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Review

Straightforward Access To a Great Diversity of Complex Biorelevant #-Lactams Thanks To a Tunable Cascade Multicomponent Process

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Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.9b00438 • Publication Date (Web): 10 Feb 2020

Just Accepted

Straightforward Access To a Great Diversity of Complex Biorelevant γ-Lactams Thanks To a Tunable Cascade Multicomponent Process

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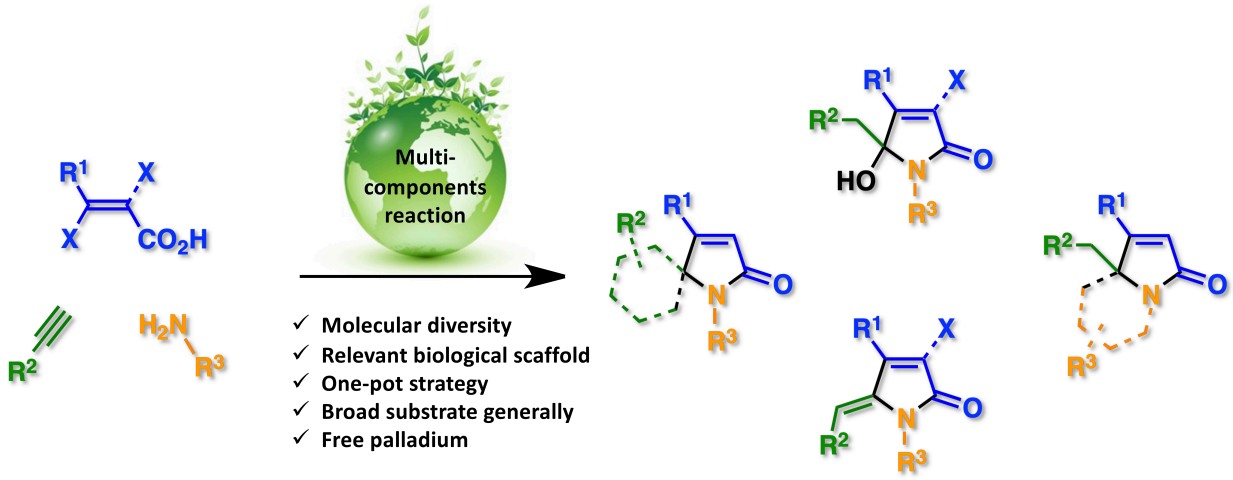


ABSTRACT. The current article reviews the preparation of a great diversity of complex biorelevant γ-lactams backbones thanks to scalable copper(I)-catalyzed cascade multicomponent processes.

KEYWORDS. Lactams, Copper Catalysis, Heterocyclic Compounds, Multicomponent Reaction, γ-Hydroxybutyrolactams, Spirolactams

1. INTRODUCTION

1*H*-Pyrrol-2(5*H*)-ones **1** represent important heterocycles found in many natural products and molecules with a variety of pharmaceutical uses.[1] Several examples possessing interesting structural and biological activities include codinaeopsin **2**,[2] axinellamide **3**,[3] pulchellalactam **4**,[4] pandamarine **5**,[5] and erysotramidine **6**[6] (Figure 1). Among them, 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones **7**, also known as γ-hydroxy-γ-lactams, have gained a lot of interests due to their versatility in organic synthesis and medicinal chemistry.[7] As a consequence, numbers of synthetic strategies have been devised to access these heterocycles including intra- and intermolecular routes as well as oxidation reactions of heterocyclic compounds.[8] More specifically, several groups have designed efficient and attractive routes, based on multicomponent reactions (MCRs),[9] to address a modular preparation of these γ-hydroxy-γ-lactams **7**.

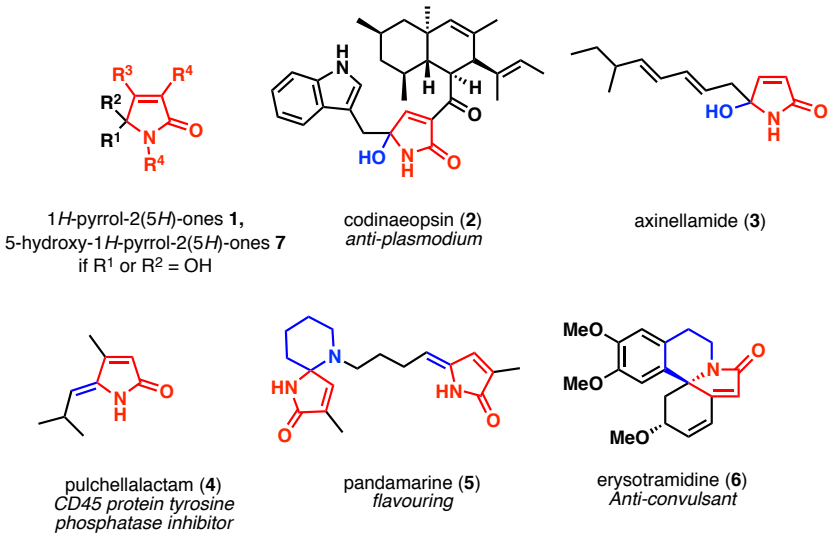
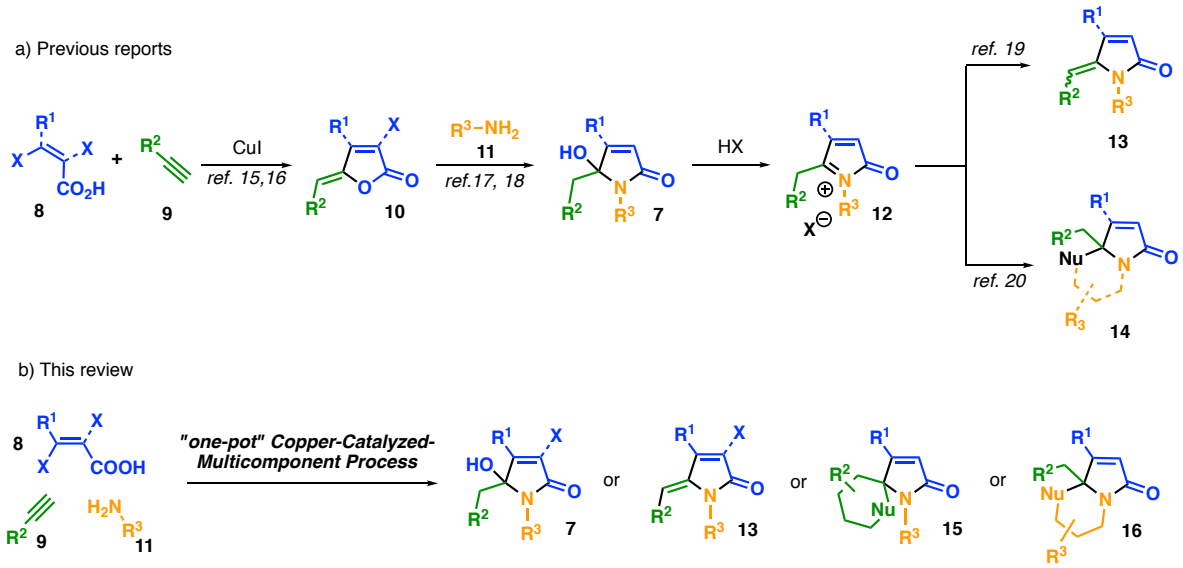


