
| 4 |  **10aa** |  **12d** | 96[a] |
| 5 |  **10ab** |  **12e** | 85[a] |
| 6 |  **10ac** |  **12f** | 71[a] |
| 7 |  **10ba** |  **12g** | 90[a] |
| 8 |  **10ca** |  **12h** | 92[a] |
| 9 |  **5** |  **12i** | 95 |

[a] Isolated yield after the two steps of ester hydrolysis and gold-catalyzed cycloisomerization.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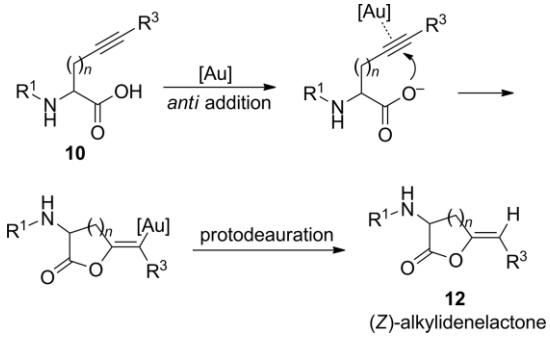
ing groups (Table 1, Entries 2 and 4) showing that the efficiency of cycloisomerization is controlled, to some extent, by electronic factors. The reaction of the propargylglycine methyl ester (Table 1, Entry 7) with a terminal alkyne failed to afford the pyrroline.

On the other hand, C–O functionalization can be achieved from the carboxylic acid derivatives of **8**, **9** and **10** ($R^2$ = H) employing Pale's conditions[10] of catalytic AuCl and $K_2CO_3$ in acetonitrile at room temp.; $K_2CO_3$ is necessary to obtain good yields of the enol-lactone product; the yield of product in its absence is significantly lower than is the case when $K_2CO_3$ is included. In order to explore the scope of this gold-catalyzed cycloisomerization and to prepare a number of enol-lactones, several alkyne-containing amino acids were subjected to cycloisomerization conditions (Table 2). In general, the reactions were complete in a short period of time and exhibited a high 5-*exo*-*dig* regioselectivity ($n$ = 1). Despite the known reactivity of enol-lactones,[5b] the isolated yields were excellent. In accord with the *anti* intramolecular addition mechanism (Scheme 5), in all cases the (*Z*)-γ-lactones were obtained. This stereochemistry was assigned on the basis of agreement between NOE experiments and the chemical shift of the vinylic hydrogen signal according to Pale's correlations (a chemical shift of $\delta \approx$ 5.50 ppm for an *anti*-vinyl hydrogen atom facing the ring oxygen atom, compared to a chemical shift for the *syn*-vinyl hydrogen signal at $\delta \approx$ 6.20 ppm).[15] In our examples, the chemical shifts of this hydrogen signal ranged from $\delta$ = 5.57 to 5.95 ppm, confirming the (*Z*) stereochemistry.




Scheme 5. Proposed reaction mechanism for gold-catalyzed cycloisomerization.

Unlike the gold-catalyzed C–N functionalization of terminal alkynes, the C–O functionalization of terminal alkynes provided enol-lactones in very satisfactory yields (Table 2, Entries 1–3, 9).

## Conclusions

Gold-catalyzed cycloisomerizations of alkyne-containing amino acids result in C–O functionalization to give, through 5-*exo*-*dig* cyclization, nine alkylidenelactones derived from amino acids in excellent yields. In contrast, the corresponding amino esters undergo gold-catalyzed intramolecular 5-*endo*-*dig* N-cycloisomerizations to afford six pyrrolinecarboxylate esters derived from amino acids in moderate to very good yields. Gold catalysis is remarkably efficient for the synthesis of both of these N- and O-heterocycles making this methodology an excellent alternative to the pre-existing strategies.

## Experimental Section

**General:** Chemical reagents were purchased from commercial sources and were used without further purification unless noted otherwise. Solvents were of analytical grade or were purified by standard procedures prior to use. $^1$H NMR spectra were recorded with a Bruker Avance at 300 MHz spectrometer in $CDCl_3$, in the presence of TMS ($\delta$ = 0.00 ppm) as the internal standard unless otherwise noted. $^{13}$C NMR assignments were made on the basis of chemical shifts and proton multiplicities (from inverse HSQC spectra). High-resolution mass spectra were recorded with a Bruker micrOTOF-Q II spectrometer. Analytical thin-layer chromatography (TLC) was carried out with silica gel 60 $F_{254}$ pre-coated aluminum sheets. Flash column chromatography was performed using silica gel 60 (230–400 mesh).

