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# A tunable copper-catalyzed multicomponent reaction towards alkaloid-inspired indole/lactam polycycles†

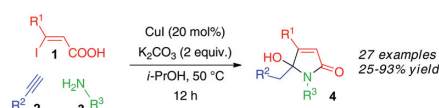
M. I. D. Mardjan, S. Perie, J.-L. Parrain\* and L. Commeiras \*

A versatile copper(I)-catalyzed cascade multicomponent reaction strategy between readily available (*Z*)-3-iodoacrylic acids, terminal alkynes, and primary amines is reported, leading to a great diversity of complex heterocyclic backbones based on biorelevant indole/lactam scaffolds.

## Introduction

Indole, which is one of the most important heterocyclic ring systems, is known to play an important role in several physiological and biochemical processes.<sup>1</sup> For example tryptophan is an  $\alpha$ -amino acid that is used in the biosynthesis of proteins and it is also a precursor to neurotransmitters such as serotonin and melatonin. In addition, the indole nucleus is an inescapable structural component in many pharmaceutical agents displaying a broad spectrum of biological activities. Therefore, the interesting biological activities of such naturally or pharmaceutically occurring compounds bearing an indole moiety have captured the attention of the organic synthetic community and the discovery of new therapeutics is still of interest. As a matter of fact, the collection data of natural indole-inspired compounds for pharmaceutical tests suffer from the lack of general preparations addressing the substituent and scaffold diversity. Consequently, novel ways to prepare polycyclic indole scaffolds are thus very much desired and multicomponent reactions (MCRs) appear to be one of the most efficient tools and attractive strategies.<sup>2</sup> Recently, we have developed a highly efficient copper-catalyzed multicomponent reaction (MCR) starting from readily available (*Z*)-3-iodoacrylic acids **1**, terminal alkynes **2**, and primary amines **3** to smoothly access 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones **4** in good yields (Scheme 1).<sup>3</sup>

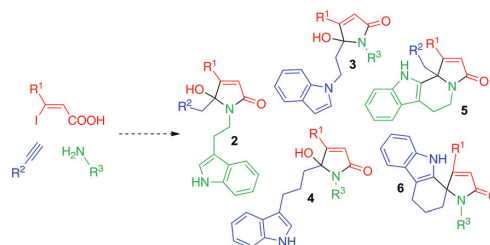
These latter are important five-membered heterocyclic compounds that not only can be found in several natural



**Scheme 1** Copper(I) mediated-MCR process for the synthesis of  $\gamma$ -hydroxybutyrolactams.

products,<sup>4</sup> designed pharmaceutical molecules with significant biological properties<sup>5</sup> but also as versatile building blocks in organic synthesis.<sup>6</sup>

Consequently, to address the modular preparation of indole alkaloids and having in mind that  $\gamma$ -hydroxybutyrolactams are both relevant scaffolds and excellent precursors of acyliminium derivatives, we planned to extend the copper-catalyzed MCR process for the preparation of substrates bearing an indole moiety (**5**, **6**) and to build up, *via* a “one-pot” procedure including an intramolecular Pictet–Spengler reaction, a collection of diverse indole/lactam polycyclic derivatives such as fused tetrahydro- $\beta$ -carboline-butylolactam derivatives **7** and spiro-indolo-butylolactams **8** (Scheme 2).



**Scheme 2** Versatile MCR process.

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## Results and discussion

### Synthesis of indolo- $\gamma$ -hydroxybutyrolactams

In the first instance, we turned our attention to the preparation of  $\gamma$ -hydroxybutyrolactams bearing an indole moiety. For this purpose, we explored several opportunities. The indole scaffold could be easily incorporated either on the primary amine or on the terminal alkyne. Our preliminary study<sup>3</sup> has shown that starting from tryptamine **9**, hydroxybutyrolactams **5a** and **5e** were obtained in very good yields (83 and 81% yield respectively).