Figure 1. Natural product containing the γ-lactam moiety

These MCRs mainly involve a three-component reaction between aldehydes, 1,3-dicarbonyl compounds and isocyanides,[10] or dialkylacetylenedicarboxylates, benzoyl chlorides and isocyanides,[11] or primary amines, dimethylacetylenedicarboxylate and oxalyl chloride,[12] or dibenzoylacetylene, aryl sulfonyl isocyanates and amines.[13] More recently, an elegant enantioselective MCR between ketones, carboxylic acids and a nitroalkenes, catalyzed by a chiral proline ester derivative, has been also reported by Cossío and co-workers.[14]

In addition, it has been reported in 2009 that the palladium-free Sonogashira coupling between (*Z*)-3-iodoacrylic acids **8** and terminal alkynes **9**, followed by a 5-*exo*-dig *oxa*-cyclisation offered a convenient access to γ-alkylidenebutenolides **10** (scheme 1a).[15,16]It is also generally known and commonly used, that treatment of γ-alkylidenebutenolides **10** with primary amines **11** lead to the formation of γ-hydroxy-γ-butyrolactams **7** (Scheme 1a).[17,18] Moreover, the treatment of γ-hydroxybutyrolactams **7** with acid sources results in the formation of the corresponding *N*-acyliminium ions **12** which can evolve either to γ-alkylidene-γ-butyrolactams **13**[19] or γ-functionalized lactams **14**[20] (Scheme 1a). By taking advantage of these transformations, Commeiras and co-workers proposed new multicomponent synthetic strategies between readily or commercially available (*Z*)-3-iodoacrylic acids, as well as (*E*)-2,3-dihalogenoacrylic acids **8**, terminal alkynes **9**, and primary amines **11** in the presence of copper(I) catalyst providing either γ-hydroxy-γ-butyrolactams **7** or various γ-lactam motifs **13**-**16**.[21,22] In this review, we provide a comprehensive survey of this copper(I)-mediated multicomponent process, which could be compared to a (3+1+1) ring construction cyclization approach, able to prepare, in a simple and atom economic transformation, a great diversity of complex biorelevant γ-hydroxy-γ-butyrolactams **7** and their one-pot post-functionalization (Scheme 1b).