**Diethyl α-Acetamido-α-propargylmalonate (2):**[5a] Propargyl bromide (2.98 mL, 34.55 mmol) and $Cs_2CO_3$ (7.5 g, 23 mmol) were added to a solution of diethyl acetamidomalonate (**1**) (5.0 g, 23 mmol) in $CH_3CN$ (50 mL). The resulting heterogeneous mixture was stirred at room temp. for 18 h. Then, the reaction mixture was filtered, concentrated, and the residue was dissolved in AcOEt. The organic solution was washed with water, brine and dried with $Na_2SO_4$. Evaporation of the solvent gave the crude product as a yellowish white solid, which was purified by column chromatography (AcOEt/hexane) to give **2** as a white solid (6.73 g, 99 %). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.27 (t, $J$ = 7.1 Hz, 6 H), 1.98 (t, $J$ = 2.6 Hz, 1 H), 2.07 (s, 3 H), 3.29 (d, $J$ = 2.9 Hz, 2 H), 4.28 (qd, $J$ = 7.1, 1.8 Hz, 4 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 13.9, 22.9, 23.8, 62.9, 65.2, 71.3, 78.2, 167, 169.2 ppm.

**But-3-yn-1-yl 4-Methylbenzenesulfonate:** Tosyl chloride (0.75 g, 3.96 mmol) was added to a solution of 3-butyn-1-ol (0.2 mL, 2.64 mmol) in anhydrous $Et_2O$ (7 mL) at 0 °C. The resulting mixture was stirred for 15 min. After this time, KOH (0.44 g, 7.9 mmol) was added, and the solution was stirred at room temp. overnight. The resulting suspension was washed with HCl (5 %), dried with $Na_2SO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography (AcOEt/hexanes) to yield 0.590 g (99 %) of the desired product as colorless oil.

**Diethyl α-Acetamido-α-homopropargylmalonate (3):**[5a] Potassium *tert*-butoxide (0.167 g, 1.48 mmol) was added to a diethyl acetamidomalonate solution (0.3 g, 1.38 mmol) in dry dioxane (6 mL) at 0 °C. The resulting suspension was stirred vigorously at 60 °C for 2 h. Then, but-3-yn-1-yl 4-methylbenzenesulfonate (0.3 g, 1.38 mmol) was slowly added, and the obtained mixture was refluxed for 48 h. The resulting suspension was vacuum-filtered and the residue washed with $Et_2O$ (3 × 5 mL). The filtrate was concentrated in vacuo to give a yellow oil, which was purified by column chromatography (AcOEt/hexane) to yield 0.107 g (35 %) of product as slightly yellow crystals. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.26 (t, $J$ = 7.1 Hz, 6 H), 1.92 (t, $J$ = 2.7 Hz, 1 H), 2.03 (s, 3 H), 2.1 (m, 2 H), 2.61 (t, $J$ = 7.4 Hz, 2 H), 4.16–4.33 (m, 4 H), 6.82 (br. s, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 13.3, 13.9, 22.9, 30.8, 62.6, 65.7, 68.9, 82.6, 167.7, 169.2 ppm.

***N*-Acetyl-2-aminopent-4-ynoic Acid (4):**[5a] KOH (3.25 g, 58 mmol) was added portionwise to a well-stirred suspension of **2** (6.73 g, 26.3 mmol) in MeOH/$H_2O$ (5:1) (600 mL). The mixture was heated at reflux for 4 h. The solvents were evaporated to dryness, and the residue was dissolved with AcOEt and treated with 2 N HCl to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pH = 1. The aqueous phase was extracted with AcOEt, the combined organic layers were dried with $Na_2SO_4$ and the solvents evaporated to obtain the crude compound. Recrystallization from EtOAc afforded 2.8 g (70 %) of the desired *N*-acetyl-protected alkynyl amino acid **4**. $^1$H NMR (300 MHz, [D$_4$]methanol): $\delta$ = 2.01 (s, 3 H), 2.36 (t, *J* = 2.4 Hz, 1 H), 2.62–2.77 (m, 2 H), 4.52–4.56 (m, 1 H) ppm. $^{13}$C NMR (75 MHz, [D$_4$]methanol): $\delta$ = 22.5, 52.8, 72.2, 72.3, 80.3, 173.4, 173.5 ppm.

***N*-Acetyl-2-aminohex-5-ynoic Acid (5):**[5a] Compound **5** can be prepared from **3** (0.107 g, 0.4 mmol) as described above. The product was isolated as white crystals (0.585 g; 70 % yield). $^1$H NMR (300 MHz, [D$_6$]acetone): $\delta$ = 1.81–1.89 (m, 1 H), 1.93 (s, 3 H), 1.97–2.04 (m, 1 H), 2.24–2.30 (m, 2 H), 2.34 (t, *J* = 2.7 Hz, 1 H), 4.47–4.54 (m, 1 H), 7.45 (s, 1 H) ppm. $^{13}$C NMR (75 MHz, [D$_6$]acetone): $\delta$ = 15.8, 22.7, 31.7, 52.4, 70.8, 83.9, 171.3, 173.5 ppm.

**2-Aminopent-4-ynoic Acid Hydrochloride (6):**[5a] A solution of *N*-acetyl-2-aminopent-4-ynoic acid (**4**, 0.199 g, 1.28 mmol) in HCl (2 N) (4 mL) was stirred at reflux for 2 h. The solvent was evaporated in vacuo to give 2-aminopent-4-ynoic acid hydrochloride (**6**) (0.187 g, 98 %), which was used without further purification. $^1$H NMR (300 MHz, D$_2$O): $\delta$ = 2.54 (td, *J* = 2.7, 0.9 Hz, 1 H), 2.92 (dt, *J* = 5.5, 2.8 Hz, 2 H), 4.22 (d, *J* = 5.5 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, D$_2$O): $\delta$ = 19.9, 51.3, 74.2, 76.5, 170.3 ppm.

