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# Stereocontrolled access to $\delta$ -lactone-fused- $\gamma$ -lactams bearing angular benzylic quaternary stereocenters<sup>†</sup>

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C-fused  $\gamma$ -lactam-lactones are resident in several bioactive molecules, including anticancer agents such as omuralide. In this embodiment, we report mild conditions for the catalytic halolactonization of lactam-tethered 5-aryl-4(*E*)-pentenoic acids. The use of dichloromethane as the solvent and Ph<sub>3</sub>P=S as the catalyst led to predominant 6-*endo-trig* cyclization and furnished the *trans*-fused- $\gamma$ -lactam- $\delta$ -lactones. The transformation is modular, regioselective, chemoselective, and diastereoselective. The  $\gamma$ -lactam- $\delta$ -lactones bear angular quaternary benzylic stereocenters, which is noteworthy since the presence of a quaternary carbon in bioactive small molecules often promotes an element of conformational restriction that imparts potency, selectivity, and metabolic stability. The generated halogen and lactone motifs are important functional handles for late-stage diversification.

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There are high incentives for the construction of architecturally complex sp<sup>3</sup>-enriched azaheterocyclic scaffolds. Specifically, the lactam topology is omnipresent in medicinal chemistry and drug discovery programs.1 In addition to their well-studied antibiotic activity,2 several functionalized lactams act as opioid receptor agonists,3 HIV-1 integrase inhibitors,4 anticancer,<sup>5</sup> antidepressant,<sup>6</sup> and anti-inflammatory agents.<sup>7</sup> Meanwhile, lactones are ubiquitous architectures in a variety of natural products and pharmaceuticals.8 Lactones are also frequently used as versatile building blocks for accessing other oxygen-containing heterocycles and carboxylic acid derivatives.9 Importantly, sp<sup>3</sup>-rich fused  $\gamma$ -lactam-lactones are resident in bioactive molecules such as neooxazolomycin, UCS 1025 A, and omuralide (Fig. 1). Lovering has articulated that both molecular complexity (as measured by Fsp<sup>3</sup>, where Fsp<sup>3</sup> refers to the ratio of sp<sup>3</sup> hybridized carbons to the total number of carbons) and the presence of carbon stereocenters correlate with success as compounds transition from discovery, through clinical testing, to drugs.10 Medicinal chemists are therefore becoming increasingly keen on escaping flatland in view of exploring 3Dstructural space, which makes these sp<sup>3</sup>-rich fused lactamlactones valued targets for pharmaceutical companies. Some elegant strategies have fittingly emerged for the construction of fused lactam-lactones, including those developed by Wee<sup>11</sup> (using C-H insertion) and Burton<sup>12</sup> (via oxidative radical cyclization).

Our interest in the synthesis and post-diversification of 1,3azadiene-cyclic anhydride annulation products<sup>13</sup> prompted us to explore a lactamization/lactonization sequence as a method to rapidly construct sp<sup>3</sup>-rich fused  $\gamma$ -lactam- $\delta$ -lactones bearing quaternary and contiguous stereocenters. Toward this end, we sought to interrogate lactam-bearing alkenoic acids of type **3** in a catalytic halolactonization protocol (Fig. 2). Molecules containing all-carbon quaternary stereocenters have the propensity



Fig. 1 Examples of C-fused bioactive γ-lactam-lactones.



Fig. 2 Proposed plan for the synthesis of fused  $\gamma\text{-lactam-fused-}\delta\text{-lactones.}$ 

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to mitigate a spectrum of structural diversity issues in medicinal chemistry mainly because the presence of a quaternary carbon in bioactive small molecules promotes an element of conformational restriction that imparts potency, selectivity, and metabolic stability.<sup>14</sup> Indeed, of the top 120 chiral smallmolecule pharmaceuticals by retail sales in the United States in 2018, 13% contained a quaternary stereocenter.<sup>15</sup>

Among the reported methods for the construction of common-ring lactones,<sup>16</sup> halogen-initiated cyclization of unsaturated carboxylic acids is an attractive approach for the stereoselective synthesis of halogenated lactones.<sup>17,18</sup> The transformation is very versatile given that the generated halogen and lactone motifs are important functional handles for late-stage diversification. In these studies, we show that lactam-tethered alkenoic acids of type **3** undergo efficient catalytic halolactonization to furnish fused  $\gamma$ -lactam- $\delta$ -lactones of type **4**.

We initiated studies toward the construction of fused  $\gamma$ lactam-lactones by benchmarking our optimization efforts for bromolactonization of alkenoic acid 3a with the reaction conditions described in Table 1. Dichloromethane emerged as the preferred reaction medium (entries 1-4). Other sources of bromine that were surveyed were less efficient than N-bromosuccinimide (entries 5 and 6). Ph<sub>3</sub>P=S emerged as the most effective catalyst (entries 7-12). Other reaction conditions known to promote bromolactonization of simple alkenoic acids were also surveyed (entries 13-17). Under the optimized conditions, lactam-lactone 4a was obtained in good yield, high anti-stereoselectivity, and in impeccable 6-endo selectivity. A widely accepted mechanism for this electrophilic halolactonization is that an electrophilic halogen is first transferred from a halogen source to the olefin to form a halonium ion, followed by an intramolecular attack by the carboxylate group. The observed anti addition in a Markovnikov sense is the expected outcome for such 5-aryl-4(E)-pentenoic acids, characterized by an unsymmetrical build-up of positive charge next to the aryl group in the transition state.<sup>19</sup> Previous ab initio simulations revealed some syn-directing noncovalent interactions such as hydrogen bonding between the nucleophile and the halogen source, which control the formation of the syn-product.<sup>20</sup> The disruption of these syn-directing interactions by a basic additive or a protic solvent, results in a strongly increased diastereoselectivity toward the anti-product. Thus, we surmise that Ph<sub>3</sub>P=S enhances the anti-diastereoselectivity. This is further supported by observations that in the absence of Ph<sub>3</sub>P=S (entry 7), 4a was obtained in 83 : 17 (anti : syn) ratio.