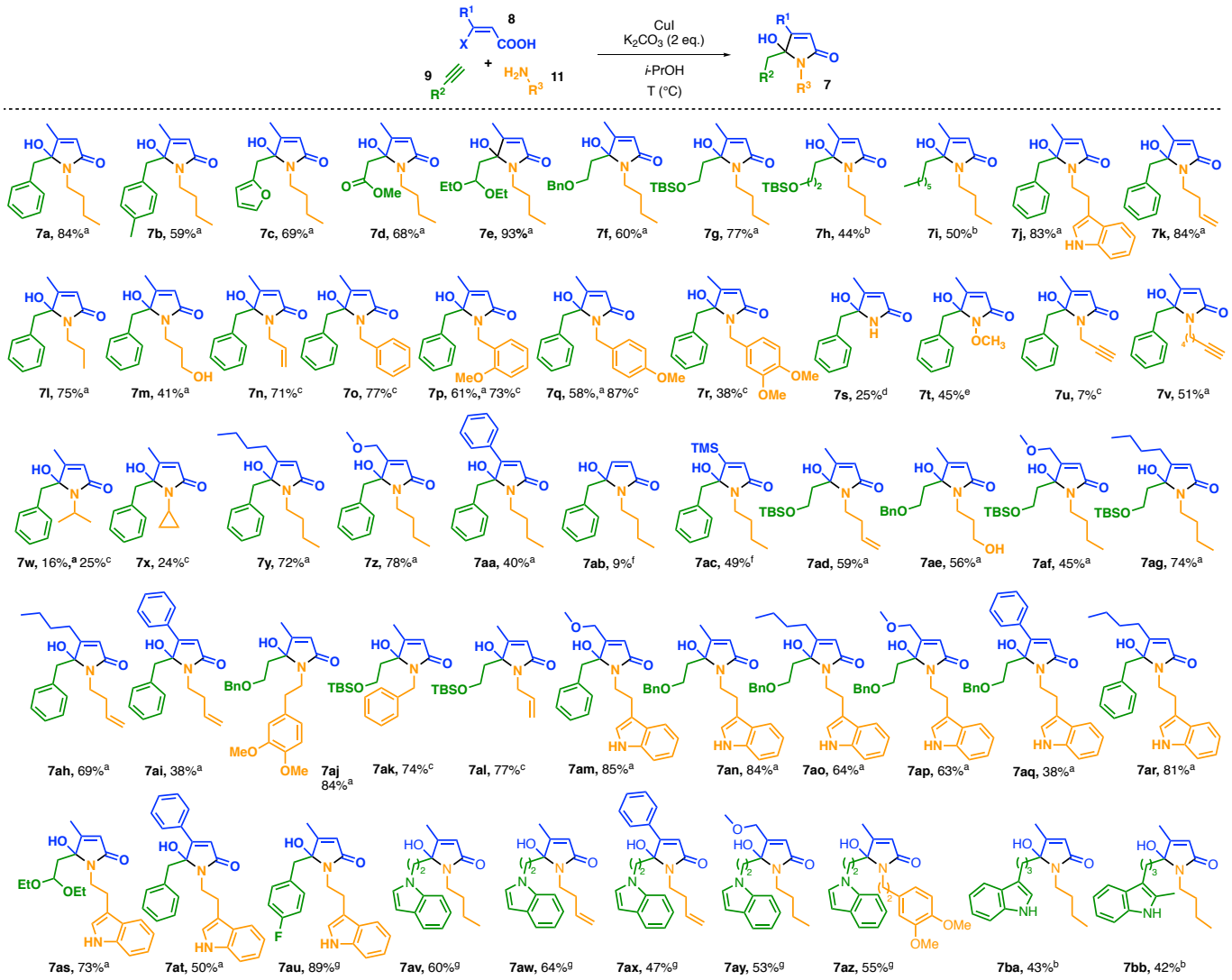


Scheme 1. The proposed cascade strategies for direct synthesis of various γ-lactam motifs

2. SYNTHESIS OF γ-HYDROXYBUTYROLACTAMS 7. Initially, the authors have shown that the optimum reaction conditions were obtained when the process was conducted in degassed *i*-PrOH at 50 °C for 12 h using 1 equiv. of the acrylic acid (((*Z*)-3-iodobut-2-enoic acid **8a**), 2 equiv. of the terminal alkyne (phenylacetylene **9a**) and 2 equiv. of primary amine (butylamine **11a**), 2 equiv. of K_2CO_3 and 20 mol% of CuI.[15] Under these conditions, the γ-hydroxy-γ-butyrolactam **7a** was obtained in excellent 84% isolated yield on a 2 mmol scale (Scheme 1). It is worth noting that the γ-hydroxy-γ-butyrolactam **7a** was prepared thanks to one-pot-cascade reactions involving palladium free Sonogashira coupling-heterocyclization-nucleophilic addition, in which one C-C, one C-O and two C-N bonds were created, without the formation of side products arising from the potential reactions such as Ullmann coupling as well as 1,4- and 1,6-conjugate addition between the lactone intermediate **10a** and primary amine. In addition, the scale-up to 20 mmol of (*Z*)-3-iodobut-2-enoic acid **8a** was readily accomplished without requiring the

optimization of the previous reaction conditions. The γ-hydroxy-γ-butyrolactam **7a** was isolated with the same excellent yield (82%, 4.27 g).

The applicability and the generality of this process has been demonstrated by the preparation of a large library, more than 60 examples, of γ-hydroxybutyrolactams **7** (Schemes 2 and 3). Indeed, diversely substituted and functionalized starting materials are tolerated and have been converted to the desired targets **7**.



[a] 1 eq. of **8**, 2 eq. of **9**, 2 eq. of **11**, 20 mol% of CuI, 50 °C, 12 h.; [b] 1 eq. of **8**, 2 eq. of **9**, 4 eq. of **11**, 20 mol% of CuI, 45 °C,12 h.; [c] 1 eq. of **8**, 2 eq. of **9**, 3 eq. of **11**, 20 mol% of CuI, 50 °C, 12 h.; [d] 1 eq. of **8**, 2 eq. of **9**, 10 eq. of **11**, 20 mol% of CuI, 50 °C, 48 h.; [e] 1 eq. of **8**, 2 eq. of **9**, 3 eq. of **11**, 20 mol% of CuI, 6 eq. of NEt_3, 50 °C, 72 h.; [f] 1 eq. of **8**, 2 eq. of **9**, 2 eq. of **11**, 1 eq. of CuI, 50 °C, 12 h.; [g] 1 eq. of **8**, 2 eq. of **9**, 3 eq. of **11**, 1 eq. of CuI, 50 °C, 12 h.

Scheme 2. Scope of the MCR process

Terminal alkynes bearing both aromatic and heteroaromatic rings and terminal alkynes substituted with different functional groups, such as methyl ester, diethyl acetal and benzyl as well as silicon-protected-propargyl alcohol, are tolerated in the multicomponent reaction. Application of alkynes containing longer aliphatic chain such as TBS-protected but-4-ynol and oct-1-yne, produced the corresponding lactams **7h-i** but in lower yield (up to 50%) due to the formation of 6-membered-lactones (13% and 10%, respectively as the thermodynamic products generated from 6-*endo*-heterocyclization step).[23] Unfortunately, these 6-membered-lactones are unreactive towards primary amine. For these non-activated alkynes, the optimization of the reaction conditions revealed that it is necessary to perform the reaction at 45 °C in the presence of 4 equiv. of primary amines to obtain better results. The authors found that this reaction was dependent on the nucleophilicity of the primary amines **11**. Compared to nucleophilic amines, such as butylamine, tryptamine, homoallylamine and propylamine for which only 2 equivalents are required, 3 equiv. of amines possessing less nucleophilic character (for instance, allyl and benzylamine) were necessary to completely convert the lactones intermediates **10** into the γ-hydroxy-γ-lactams. In the case of 2-methoxybenzylamine and 4-methoxybenzylamine, the reaction could be conducted by using 2 equiv. of the corresponding primary amine to give the desired products **7p-q** but in lower yield (61 and 58% yields respectively) compared with the use of 3 equiv. of **11**. The major limitation of the reaction was obtained with low-nucleophilic aniline derivatives (aniline and 4-methoxyaniline) since the hydroxylactams **7** were not detected. The low-nucleophilic behavior of non-alkyl primary amine was also observed with ammonia. The resulting scaffold **7s** was isolated in moderate yield (25%) even by using 10 equiv. of NH_3 solution (2M in *i*-PrOH) for 48h. It is

worth mentioning that beneficial alpha-effect occurred starting from methoxyamine hydrochloride; **7t** was isolated in better yield (45%).