***N*-Boc-Propargylglycine (8b):**[5a] To a solution of 2-aminopent-4-ynoic acid hydrochloride (**6**) (0.2 g, 1.34 mmol) in water (5 mL) and dioxane (5 mL) was added $Boc_2O$ (434 mg, 1.99 mmol) and DIEA (0.695 mL, 3.98 mmol). After stirring at room temp. for 3 h, the solution was acidified to pH = 3 by addition of HCl (10 %), and extracted with AcOEt. The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated, providing a yellow oil, which was purified by column chromatography (AcOEt/hexane) to give 0.216 g (82 %) of the title compound. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.47 (s, 9 H), 2.09 (t, *J* = 2.4 Hz, 1 H), 2.72–2.77 (m, 2 H), 4.49–4.54 (m, 1 H), 5.38 (d, *J* = 8.1 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 22.5, 28.2, 51.7, 71.8, 80.6, 155.4, 174.7 ppm.

***N*-Tosylpropargylglycine (8c):**[5b] A mixture of 2-aminopent-4-ynoic acid hydrochloride (**6**) (441.7 mg; 2.95 mmol; 1 equiv.), $Na_2CO_3$ (650 mg; 6.12 mmol; 2.11 equiv.) and *p*TsCl (505.22 mg; 2.65 mmol; 0.9 equiv.) in *p*-dioxane/$H_2O$ (1:1; 8 mL) was stirred at room temp. overnigt. The reaction mixture was concentrated, and the pH adjusted to 4.0 with 10 % HCl. The aqueous layer was extracted with AcOEt (3 ×), dried with $Na_2SO_4$ and concentrated. The resulting crude product was purified by recrystallization from chloroform/hexane to give compound **8c** in 95 % yield. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.06 (t, *J* = 2.6 Hz, 1 H), 2.43 (s, 3 H), 2.62–2.8 (m, 2 H), 4.14–4.20 (m, 1 H), 5.5 (d, *J* = 8.8 Hz, 1 H), 7.31 (d, *J* = 8.3 Hz, 2 H), 7.76 (d, *J* = 8.3 Hz, 2 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 21.5, 23.8, 53.7, 72.7, 77.2, 127.2, 129.8, 144.1 ppm.

**General Procedure for the Synthesis of Methyl Esters 8 and 9:** To a stirred solution of the *N*-protected amino acid (1 equiv.) in methanol (50 mL) was added acetyl chloride (2.4 equiv.) at 0 °C. The mixture was stirred at room temp. overnight, and the solvent was evaporated under reduced pressure. The resulting crude product was dissolved in AcOEt, washed with $NaHCO_3$ (10 %) three times and dried with $Na_2SO_4$. Concentration of the organic solution gave the desired ester, which was purified by column chromatography (5 % AcOEt in hexane). In the case of *N*-Boc-protected amino acids, the ester was dissolved in $CH_2Cl_2$ and treated with an ethereal solution of diazomethane at 0 °C until a yellowish color persisted. The reaction mixture was stirred for 30 min, and diazomethane was quenched by the addition of AcOH until discoloration. The solvent was evaporated under reduced pressure, and the crude material was purified by flash column chromatography (hexane/AcOEt).

**Methyl 2-Acetylamino-4-pentynoate (8aa):**[23] Yield 90 %. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.03 (t, *J* = 2.6 Hz, 1 H), 2.06 (s, 3 H), 2.75–2.77 (m, 2 H), 3.79 (s, 3 H), 4.70–4.80 (m, 1 H), 6.4 (d, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 22.4, 23.0, 50.6, 52.7, 71.5, 78.4, 169.8, 170.8 ppm.

**Methyl 2-[(*tert*-Butoxycarbonyl)amino]-4-pentynoate (8ba):**[18] Yield 96 %. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.45 (s, 9 H), 2.04 (t, *J* = 2.5 Hz, 1 H), 2.65–2.77 (m, 2 H), 3.77 (s, 3 H), 4.47 (m, 1 H), 5.36 (d, *J* = 7.4 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 22.9, 28.2, 51.9, 52.6, 71.6, 78.5, 80.2, 155.0, 171.1 ppm.

**Methyl 2-[(4-Toluenesulfonyl)amino]-4-pentynoate (8ca):**[5b] Yield 94 %. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.03 (t, *J* = 2.6 Hz, 1 H), 2.41 (s, 3 H), 2.58–2.75 (m, 2 H), 3.60 (s, 3 H), 4.11 (dt, *J* = 8.8, 5.1 Hz, 1 H), 5.55 (d, *J* = 8.8 Hz, 1 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 7.73 (d, *J* = 8.2 Hz, 2 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 21.0, 23.5, 52.4, 53.5, 71.8, 126.7, 129.2, 136.3, 143.3, 169.5 ppm.