Encouraged by these results, the scope and limitations of the copper-mediated MCR process were further exploited by using a diverse set of terminal alkynes **2** and  $\beta$ -substituted-(*Z*)-3-iodoacrylic acids **1** (Scheme 3). In general, the reaction conditions are compatible with various functional groups associated with terminal alkynes, such as aromatic, protected alcohol as well as diethylacetal, and various 3-substituted iodoacrylic acids (methyl, phenyl, butyl or CH<sub>2</sub>OMe substituent) to smoothly furnish the desired  $\gamma$ -hydroxybutyrolactams **5** up to 85% yield.

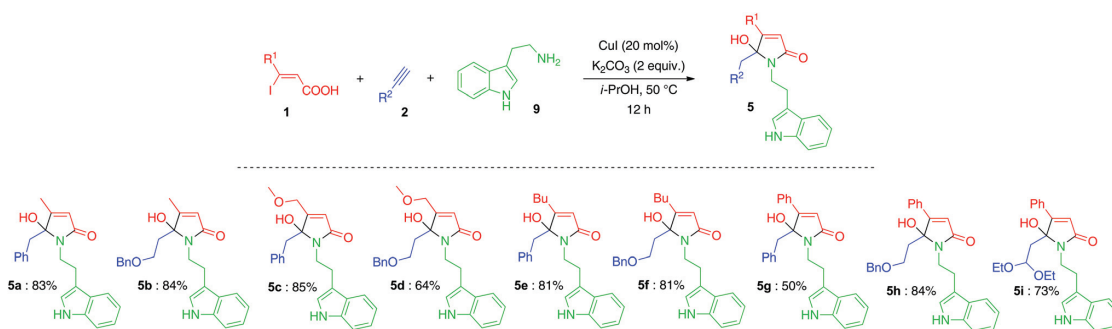
The multicomponent reaction could also be conducted with readily available one-step synthesis of *N*-propargylindole **1**,<sup>7</sup> in which the indole scaffold is incorporated on the terminal alkyne (Scheme 4). First, we initiated our investigation with 1 equiv. of (*Z*)-3-iodobut-2-enoic acid **1a**, 2 equiv. of

*N*-propargyl-indole **10** and 2 equiv. of butyl amine **3a**, in the presence of 20 mol% of copper iodide (CuI) and 2 equiv. of potassium carbonate, in isopropanol at 50 °C. Under these standard conditions, the reaction was found to be incomplete with a conversion rate of 30%. Satisfyingly, the conversion was complete by increasing the amount of both CuI (1 equiv.) and butylamine **3a** (3 equiv.). In this case, indole **6a** was obtained in 60% yield. Next, various  $\beta$ -substituted-(*Z*)-3-iodoacrylic acids **1** and primary amines **3** were tested to evaluate the generality of this strategy. To our delight, the desired hydroxylactams **6** were prepared in moderate to good yields (up to 64% yield) whatever the nature of the nucleophilic primary amines (homoallyl-, butyl- and dimethoxyhomobenzyl amine) and whatever the nature of the  $\beta$ -substituent of the  $\beta$ -substituted-(*Z*)-3-iodoacrylic acids **1** (methyl, phenyl or CH<sub>2</sub>OMe substituents).

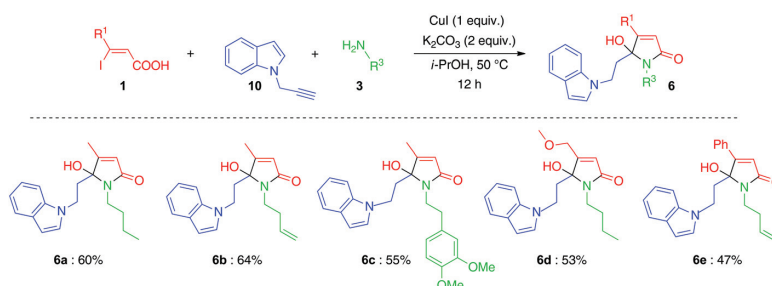
All these results demonstrated the efficiency of this multi-bond-forming transformation in which 1 C–O, 1 C–C and 2 C–N bonds are created, starting from readily commercially available starting materials.