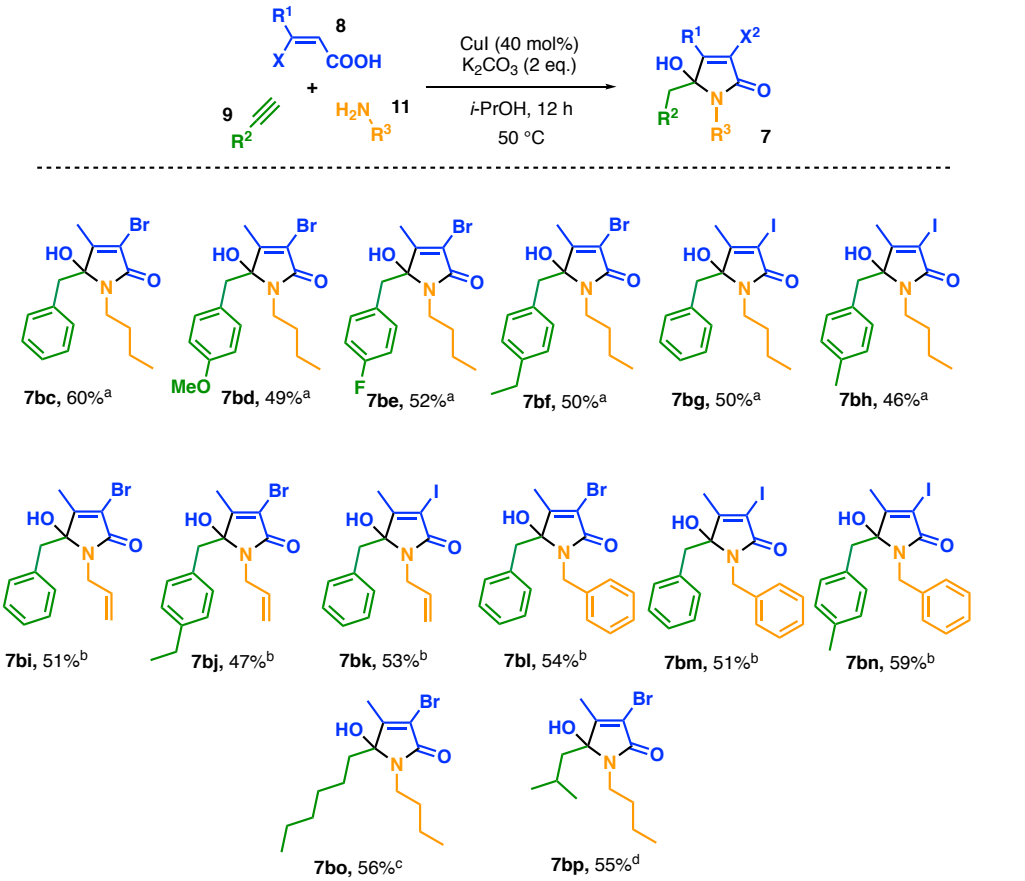
The chemoselectivity of the multicomponent process was also assessed by using alkynylamine substrates such as propargylamine and hex-5-ynylamine. While low isolated yield of hydroxylactam **7u** (7%) was observed by using propargylamine (even with 3 equiv.), hydroxylactam **7v** was obtained in moderate yield (51%) starting from hex-5-ynylamine. This result demonstrated that the Sonogashira coupling exclusively favored the triple bond of terminal aromatic alkynes compared to that of alkynylamines. The steric effect on the efficiency of the cascade process was also evaluated. When *iso*-propylamine was used as primary amine under standard otherwise conditions, a 1:0.5 mixture of the desired lactam **7w** and the residual alkylidenebutenolide **10w** was formed. Compared to hydroxylactam isomer **7l** which was isolated in 75% yield, **7w** was isolated in 16% yield. The presence of lactone **10w** would indicate that the steric hindrance may inhibit the nucleophilic addition reaction of primary amine. Increasing the amount of primary amine to 3 equiv. gave full conversion to the hydroxylactam **7w**, unfortunately with a slight increase of the yield (25%). It has been also shown that various substituents can be installed on the β-position of iodoacrylic acids to effectively produce the desired γ-hydrolactams. It should be noted that α,β-unsubstituted-γ-hydroxy-γ-lactam moiety **7ab** couldn't be generated in good yield (9%) starting from (*Z*)-3-iodo-propenoic acid. This low isolated yield could be explained by the formation of side products arising from 1,4-conjugate addition reaction and from the low stability of the lactam.[24] As an alternative pathway, the γ-lactam **7ab** could be obtained in a two-step procedure by installing a temporary disposable trimethylsilyl group on the β-position. Indeed, the reaction was conducted from (*Z*)-3-iodo-3-(trimethylsilyl)propenoic acid with 1 equiv.

of copper(I) iodide to give the β-silylated-hydroxylactam **7ac** in 49% yield, which in turn underwent the desylilation reaction using NaF to furnish **7ab** in 57%.