**General Procedure for the Sonogashira Reaction:** To a solution of *N*-protected methyl propargylglycinate (0.6 mmol, 1 equiv.) in *N*,*N*-dimethylformamide (DMF) (5 mL) were added *p*-iodotoluene (0.8 mmol, 1.2 equiv.), triethylamine (0.11 mL) and $Pd(PPh_3)_4$ (0.04 mmol). The clear brown solution rapidly darkened when copper(I) iodide (0.08 mmol) was added. The mixture was stirred under nitrogen at room temp. overnight. The solvent was evaporated in vacuo and the residue purified by chromatography (5 % AcOEt/hexane).

**Compound 10aaa:** Yield 99 %. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.06 (s, 3 H), 2.97 (d, *J* = 5.0 Hz, 2 H), 3.80 (s, 3 H), 4.77–4.89 (m, 1 H), 6.37–6.53 (m, 1 H), 7.24–7.40 (m, 5 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 23.1, 23.4, 51, 52.7, 83.6, 83.7, 122.8, 128.1, 120.2, 131.6, 169.8, 171.1 ppm. HRMS (ESI): calcd. for $C_{14}H_{16}NO_3$ $[M + H]^+$ 246.11247, found 246.11318.

**Compound 10aab:** Yield 99 %. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.07 (s, 3 H), 2.34 (s, 3 H), 2.97 (d, *J* = 5.0 Hz, 2 H), 3.81 (s, 3 H), 4.79–4.88 (m, 1 H), 7.10 (d, *J* = 8.1 Hz, 2 H), 7.27 (d, *J* = 8.1 Hz, 2 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 21.4, 23.2, 23.5, 51, 52.7, 82.8, 83.8, 119.7, 129, 131.5, 138.3, 169.8, 171.1 ppm. HRMS (ESI): calcd. for $C_{15}H_{17}NNaO_3$ $[M + Na]^+$ 282.11006, found 282.11021.

**Compound 10aac:** Yield 68 %. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.10 (s, 3 H), 3.05 (d, *J* = 4.7 Hz, 2 H), 3.85 (s, 3 H), 4.84–4.9 (m, 1 H), 6.42 (d, *J* = 8.1 Hz, 1 H), 7.4–7.55 (m, 3 H), 7.74–7.81 (m, 3 H), 7.89 (s, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 23.2, 23.6, 51.1, 52.8, 77.6, 84, 126.6, 126.6, 127.6, 127.7, 127.9, 128.5, 131.5, 169.9, 171.1 ppm. HRMS (ESI): calcd. for $C_{18}H_{18}NO_3$ $[M + H]^+$ 296.12812, found 296.12764.

**Compound 10baa:**[18] Yield 99.4 %. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.46 (s, 9 H), 2.87–3.03 (m, 2 H), 3.79 (s, 3 H), 4.47–4.62 (m, 1 H), 5.42 (d, *J* = 9.3 Hz, 1 H), 7.24–7.32 (m, 3 H), 7.34–7.42 (m, 2 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 23.8, 28.2, 52.2, 52.5, 80.1, 83.6, 83.8, 122.9, 128.1, 128.2, 131.6, 155.1, 171.3 ppm.

**Compound 10bab:** Yield 93.3 %. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.47 (s, 9 H), 2.33 (s, 3 H), 2.86–3.03 (m, 2 H), 3.79 (s, 3 H), 4.51–4.62 (m, 1 H), 5.44 (d, *J* = 8.3 Hz, 1 H), 7.09 (d, *J* = 8.1 Hz, 2 H), 7.30 (d, *J* = 8.1 Hz, 2 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 21.3, 23.8, 28.2, 52.2, 52.4, 79.9, 82.9, 83.6, 119.8, 128.8, 131.5, 138.0, 155.0, 171.3 ppm. HRMS (ESI): calcd. for $C_{18}H_{23}NO_4$ $[M + H]^+$ 317.1626, found 317.1627.

**Compound 10bac:** Yield 98.9 %. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.49 (s, 9 H), 2.95–3.09 (m, 2 H), 3.82 (s, 3 H), 4.53–4.69 (m, 1 H),


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5.51 (d, *J* = 8.1 Hz, 1 H), 7.36–7.53 (m, 3 H), 7.69–7.86 (m, 3 H), 7.92 (s, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 23.9, 28.2, 52.2, 52.5, 80.1, 83.9, 84.2, 120.2, 126.4, 126.5, 127.5, 127.6, 127.8, 128.4, 131.4, 132.6, 132.8, 155.1, 171.3 ppm. HRMS (ESI): calcd. for $C_{21}H_{23}NNaO_4$ $[M + Na]^+$ 376.15193, found 376.15106.

**Compound 10bad:** Yield 81 %. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.44 (s, 9 H), 2.82–2.99 (m, 2 H), 3.77 (s, 6 H), 4.43–4.58 (m, 1 H), 5.42 (d, *J* = 9.0 Hz, 1 H), 6.78 (d, *J* = 8.8 Hz, 2 H), 7.29 (d, *J* = 8.8 Hz, 2 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 23.4, 27.8, 51.9, 52.1, 54.8, 79.6, 81.7, 82.9, 113.4, 114.6, 132.6, 154.7, 158.9, 170.9 ppm. HRMS (ESI): calcd. for $C_{18}H_{23}NNaO_5$ $[M + Na]^+$ 356.14601, found 356.14684.