### Synthesis of fused tetrahydro- $\beta$ -carboline-lactam derivatives and indolo-(5,6)-spirolactams

Due to the presence of a carbonyl moiety on the nitrogen atom, *N*-acyliminium ions (NAI) are highly reactive species towards nucleophiles. Hence, their electrophilic reactivity is



Scheme 3 Synthesis of 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones **5** bearing an indole moiety.



Scheme 4 Synthesis of 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones **6** bearing an indole moiety.

extensively used for the creation of carbon–carbon or carbon–heteroatom bonds in both inter- or intra-molecular fashions with respect to the synthesis of alkaloid products. Given the high nucleophilic character of indole, this latter was proven to be a good candidate in the *N*-acyliminium ion process or Pictet–Spengler reaction.

By taking advantage of this reactivity, our next purpose was to investigate the reactivity of 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones **4** as an equivalent of the *N*-acyliminium ion for the direct synthesis of polyheterocyclic compounds through an intramolecular C-2 Friedel–Crafts alkylation. Indeed, considering the structure of  $\gamma$ -hydroxybutyrolactams, the nucleophiles can be installed either in the amine site or alkyne part. While the former may allow us to afford the fused tetrahydro- $\beta$ -carboline-lactam derivatives **7** (Scheme 5a), the latter may lead to the formation of (5,5)-spirolactams **8** (Scheme 5b). Our objective was to incorporate the NAI reactions into the cascade sequence, including enyne coupling/heterocyclisation/ $\gamma$ -hydroxylactam formation/NAI formation/intramolecular Friedel–Crafts alkylation.

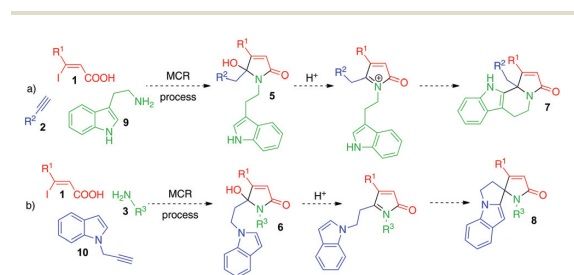
Before attempting the “one-pot” cascade towards the desired fused tetrahydro- $\beta$ -carboline-lactam derivatives **7**, we first validated the transformation from **5a** to **7a** in the presence of hydrochloric acid solution (6 M) at 50 °C (Scheme 6). Satisfyingly, the cyclisation smoothly occurred in 2 h furnishing the expected product **7a** in 79% yield.

The structure of **7a** was unambiguously confirmed by X-ray crystallographic analysis proving that the intramolecular Friedel–Craft alkylation occurred with a C-2 regioselectivity.<sup>8</sup>

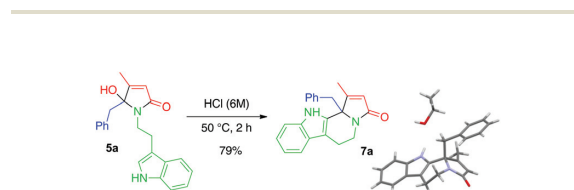
Having proved that  $\gamma$ -hydroxybutyrolactam **5a** can be transformed into fused-tetrahydro- $\beta$ -carboline-lactam **7a**, we decided to investigate the “one-pot” cascade (Scheme 7). (*Z*)- $\beta$ -Iodo- $\alpha,\beta$ -unsaturated acids **1**, phenyl acetylene and trypt-