A special attention was paid to introduce an indole moiety in order to have a rapid access to biorelevant γ-hydroxybutyrolactam/indole hybrids scaffolds. For this purpose, the indole nucleus could be incorporated either on the primary amines (starting from tryptamine) or terminal alkynes (starting from *N*-propargylindole or 3-(buty-3-yn-1yl)-1*H*-indole). Whatever the nature of the starting materials, the desired hybrid scaffolds **7am**-**7bb** were successfully prepared up to 89% yield. It is worth noting that when *N*-propargylindole was applied as starting material, 1 equiv. of CuI and 3 equiv. of primary amine were required to have a complete conversion of lactone intermediate. As previously discussed, in the case of non-activated 3-(buty-3-yn-1yl)-1*H*-indoles, the desired γ-hydroxybuterolactams **7ba** and **7bb** were prepared in moderates yields (43 and 42%, respectively) together with the non-desired pyran-2-ones (ratio of 1:0.22 and 1:0.22, respectively).

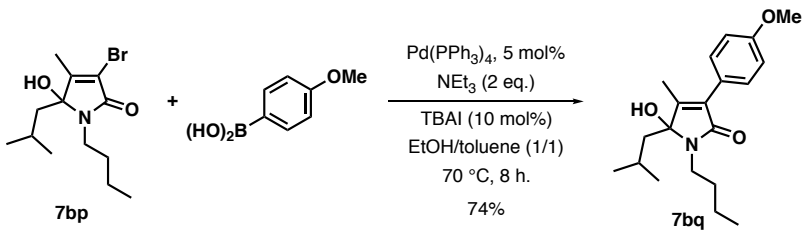
Finally, in order to increase the molecular complexity of γ-hydroxybutyrolactams, this process was also assessed starting from α,β-dihalogenoacrylic acid (Scheme 3).[25] In this case, the copper-mediated MCR would furnish α-halogeno-γ-hydroxybutyrolactams allowing α-post-functionalization by exploiting the reactivity of the resultant halogen atom. The utilization of α,β-dibromobutenoic acid or α,β-diiodobutenoic acid required a slight modification of the reaction conditions. The best results were observed when the reaction was conducted with 40 mol% of CuI at 55 °C. Under these conditions, several α-halogeno-γ-hydroxybutyrolactams were prepared in moderate yield (up to 60%) by varying both the nature of terminal alkynes and primary amines. As previously, the reaction has been scale-up to 20 mmol without loss of efficiency. **7bc** was isolated in 52% yield. Interestingly, when **7bp** is exposed to *p*-methoxyphenylboronic acid, the

Pd-catalyzed Suzuki-Miyaura coupling reaction led to the formation of α-substituted γ-hydroxybutyrolactam **7bq** in 74% yield (Scheme 4).



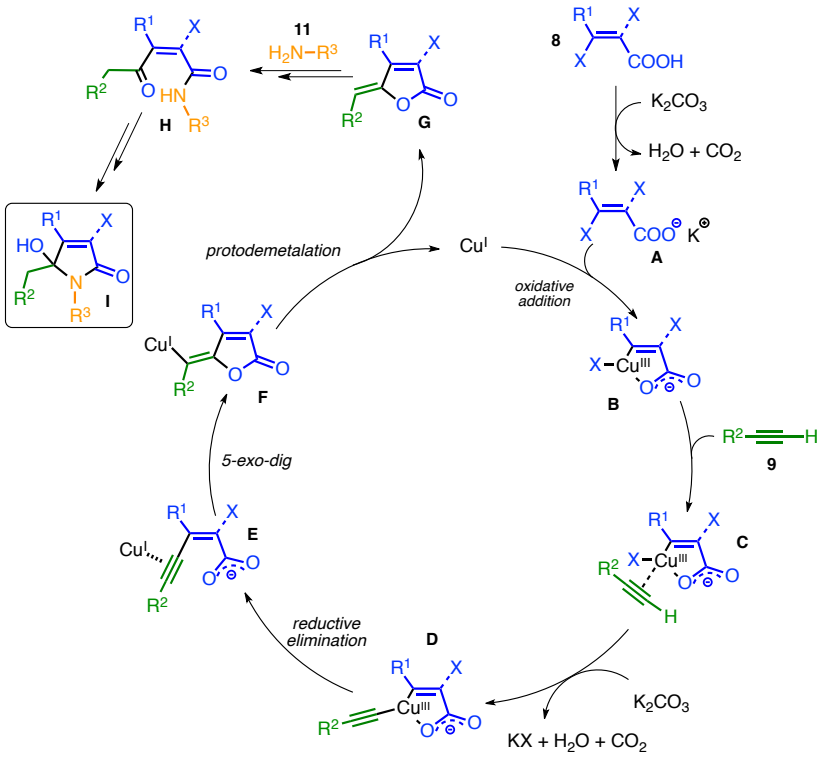
(a) 1 eq. of **8**, 2 eq. of **9** and 2 eq. of **11**; (b) 1 eq. of **8**, 2 eq. of **9** and 3 eq. of **11**,(c) 1 eq. of **8**, 2 eq. of **9** and 3eq. of **11** (d) 1 eq. of **8**, 5 eq. of **9** and 3 eq. of **11**.

Scheme 3. Preparation of α-halogeno-γ-hydroxybutyrolactams.



Scheme 4. Preparation of α-substituted γ-hydroxybutyrolactam **7bq**

Two mechanistic scenarios could be considered for this copper-mediated multicomponent process. The first one would involve a Castro-Stephens type coupling whereas the second one a Sonogashira type coupling (without palladium). The Castro-Stephens type coupling is disregarded because when the reaction of the formation of the lactone **10** is performed with one equivalent of phenylethynyl cooper reagent and (Z)-3-iodobut-2-enoic acid **8a**, no lactone **10a** was observed in the crude mixture. Therefore, a plausible mechanism, based on a Sonogashira type coupling without palladium, is depicted in Scheme 5. The first step is likely to be an oxidative addition of the copper(I) into the C–I bond of **A** to give copper(III) intermediate **B**. The next steps would involve a π-coordination of the alkyne reagent followed by the formation of complex **D** thanks to a base-mediated-deprotonation of terminal acetylenic proton. Next, the reductive elimination of the intermediate **D** followed by a 5-*exo*-dig cyclisation assisted by copper(I) would lead vinyl copper intermediate **F** which would give lactone **G** *via* protodemetalation. Finally, the nucleophilic addition of the primary amine onto the lactone **G** would furnish the desired hydroxylactams **I** via the intermediate **H**.