**Compound 10bae:**[18] Yield 93 %. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.45 (s, 9 H), 2.99 (d, *J* = 5.2 Hz, 2 H), 3.80 (s, 3 H), 4.55–4.60 (m, 1 H), 5.41 (d, *J* = 8.6 Hz, 1 H), 7.51 (d, *J* = 7.9 Hz, 2 H), 8.14 (d, *J* = 7.9 Hz, 2 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 24.1, 28.2, 52.1, 52.7, 80.3, 81.8, 90.0, 123.4, 129.9, 132.4, 146.9, 155.0, 171.0 ppm.

**Compound 10baf:** Yield 93 %. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.46 (s, 9 H), 2.97 (d, *J* = 5.2 Hz, 2 H), 3.80 (s, 3 H), 3.91 (s, 3 H), 4.55–4.91 (m, 1 H), 5.40 (d, *J* = 7.6 Hz, 1 H), 7.43 (d, *J* = 8.9 Hz, 2 H), 7.96 (d, *J* = 8.8 Hz, 2 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 24.0, 28.3, 52.2, 52.7, 53.7, 80.3, 82.9, 87.2, 127.7, 129.4, 131.6, 155.0, 166.5, 171.2 ppm. HRMS (ESI): calcd. for $C_{19}H_{23}O_6$ $[M + Na]^+$ 384.14176, found 384.14211.

**Compound 10caa:** Yield 97 %. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.41 (s, 3 H), 2.90 (t, *J* = 5.1 Hz, 2 H), 3.64 (s, 3 H), 4.20 (dt, *J* = 9.1, 5.1 Hz, 1 H), 5.45 (d, *J* = 9.1 Hz, 1 H), 7.24–7.38 (m, 7 H), 7.76 (d, *J* = 8.3 Hz, 2 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 21.5, 25, 52.9, 54.4, 82.7, 84.3, 122.7, 127.2, 128.2, 129.7, 131.7, 136.9, 143.8, 170.3 ppm. HRMS (ESI): calcd. for $C_{19}H_{20}NO_4S$ $[M + H]^+$ 358.10914, found 358.11076.

**General Procedure for C–N Cycloisomerization; Synthesis of 1-Pyrrolines:** To a solution of compound **10ba** (300 mg, 0.99 mmol) in EtOAc (5 mL), a 3 M solution of HCl in EtOAc (2 mL) was added dropwise at room temp. The mixture was stirred at room temp. and monitored by TLC. After complete conversion, the mixture was concentrated in vacuo to afford the corresponding HCl salt. A solution of the HCl salt in dioxane/water (15 mL, 1:1 v/v) was treated dropwise at room temp. with 25 % aqueous $NH_4OH$ until pH = 10. The aqueous solution was extracted with EtOAc, and the combined organic layers were dried with $Na_2SO_4$ and concentrated in vacuo. The remaining crude amino ester was subsequently dissolved in MeCN (10 mL), and $AuCl_3$ (10 mol-%) was added. The mixture was stirred at reflux temp. and monitored by TLC. Upon completion, the reaction mixture was filtered and concentrated in vacuo. The crude product was purified by chromatography (EtOAc/hexane) to afford the corresponding 1-pyrroline.

**Methyl 5-Phenyl-3,4-dihydro-2*H*-2-pyrrolecarboxylate (11a):**[18] Yield 75 %. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.20–2.37 (m, 2 H), 2.89–3.04 (m, 1 H), 3.08–3.23 (m, 1 H), 3.77 (s, 3 H), 4.86–4.97 (m, 1 H), 7.36–7.49 (m, 3 H), 7.81–7.94 (m, 2 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 26.3, 35.3, 52.2, 74.5, 127.9, 128.3, 130.8, 133.7, 173.3, 175.9 ppm. HRMS (ESI): calcd. for $C_{12}H_{13}NNaO_2$ $[M + Na]^+$ 226.08385, found 226.08451.

**Methyl 5-(4-Methylphenyl)-3,4-dihydro-2*H*-2-pyrrolecarboxylate (11b):** Yield 55 %. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.21–2.35 (m, 2 H), 2.38 (s, 3 H), 2.88–3.02 (m, 1 H), 3.05–3.15 (m, 1 H), 3.77 (s, 3 H), 4.90 (dt, *J* = 6.9, *J* = 1.7 Hz, 1 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 7.77 (d, *J* = 8.2 Hz, 2 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 21.4, 26.3, 35.3, 52.1, 74.4, 127.9, 129.0, 131.0, 141.2, 173.4, 175.8 ppm. HRMS (ESI): calcd. for $C_{13}H_{15}NNaO_2$ $[M + Na]^+$ 240.09950, found 240.09933.