amine **9** were subjected to the copper-catalyzed-multi-component reaction. After performing the reaction overnight, hydrochloric acid solution (6 M) was added to the mixture and the reaction was continued until the total consumption of hydroxylactam (4 h). Pleasingly, the “one-pot” cascade process was efficient affording the desired fused tetrahydro- $\beta$ -carboline-lactam derivative **7a** in 82% yield. Subsequently, this procedure was found to be general and a diverse set of substituents ( $R^1$  and  $R^2$  = alkyl, aromatic or protected alkoxy or aldehyde groups) were properly installed in such reaction. It is worth noting that starting from 3,3-diethoxyprop-1-yne as a terminal alkyne led us to obtain the corresponding aldehyde **7c** in 36% yield. However, most of the polyheterocyclic compounds **7** were prepared in moderate yield (32–52%). In an attempt to increase the yield of the desired product, the same “one-pot” sequence was performed by using a more diluted aqueous solution of HCl (1 M). Under this condition, indoles **7** were obtained in better yield, ranging from 53 to 86%, demonstrating the power of this strategy.

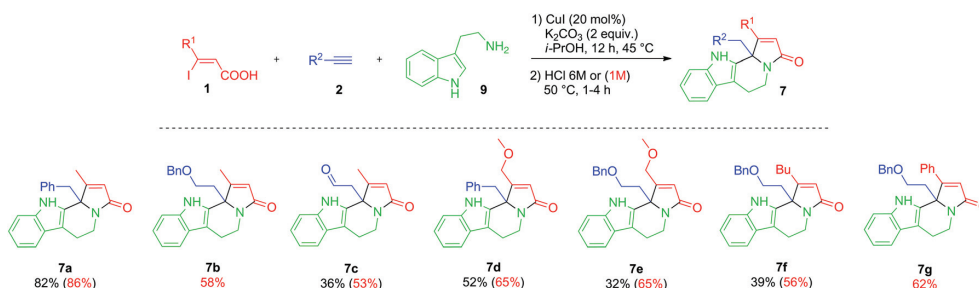
Installing the nucleophilic site (indole moiety) on the primary amine partners allowed us to access heterocyclic compounds with tetrahydro- $\beta$ -carboline scaffold, starting from terminal alkynes bearing such nucleophile sites, and is a new synthetic route to access spiro lactams derivatives **8**. Our initial efforts towards this goal focused on the reaction cascade with *N*-propargyl-indole **10** in order to prepare the corresponding (5,5)-spirolactam moiety. Unfortunately, by treating hydroxylactam **6a** with a hydrochloric acid solution (6 M) or with 1,1'-binaphthyl-2,2'-diyl-hydrogenphosphate or by applying the MCR process, the Friedel–Crafts alkylation did not occur. Instead, a dehydration reaction took place to furnish the corresponding alkylidenebutyrolactam. A way to circumvent this non-desired reactivity was to perform the reaction cascade with 3-(but-3-yn-1-yl)-1*H*-indoles **11**. Alkynes **11** were prepared in a two-step synthesis from indole through a sequence involving Michael addition<sup>9</sup> (with acrolein) and Bestmann–Ohira homologation.<sup>10</sup> As an attempt to prove our concept, we initially prepared  $\gamma$ -hydroxybutyrolactam **12a** from **11a**. Since this terminal alkyne contains a non-activated terminal alkyne function, the reaction was carried out in the presence of 4 equiv. of primary amine at 45 °C (the previously reported optimal conditions).<sup>3</sup> The desired  $\gamma$ -hydroxybutyrolactam **12a** was obtained in moderate yield (43%), together with the side product of pyran-2-one **13a** (via a 6-*endo* cyclisation of enynic acid intermediate, ratio **12** : **13a** = 1 : 0.22). Finally, the treatment of **12a** with a hydrochloric acid solution (6 M) gave the desired (5,6)-spirolactam **14a** in 79% yield (Scheme 8). The structure of the spiro lactam **14a** was unambiguously confirmed by X-ray crystallographic analysis confirming that the intramolecular Friedel–Craft alkylation occurred with a complete C-2 regioselectivity.<sup>11</sup> Having proved the concept of the synthesis of (5,6)-spirolactam, the MCR process, starting from 3-(but-3-yn-1-yl)-1*H*-indole **11a**, (*Z*)-3-iodobut-2-enoic acid **1a** and butyl amine **3a**, was then investigated.