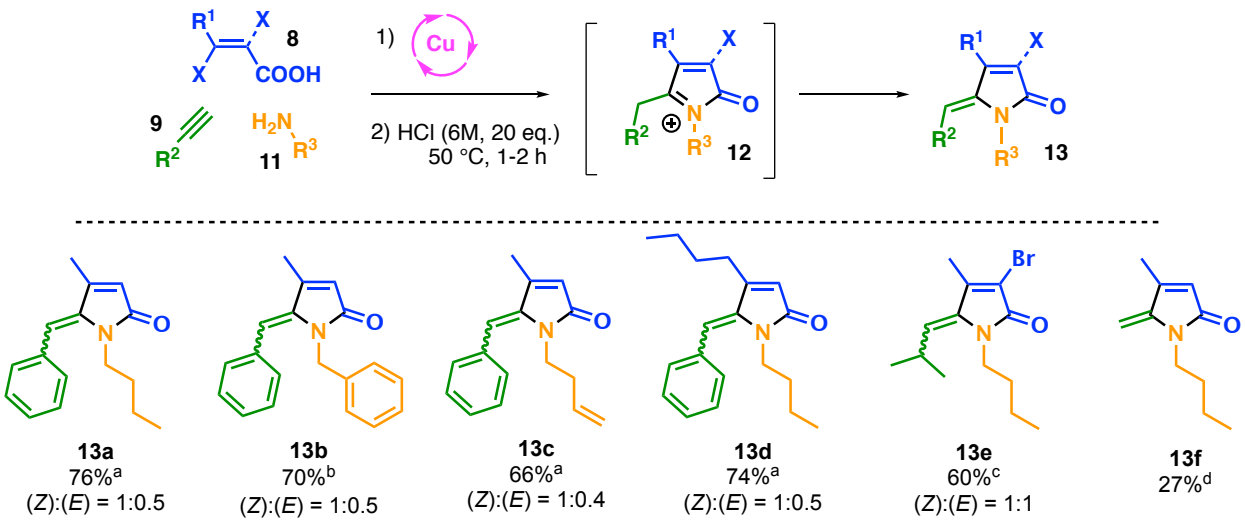


Scheme 5. Plausible mechanism for the preparation of **7**.

3. ONE-POT POST-FUNCTIONALIZATION OF 7. Encouraged by the excellent results obtained with this copper(I)-catalyzed cascade multicomponent process, Commeiras and co-workers then investigated the synthetic application of γ-hydroxy-γ-lactams **7** by exploiting their reactivity as *N*-acyliminium ion (NAI) precursors **12**.[24,26,27] Indeed, NAI are highly reactive electrophilic intermediates and they are therefore excellent candidates for the creation of both carbon-carbon or carbon-heteroatom bonds. The purpose was to extend the previously multicomponent process by adding the formation and the post-functionalization of NAI in a one-pot fashion. The incorporation of the NAI chemistry into the cascade process has been simply

carried out by quenching the copper(I)-catalyzed multicomponent reaction with an HCl acidic aqueous solution instead of a saturated aqueous NH_4Cl solution.

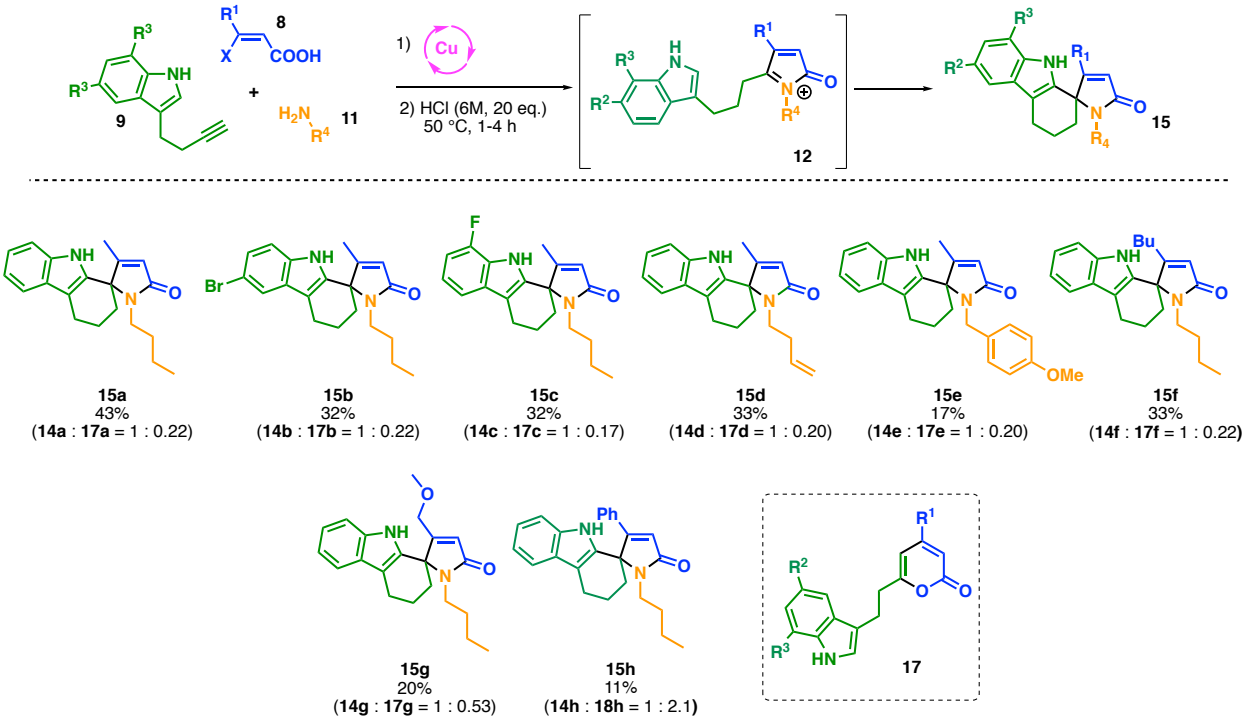
In the absence of any potential nucleophiles, the NAI intermediates **12** underwent to β-elimination reaction to give the corresponding γ-alkylidene-γ-lactams **13** as an inseparable mixture of diastereomers and in good yields (Scheme 6). Importantly, this strategy allowed to obtain the γ-methylidenebutyrolactam **13f** (54% brsm) in a very convergent way compared to those described in the literature for such scaffolds.[28] In this case, ethynyltrimethylsilane has played the role of an acetylene equivalent. It is worth noting that the moderate yield observed is presumably due to a low conversion rate (50%) of the reaction.