**Methyl 5-(Naphthyl)-3,4-dihydro-2*H*-2-pyrrolecarboxylate (11c):** Yield 71 %. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.28–2.41 (m, 2 H), 3.00–3.17 (m, 2 H), 3.19–3.36 (m, 1 H), 3.81 (s, 3 H), 4.98 (m, 1 H), 7.42–7.58 (m, 2 H), 7.78–7.94 (m, 3 H), 8.11 (dd, *J* = 8.6, 1.9 Hz, 1 H), 8.21 (s, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 26.3, 35.3, 52.2, 74.5, 76.6, 124.6, 126.4, 127.3, 127.6, 128.1, 128.7, 128.7, 131.1, 132.7, 134.5, 173.3, 176.0 ppm. HRMS (ESI): calcd. for $C_{16}H_{16}NO_2$ $[M + H]^+$ 254.11756, found 254.11804.

**Methyl 5-(4-Methoxyphenyl)-3,4-dihydro-2*H*-2-pyrrolecarboxylate (11d):** Yield 41 %. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.19–2.35 (m, 2 H), 2.83–3.00 (m, 1 H), 3.02–3.13 (m, 1 H), 3.72 (s, 3 H) 3.82 (s, 3 H), 4.87 (ddt, *J* = 8.6, 6.6, 1.9, Hz, 1 H), 6.89 (d, *J* = 8.92 Hz, 2 H), 7.81 (d, *J* = 8.92 Hz, 2 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 26.3, 35.2, 52.1, 55.2, 74.3, 113.6, 113.8, 126.5, 129.6, 161.7, 173.5, 175.2 ppm. HRMS (ESI): calcd. for $C_{13}H_{15}NNaO_3$ $[M + Na]^+$ 256.09441, found 256.09436.

**Methyl 5-(4-Nitrophenyl)-3,4-dihydro-2*H*-2-pyrrolecarboxylate (11e):**[18] Yield 90 %. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.29–2.45 (m, 2 H), 2.96–3.10 (m, 1 H), 3.13–3.27 (m, 1 H), 3.80 (s, 3 H), 4.94–5.02 (m, 1 H), 8.02–8.10 (m, 2 H), 8.24–8.35 (m, 2 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 26.3, 35.6, 52.4, 74.8, 123.6, 128.9, 139.3, 149.2, 172.7, 174.3 ppm. HRMS (ESI): calcd. for $C_{12}H_{13}N_2O_4$ $[M + H]^+$ 249.08698, found 249.08621.

**Methyl 5-[4-(Methoxycarbonyl)phenyl]-3,4-dihydro-2*H*-2-pyrrolecarboxylate (11f):** Yield 87 %. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.21–2.44 (m, 2 H), 2.93–3.06 (m, 1 H), 3.12–3.24 (m, 1 H), 3.78 (s, 3 H), 3.92 (s, 3 H), 4.87–4.99 (m, 1 H), 7.89–8.00 (m, 2 H), 8.02–8.10 (m, 2 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 26.3, 35.5, 52.2, 52.3, 74.7, 127.9, 129.6, 132.0, 137.6, 166.5, 172.9, 175.3 ppm. HRMS (ESI): calcd. for $C_{14}H_{16}NO_4$ $[M + H]^+$ 262.10738, found 262.10792.

**Representative Experimental Procedure for the Synthesis of γ-Lactones:** The methyl ester derivatives were dissolved in THF/$H_2O$ (6 mL, 2:1) and cooled to 0 °C. Then, a 1 M solution of LiOH (0.8 mL) was added. The mixture was stirred at room temp., and the reaction was monitored by TLC. After complete conversion, the reaction mixture was poured into a beaker with ice, and a solution of HCl (1 M) was added until the pH was acidic. The aqueous solution was extracted with EtOAc, and the combined organic layers were dried with $Na_2SO_4$ and concentrated in vacuo. The product was used in the next step without further purification. AuCl (0.1 equiv.) and then $K_2CO_3$ (0.1 equiv.) were added to a solution of the amino acid compound (1 equiv.) in MeCN (3 mL/mmol) at room temperature. The reaction mixture, initially a white suspension, turned into a dark brown solution within minutes. After disappearance of the starting material (TLC monitoring, usually 2 h), the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to give the crude product. Due to the instability of these enol-lactones, the compounds were purified by passage through a short pad of silica (eluent: EtOAc) as described in the literature.[9,12]

**Compound 10aa:** Yield 99.4 %. $^1$H NMR (300 MHz, [$D_4$]methanol): $\delta$ = 2.03 (s, 3 H), 2.93 (dd, *J* = 6.2, 4.0 Hz, 2 H), 4.64 (dd, *J* = 6.9, 5.5 Hz, 1 H), 7.25–7.41 (m, 5 H) ppm. $^{13}$C NMR (75 MHz, [$D_4$]methanol): $\delta$ = 22.5, 23.6, 53.1, 83.8, 85.9, 124.9 129.2, 129.5, 132.8, 173.5, 173.7 ppm. HRMS (ESI): calcd. for $C_{13}H_{13}NNaO_3$ $[M + Na]^+$ 254.07876, found 254.07927.

**Compound 10ab:** Yield 90 %. $^1$H NMR (300 MHz, [$D_6$]acetone): $\delta$ = 1.99 (s, 3 H), 2.31 (s, 3 H), 2.94 (d, *J* = 5.7 Hz, 2 H), 4.72 (m, 1 H), 7.14 (d, *J* = 8.1 Hz, 2 H), 7.26 (d, *J* = 8.1 Hz, 2 H) ppm. $^{13}$C NMR (75 MHz, [$D_6$]acetone): $\delta$ = 21.8, 23.2, 23.4, 52.6, 85.8, 121.9, 130.3,


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132.8, 139.3, 170.8, 172.5 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}NNaO_3$ $[M + Na]^+$ 268.09441, found 268.09429.