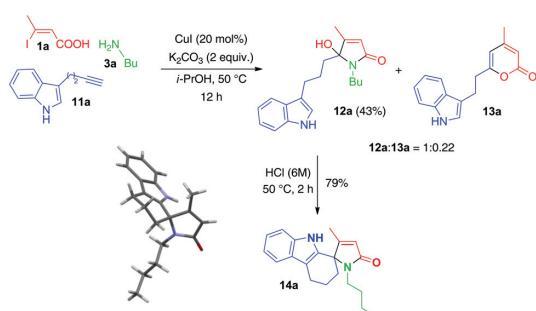
**Scheme 5** Multi-bond-forming transformation for a straightforward synthesis of **7** and **8**.



**Scheme 6** Transformation of **5a** to **7a**.



Scheme 7 Synthesis of fused tetrahydro- $\beta$ -carboline-lactam derivatives 7.



Scheme 8 Proof of concept of the preparation of (5,6)-spirolactam 14a.

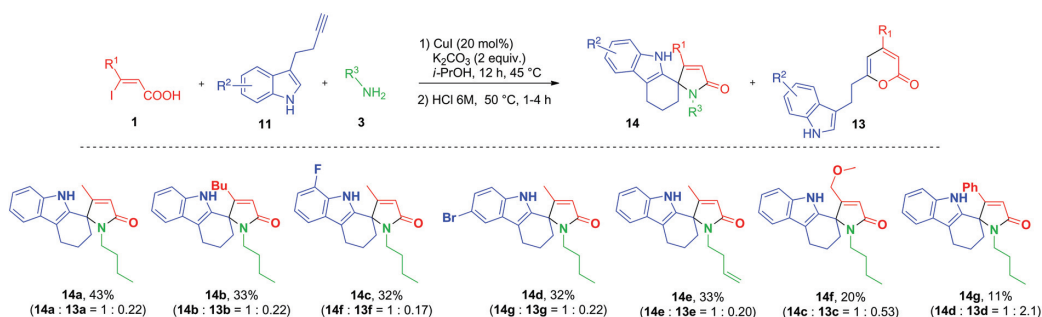
Pleasingly, the corresponding (5,6)-spirolactam **14a** was obtained in 43% isolated yield (Scheme 9). This moderate yield could be explained by the formation of pyran-2-one **13a** (20%) that was found to be inert under the reaction conditions. Although **14a** was obtained in 43% yield (which in fact corresponds to an 81% average yield per step), the “one-pot” cascade provides a useful method for building (5,6)-spirolactam scaffolds from readily available compounds, which encouraged us to carry out further explorations. Therefore, several (*Z*)- $\beta$ -iodo- $\alpha,\beta$ -unsaturated acids **1**, primary amines **3**, as well as indole derivatives **11** were tested (Scheme 9). As a

general trend, the isolated yields of the (5,6)-spirolactams **8a–8e** were found to be relatively moderate (30–40%) due to, equally, the formation of the 6-membered lactones **12** (around 20%). However, these isolated yields can be considered as satisfactory regarding the number of steps of this MCR cascade including as well the construction of a quaternary center. It is worth noting that the relative amount of **12** was found to be dependent on the nature of the substituent on the acid partner **1**.