[a] 1 eq. of **8**, 2 eq. of **9**, 2 eq. of **11**, 20 mol% of CuI, 50 °C; [b] 1 eq. of **8**, 2 eq. of **9**, 3 eq. of **11**, 20 mol% of CuI; [c] 1 eq. of **8**, 5 eq. of **9** and 3 eq. of **11**; 20 mol% of CuI; [d] 1) 1 eq. of **8**, 5 eq. of **9**, 2 eq. of **11**, 100 mol% of CuI, 75 °C, 12 h.; 2) HCl, (6M, 20 eq., 75 °C)

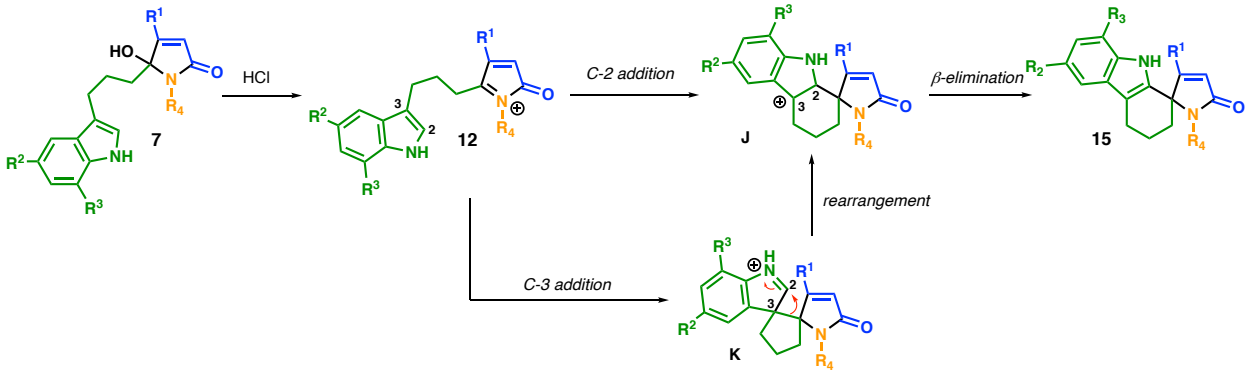
Scheme 6. Cascade multicomponent process towards the synthesis of γ-alkylidene-γ-lactams **13**

On contrary, in presence of nucleophiles, the NAI intermediates **12** could be trapped by these later. Thanks to both an intramolecular reaction and depending the position of the nucleophiles, the synthesis of different polyheterocyclic lactams **15**-**16** have been envisaged. Indeed, while the installation of nucleophilic site into the terminal alkynes provided the corresponding spirolactams **15**, nucleophile-substituted-primary amines provided fused heterocycle-lactam derivatives **16**. The authors have shown that (5,6)-spirolactams **15** were generated when non-activated indole-substituted-terminal alkynes **9**, namely 3-(but-3-yn-1-yl)-1*H*-indole derivatives were subjected into the process (Scheme 7). The tolerably yield of **15** is generally due to the formation of 20% of the non-desired and unreactive six-membered lactone **17**. Even if the yields of the isolated desired products are relatively moderate, this useful cascade multicomponent process allows the synthesis of (5,6)-spirocyclic scaffolds *via* the construction of 2 C-C and 2 C-N bonds together with a quaternary center from readily available starting materials.



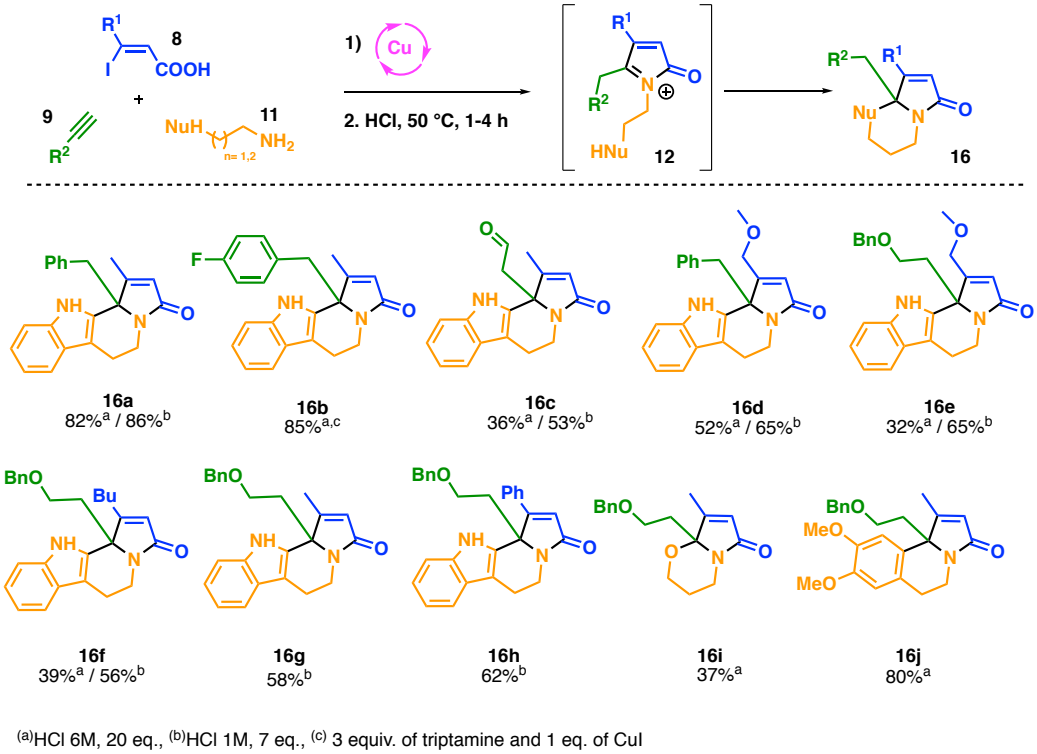
Scheme 7. Cascade multicomponent process towards the synthesis of (5,6)-spirolactams **15**