**Compound 10ac:** Yield 96 %. $^1H$ NMR (300 MHz, [D$_6$]acetone): $\delta$ = 2.01 (s, 3 H), 3.02 (d, $J$ = 5.7 Hz, 2 H), 4.72–4.79 (m, 1 H), 7.49–7.63 (m, 3 H), 7.83–8.00 (m, 4 H) ppm. $^{13}C$ NMR (75 MHz, [D$_6$]acetone): $\delta$ = 23.5, 24.4, 52.9, 84.5, 87.4, 122.6, 128.2, 129.2, 129.3, 129.6, 130.1, 132.7, 134.5, 134.8, 171.1, 172.8 ppm. HRMS (ESI): calcd. for $C_{17}H_{16}NO_3$ $[M + H]^+$ 282.11247, found 282.11195.

**Compound 10ba:** Yield 87 %. $^1H$ NMR (300 MHz, [D$_6$]acetone): $\delta$ = 1.46 (s, 9 H), 3.00 (br. s, 2 H), 4.61–4.63 (m, 1 H), 5.45 (d, $J$ = 7.6 Hz, 1 H), 7.28 (br. s, 3 H), 7.39 (br. s, 2 H) ppm. $^{13}C$ NMR (75 MHz, [D$_6$]acetone): $\delta$ = 23.5, 28.2, 52.1, 80.5, 83.6, 83.7, 122.9, 128, 128.1, 131.7, 155.4, 175.3 ppm. HRMS (ESI): calcd. for $C_{16}H_{18}NNa_2O_4$ $[M + Na]^+$ 334.10257, found 334.10297.

**Compound 10ca:** Yield 94 %. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 2.38 (s, 3 H), 2.91 (t, $J$ = 4.7 Hz, 2 H), 4.18–4.27 (m, 1 H), 5.55 (d, $J$ = 8.1 Hz, 3 H), 7.21–7.38 (m, 7 H), 7.76 (d, $J$ = 8.3 Hz, 2 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 21.5, 24.7, 54.1, 82.4, 84.5, 122.5, 127.1, 128.2, 128.35, 129.8, 131.7, 136.7, 143.9, 173.5 ppm. HRMS (ESI): calcd. for $C_{18}H_{17}NNaO_4S$ $[M + Na]^+$ 366.07705, found 366.07624.

***N*-(5-Methylene-2-oxotetrahydrofuran-3-yl)acetamide (12a):** Yield 95 %. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 2.06 (s, 3 H), 2.78–288 (m, 1 H), 3.29–3.37 (m, 1 H), 4.34 (br. s, 1 H), 4.58–4.67 (m, 1 H), 4.83 (br. s, 1 H), 6.28 (br. s, 1 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 23.1, 33.8, 50.1, 91, 152.6, 170.9 ppm. HRMS (ESI): calcd. for $C_7H_9NNaO_3$ $[M + Na]^+$ 178.04746, found 178.04674.

***tert*-Butyl (5-Methylene-2-oxotetrahydrofuran-3-yl)carbamate (12b):** Yield 94 %. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 1.46 (s, 9 H) 2.88–2.92 (m, 1 H) 3.22–3.3 (m, 1 H) 4.41 (br. S, 2 H) 4.8 (br. s, 1 H) 5.21 (d, $J$ = 5.5 Hz, 1 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 28.2, 33.4, 50.5, 80.9, 90.4, 152.2, 173 ppm. HRMS (ESI): calcd. for $C_{10}H_{15}NNaO_4$ $[M + Na]^+$ 236.08933, found 236.08967.

**4-Methyl-*N*-(5-methylene-2-oxotetrahydrofuran-3-yl)benzenesulfonamide (12c):** Yield 97 %. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 2.46 (s, 3 H), 2.84–2.95 (m, 1 H), 3.25–3.33 (m, 1 H), 4.06–4.14 (m, 1 H), 4.47 (br. s, 1 H), 4.84 (br. s, 1 H), 5.16 (d, $J$ = 3.8 Hz, 1 H), 7.36 (d, $J$ = 8.1 Hz, 2 H), 7.80 (d, $J$ = 8.1 Hz, 2 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 21.6, 34.7, 52.1, 91.5, 127.3, 130, 135.6, 144.5, 151.6, 171.8 ppm. HRMS (ESI): calcd. for $C_{12}H_{13}NNaO_4S$ $[M + Na]^+$ 290.04575, found 290.04541.