The more electron withdrawing group the substituent was, the higher relative amount of lactone **12** would be. Indeed, starting from  $\text{CH}_2\text{OME}$  or phenyl  $\beta$ -substituted-(*Z*)-3-iodoacrylic acids **1**, the amount of the 6-membered lactones **12f** and **12g** is 35 and 68% respectively.<sup>12</sup>

## Conclusions

In summary, we have described straightforward and versatile copper-catalyzed multi-bond-forming transformations for the construction of pharmaceutically interesting complex polyheterocyclic scaffolds containing an indole moiety. These processes feature readily available starting materials, mild reaction conditions, and tolerance of a wide range of functional groups. The generation of molecular complexity in a “one-pot” process should make this method a useful organic synthetic tool.



Scheme 9 Synthesis of (5,6)-spirolactams 8.

## Experimental section

### General procedure for the synthesis of 5

(*Z*)-3-Substituted-3-iodoprop-2-enoic acid derivative **1** (2.0 mmol, 1 equiv.) was dissolved in *i*-PrOH (7 mL) in an oven-dried-Schlenk tube.  $K_2CO_3$  (553 mg, 4.0 mmol, 2 equiv.) was then added to the solution and the suspension was stirred for 10 min under argon. The mixture was then degassed at  $-78$  °C for  $2 \times 10$  min and the vessel was backfilled with argon. After warming to room temperature, terminal alkyne **2** (4.0 mmol, 2 equiv.), tryptamine **9** (641 mg, 4.0 mmol, 2 equiv.) and CuI (76 mg, 0.4 mmol, 0.2 equiv.) were respectively added into the mixture. The mixture was then rapidly degassed and the vessel was backfilled with argon. The sealed Schlenk tube was placed in the preheated oil bath (50 °C) and was stirred overnight. The reaction mixture was cooled to 0 °C, then quenched by the addition of an aqueous saturated  $NH_4Cl$  solution and stirred for further 15 min. The mixture was filtered through a pad of Celite®. The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over  $Na_2SO_4$  and concentrated under reduced pressure. The crude product was then purified by flash chromatography on silica gel using petroleum ether : ethyl acetate as the eluent.

### General procedure for the synthesis of 6

(*Z*)-3-Substituted-3-iodoprop-2-enoic acid derivative **1** (1.0 mmol, 1 equiv.) was dissolved in *i*-PrOH (3.5 mL) in an oven-dried-Schlenk tube.  $K_2CO_3$  (277 mg, 2.0 mmol, 2 equiv.) was then added to the solution and the suspension was stirred for 10 min under argon. The mixture was then degassed at  $-78$  °C for  $2 \times 10$  min and the vessel was backfilled with argon. After warming to room temperature, 1-prop-2-yn-1-yl-1*H*-indole **10** (310 mg, 2.0 mmol, 2 equiv.), primary amine **3** (3.0 mmol, 3 equiv.) and CuI (190 mg, 1.0 mmol, 1 equiv.) were respectively added into the mixture. The mixture was then rapidly degassed and the vessel was backfilled with argon. The sealed Schlenk tube was placed in the preheated oil bath (50 °C) and was stirred overnight. The reaction mixture was cooled to 0 °C, then quenched by the addition of an aqueous saturated  $NH_4Cl$  solution and stirred for further 15 min. The mixture was filtered through a pad of Celite®. The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over  $Na_2SO_4$  and concentrated under reduced pressure. The crude product was then purified by flash chromatography on silica gel using petroleum ether : ethyl acetate as the eluent.

### General procedure for the synthesis of 7

(*Z*)-3-Substituted-3-iodoprop-2-enoic acid derivative **1** (1.0 mmol, 1 equiv.) was dissolved in *i*-PrOH (3.5 mL) in an oven-dried-Schlenk tube.  $K_2CO_3$  (277 mg, 2.0 mmol, 2 equiv.) was then added to the solution and the suspension was stirred for 10 min under argon. The mixture was then degassed at  $-78$  °C for  $2 \times 10$  min and the vessel was backfilled with argon. After warming to room temperature, terminal alkyne **2** (2.0 mmol, 2 equiv.), tryptamine **9** (320 mg, 2.0 mmol, 2 equiv.) and CuI