Concerning the mechanism of the formation of the corresponding spirolactams, the nucleophilic addition of the indole moiety may occur either from C-2 or C-3 positions (Scheme 9). The C-2 addition would produce the carbocation **J**, which in turn would undergo β-elimination to give the desired spirolactam **15**. On the other hand, the C-3 addition would provide the spiro-compound intermediate **J**. The latter would undergo rearrangement to give **I**, followed by a β-elimination to furnish the final product **15**.



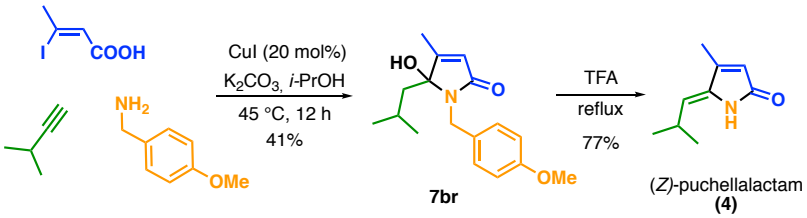
Scheme 8. Plausible mechanism for the formation of spirolactams **15**.

Performing the same previous multicomponent process (copper(I)-catalyzed multicomponent process followed with the sequential addition of aqueous HCl 6M solution), by mixing tryptamine, different terminal alkynes and (*Z*)-3-iodoprop-2-enoic acid derivatives, allowed the formation of polyheterocycles **16a-h** containing a tetrahydro-β-carboline moiety, in moderate to very good yields, through an intramolecular C-2 Friedel-Craft alkylation (Scheme 9). Attempts to improve the effectiveness of the cascade process were successfully conducted by using a less concentrated aqueous solution of HCl (1M). Under this condition, the polyheterocyclic compounds were obtained in better yields (from 53 to 86% yields). It is worth noting that this cascade process has been scale-up to 20 mmol. Under these conditions, **16a** was obtained in 61% yield (4 g). It was also demonstrated that the application of 3-aminopropanol allowed to obtain another polyheterocyclic scaffold **16i** of oxazinopyrrolone in 37% yield. Moreover, the extended cascade process could be exploited to directly produce (80% yield) polyheterocycle **16j**, scaffold found in the natural product erysothramidine **6**.



Scheme 9. Cascade multicomponent process towards polyheterocyclic lactam derivatives **16**

Lastly, in addition to these systematic studies, the utility of the copper(I)-mediated MCR process was nicely illustrated by the total synthesis of a natural product namely (*Z*)-pulchellalactam (**4**), which is an inhibitor of the CD45 protein tyrosine phosphatase,[4] in a two-step procedure (γ-hydroxybutyrolactam formation followed by a dehydration reactions) from (*Z*)-3-iodobut-2-enoic acid, *iso*-propylacetylene and *N*-*p*-methoxybenzylamine (Scheme 10). Indeed, using slightly modified conditions (4 equiv. of *iso*-propylacetylene and 3 equiv. *p*-methoxybenzyl amine), the γ-hydroxybutyrolactam **7br** was obtained in 41% yields. The γ-hydroxybutyrolactam **7br** was then subjected to TFA to give a 9:1 separable mixture of (*Z*)- and (*E*)-pulchellalactam **4** in which the natural product was isolated in 77% yield.



Scheme 10. Total synthesis of (Z)-puchellalactam (**4**)

4. SUMMARY

Several methods to synthesize γ-hydroxy-γ-butyrolactams have been reported in the literature. However, strategies based on multicomponent reactions (MCRs) to address a modular preparation of these scaffolds are the most suitable. In this context, a scalable and tunable cascade multicomponent process, starting from the readily available (*Z*)-3-iodoacrylic acids, as well as (*E*)-2,3-dihalogenoacrylic acids, terminal alkynes, and primary amines in the presence of copper(I) catalyst, was developed allowing the preparation of large library of the hydroxylactams. It was also demonstrated that the cascade reaction can be extended by exploiting the chemistry of γ-hydroxy-γ-lactams as the equivalent of *N*-acyliminium ions. A high diversity of γ-alkylidene-γ-lactams, spirolactams and polyheterocyclic lactams can be simply accessed in a single operation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Synthesis procedures, ^{1}H and ^{13}C NMR spectra of each compound.

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ACKNOWLEDGMENT

M.I.D.M. thanks The Ministry of Research, Technology and Higher Education (Republic of Indonesia), the CNRS and Aix Marseille Université (UMR 7313) for financial support. A.M. thanks Dr. Frédéric Montigny (Analysis Department, Tours University) for HRMS analysis.

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