**(Z)-*N*-(5-Benzylidene-2-oxotetrahydrofuran-3-yl)acetamide (12d):** Yield 96 %. $^1H$ NMR (300 MHz, [D$_6$]acetone): $\delta$ = 1.96 (s, 3 H), 3.09–3.18 (m, 1 H), 3.27–3.36 (m, 1 H), 4.66–4.75 (m, 1 H), 5.64 (s, 1 H), 7.19 (tt, $J$ = 1.2, 7.4 Hz, 1 H), 7.32 (t, $J$ = 7.4 Hz, 2 H), 7.56 (d, $J$ = 7.4 Hz, 2 H) ppm. $^{13}C$ NMR (75 MHz, [D$_6$]acetone): $\delta$ = 22.5, 33.9, 49, 104.9, 127.3, 129.1, 129.2, 135.5, 147.8, 170.6, 173.6 ppm. HRMS (ESI): calcd. for $C_{13}H_{13}NNaO_3$ $[M + Na]^+$ 254.07876, found 254.07867.

**(Z)-*N*-[5-(4-Methylbenzylidene)-2-oxotetrahydrofuran-3-yl]acetamide (12e):** Yield 85 %. $^1H$ NMR (300 MHz, [D$_6$]acetone): $\delta$ = 1.96 (s, 3 H), 2.30 (s, 3 H), 3.09–3.16 (m, 1 H), 3.25–3.34 (m, 1 H), 4.66–4.75 (m, 1 H), 5.58 (s, 1 H), 7.14 (d, $J$ = 8.2 Hz, 2 H), 7.43 (d, $J$ = 8.2 Hz, 2 H) ppm. $^{13}C$ NMR (75 MHz, [D$_6$]acetone): $\delta$ = 21.6, 22.9, 34.2, 49.4, 105.3, 129.5, 130.3, 132.7, 137.3, 147.3, 170.9, 174.1 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}NNaO_3$ $[M + Na]^+$ 268.09441, found 268.09470.

**(Z)-*N*-[5-(Naphthalen-2-ylmethylene)-2-oxotetrahydrofuran-3-yl]acetamide (12f):** Yield 71 %. $^1H$ NMR (300 MHz, [D$_6$]acetone): $\delta$ = 1.28 (s, 3 H), 3.15–3.26 (m, 1 H), 3.32–3.42 (m, 1 H), 5.78 (s, 1 H), 7.7–8.16 (m, 7 H) ppm. $^{13}C$ NMR (75 MHz, [D$_6$]acetone): $\delta$ = 22.5, 33.9, 49, 104.9, 126.6, 127.1, 127.5, 127.7, 128.3, 128.5, 128.8, 130.3, 133.2, 134.6, 148.4, 170.6, 173.7 ppm. HRMS (ESI): calcd. for $C_{17}H_{16}NO_3$ $[M + H]^+$ 282.11247, found 282.11310.

***tert*-Butyl (*Z*)-(5-Benzylidene-2-oxotetrahydrofuran-3-yl)carbamate (12g):** Yield 90 %. $^1H$ NMR (300 MHz, [D$_6$]acetone): $\delta$ = 1.43 (s, 9 H), 3.11–3.20 (m, 1 H), 3.30–3.38 (m, 1 H), 4.61–4.7 (m, 1 H), 5.65 (s, 1 H), 7.17–7.57 (m, 5 H) ppm. $^{13}C$ NMR (75 MHz, [D$_6$]acetone): $\delta$ = 1.5, 28.6, 33.9, 49.9, 80.2, 105, 127.4, 129.2, 129.3, 135.5, 147.6, 156.2, 174 ppm. HRMS (ESI): calcd. for $C_{16}H_{17}NNaO_4$ $[M + Na]^+$ 312.12063 found 312.12065.

**(Z)-*N*-(5-Benzylidene-2-oxotetrahydrofuran-3-yl)-4-methylbenzenesulfonamide (12h):** Yield 92 %. $^1H$ NMR (300 MHz, [D$_6$]-acetone): $\delta$ = 2.44 (s, 3 H), 2.87–2.97 (m, 1 H), 3.19–3.27 (m, 1 H), 4.7–4.76 (m, 1 H), 5.62 (s, 1 H), 5.63 (s, 1 H), 7.17–8.06 (m, 10 H) ppm. $^{13}C$ NMR (75 MHz, [D$_6$]acetone): $\delta$ = 21.8, 35.5, 52.4, 106, 127.8, 128.2, 129.4, 129.5, 129.6, 130.8, 130.9, 134, 135.3, 139.8, 144.7, 146.8, 173.1 ppm. HRMS (ESI): calcd. for $C_{18}H_{17}NNaO_4S$ $[M + Na]^+$ 366.07705 found 366.07679.

***N*-(6-Methylene-2-oxotetrahydro-2*H*-pyran-3-yl)acetamide (12i):** Yield 95 %. $^1H$ NMR (300 MHz, [D$_6$]acetone): $\delta$ = 1.93 (s, 3 H), 2.09 (s, 2 H), 2.54–2.62 (m, 1 H), 2.66–2.74 (m, 1 H), 3.31 (s, 1 H), 3.66 (s, 1 H), 3.37–4.46 (m, 1 H) ppm. $^{13}C$ NMR (75 MHz, [D$_6$]acetone): $\delta$ = 22.7, 26.6, 39.8, 52.3, 94.1, 156.4, 168.5, 173.6 ppm. HRMS (ESI): calcd. for $C_8H_{12}NO_3$ $[M + Na]^+$ 170.08161, found 170.08157.

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