(38 mg, 0.2 mmol, 0.2 equiv.) were respectively added into the mixture. The mixture was then rapidly degassed and the vessel was backfilled with argon. The sealed Schlenk tube was placed in the preheated oil bath (50 °C) and was stirred overnight. The reaction mixture was cooled to 0 °C, and then a solution of hydrochloric acid (3.4 mL, 6 M, 20 equiv.) was added dropwise. The reaction was then heated at 50 °C until the disappearance of the  $\gamma$ -hydroxybutyrolactam checked by TLC. The reaction mixture was cooled to 0 °C and then filtered through a pad of Celite®. The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over  $Na_2SO_4$  and concentrated under reduced pressure. The crude product was then purified by flash chromatography on silica gel using petroleum ether : ethyl acetate as the eluent.

Or (*Z*)-3-Substituted-3-iodoprop-2-enoic acid derivative **1** (0.5 mmol, 1 equiv.) was dissolved in *i*-PrOH (1.75 mL) in an oven-dried-Schlenk tube.  $K_2CO_3$  (138 mg, 1.0 mmol, 2 equiv.) was then added to the solution and the suspension was stirred for 10 min under argon. The mixture was then degassed at  $-78$  °C for  $2 \times 10$  min and the vessel was backfilled with argon. After warming to room temperature, terminal alkyne **2** (1.0 mmol, 2 equiv.), tryptamine **9** (160 mg, 1.0 mmol, 2 equiv.) and CuI (19 mg, 0.1 mmol, 0.2 equiv.) were respectively added into the mixture. The mixture was then rapidly degassed and the vessel was backfilled with argon. The sealed Schlenk tube was placed in the preheated oil bath (50 °C) and was stirred overnight. The reaction mixture was cooled to 0 °C, and then a solution of hydrochloric acid (3.5 mL, 1 M, 7 equiv.) was added dropwise. The reaction was then heated at 50 °C until the disappearance of the  $\gamma$ -hydroxybutyrolactam checked by TLC. The reaction mixture was cooled to 0 °C and then filtered through a pad of Celite®. The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over  $Na_2SO_4$  and concentrated under reduced pressure. The crude product was then purified by flash chromatography on silica gel using petroleum ether : ethyl acetate (stated below) as the eluent.

### General procedure for the synthesis of 14

(*Z*)-3-Substituted-3-iodoprop-2-enoic acid derivative **1** (0.5 mmol, 1 equiv.) was dissolved in *i*-PrOH (1.75 mL) in an oven-dried-Schlenk tube.  $K_2CO_3$  (139 mg, 1.0 mmol, 2 equiv.) was then added to the solution and the suspension was stirred for 10 min under argon. The mixture was then degassed at  $-78$  °C for  $2 \times 10$  min and the vessel was backfilled with argon. After warming to room temperature, terminal alkyne **2** (1.0 mmol, 2 equiv.), primary amine **3** (2.0 mmol, 4 equiv.) and CuI (19 mg, 0.1 mmol, 0.2 equiv.) were respectively added into the mixture. The mixture was then rapidly degassed and the vessel was backfilled with argon. The sealed Schlenk tube was placed in the preheated oil bath (45 °C) and was stirred overnight. The reaction mixture was cooled to 0 °C, and then 1.7 mL of a solution of hydrochloric acid (6 M, 20 equiv.) was added dropwise. The reaction was then heated at 50 °C until the disappearance of the  $\gamma$ -hydroxybutyrolactam checked by

TLC. The reaction mixture was cooled to 0 °C and then filtered through a pad of Celite®. The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was then purified by flash chromatography on silica gel using petroleum ether: ethyl acetate as the eluent.

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- The ratio of **13** and **14** was calculated from the crude <sup>1</sup>H NMR spectrum.