The scope of the transformation with respect to the nature of the styrenyl group and the substituent on nitrogen (alkyl, aryl, allyl, and benzyl) has been explored. Gratifyingly, several  $\gamma$ lactam-tethered alkenoic acids undergo 6-*endo* bromolactonization, giving rise to the 5,6-bicycles depicted in Scheme 1 (see **4a–s**). Electron-deficient styrenoic acids are more competent than their electron-rich congeners, owing to their ability to further stabilize the benzylic positive charge (**4b** *vs.* **4c**). The *N*substituent has a profound effect on the diastereoselectivity as exemplified by the switch from a *tert*-butyl group to a less bulky but electronically similar isopropyl substituent (**4a** *vs.* **4g**). 
 Table 1
 Optimization of the bromolactonization of lactam acid 3a



Entry	Deviation from conditions A	% yield of <b>4a</b> (isolated)
1	1.2-Dichloroethane as solvent	75
)	N N-Dimethylformamide as solvent	$0^a$
3	Acetonitrile as solvent	79
l 1	Methanol as solvent	83
5	$Br_2$ in place of NBS	0
5	DBH in place of NBS	68
7	$Ph_3P = S$ omitted	22
3	$Ph_3P=0$ in place of $Ph_3P=S$	73
)	$Ph_3P$ =Se in place of $Ph_3P$ =S	82
10	$(PhSe)_2$ in place of $Ph_3P=S$	68
1	$Cy_3P = S$ in place of $Ph_3P = S$	77
12	<i>n</i> -Bu <sub>3</sub> P=S in place of Ph <sub>3</sub> P=S	73
13	Conditions B in place of conditions A	80
4	Conditions C in place of conditions A	79
15	Conditions D in place of conditions A	52
16	Conditions E in place of conditions A	80
17	Conditions F in place of conditions A	76



<sup>a</sup> The 5-exo cyclization product was formed predominantly in 69% yield.

Encouragingly, several *N*-arylated  $\gamma$ -lactam-tethered alkenoic acids underwent productive 6-*endo*-cyclization (see **4i**–**n**), which is noteworthy since *N*-aryl  $\gamma$ -lactams are embedded in several pharmacologically pertinent targets. As a testament to the remarkable chemoselectivity of the transformation, lactamtethered alkenoic acids bearing an *N*-allyl substituent react with NBS to afford bicycles **4o**/**p**, without complications arising from bromolactonization of the kinetically more accessible allyl group. We attribute this chemoselective bromolactonization to conformational constraints and to the more activated nature of the styrenyl double bond. The use of trisubstituted alkenoic acids has facilitated the stereocontrolled construction of



Scheme 1 Regioselective 6-*endo*-cyclization of  $\gamma$ -lactam-tethered alkenoic acids by catalytic halolactonization.

lactam-lactones bearing two tetrasubstituted stereocenters (see 4q-s). This is noteworthy since halolactonization reactions of trisubstituted alkenes are not often stereospecific.<sup>19</sup> The

successful and efficient synthesis of 4r/s suggests that the electronic benefit of the two phenyl groups far outweighs the presumed steric encumbrance.

Iodolactonization with *N*-iodosuccinimide (NIS) also proceeded regio- and diastereoselectively (see 4t-z). In these cases, the iodolactonization was performed at 0 °C, owing to the enhanced reactivity of NIS. The results indicate that the *anti*: *syn* ratio is further enhanced when NIS is used in place of NBS (4g vs. 4y or 4p vs. 4w).

In summary, the site-selective, diastereoselective, and scalable synthesis of halogenated fused  $\gamma$ -lactam- $\delta$ -lactones has been accomplished, through the deployment of  $\gamma$ -lactamtethered alkenoic acids<sup>21</sup> in a catalytic halolactonization protocol. The expected 6-*endo* cyclization of these lactamtethered 5-aryl-4(*E*)-pentenoic acids predominates in dichloromethane. These sp<sup>3</sup>-rich fused  $\gamma$ -lactam- $\delta$ -lactones bear medicinally relevant quaternary and contiguous stereocenters. We anticipate that this practical, cost-effective, and catalytic strategy would undeniably expand the 3D-structural space for the discovery of new  $\gamma$ , $\delta$ -lactam-lactones with medicinal value. Post-modification of these versatile N,O-heterocycles is underway. Additionally, efforts to render the transformation enantioselective will be reported indue course following completion of the studies.

#### Author contributions

M. J. R. – investigation, data curation, validation; C. B. – investigation, methodology; T. K. B. – conceptualization, project administration, supervision, writing – original draft, internal funding acquisition.

# Conflicts of interest

There are no conflicts of interest to declare.

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