


 Cite this: *RSC Adv.*, 2022, 12, 28685

# Contra-thermodynamic halolactonization of lactam-tethered 5-aryl-4(*E*)-pentenoic acids for the flexible and stereocontrolled synthesis of fused lactam-halolactones†

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Halolactonization of alkenoic acids enables the construction of oxygen-heterocycles *via* intramolecular halonium-induced nucleophilic addition. Although the literature is currently inundated with halolactonizations of 5-aryl-4(*E*)-pentenoic acids that predictably afford the 6-*endo* cyclization adducts, methods that reliably alter the innate regioselectivity bias to instead deliver the thermodynamically less favored 5-*exo* cyclization products are relatively rare. Here, we attempt to bridge this gap and have found mild conditions for contra-thermodynamic halolactonization of lactam-tethered 5-aryl-4(*E*)-pentenoic acids that lead to the formation of *trans*-fused lactam- $\gamma$ -lactones. The natural proclivity for these 5-aryl-4(*E*)-pentenoic acids to undergo 6-*endo* cyclization is overridden and 5-*exo-trig* cyclization predominates. The success of the approach hinges on the use of *N,N*-dimethylformamide (DMF) as the solvent and *N*-methylmorpholine oxide as the catalyst. The lactam-lactone products are synthesized in high diastereoselectivity, modularity, and chemoselectivity. Notably, most of the bicycles contain one benzylic quaternary stereocenter as well as an  $\alpha$ -alkoxy quaternary stereocenter.

 Received 6th July 2022  
 Accepted 1st October 2022

DOI: 10.1039/d2ra04177d

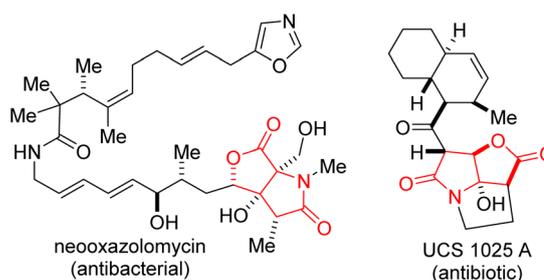
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## Introduction

Functionalized lactones constitute the core of several natural products and pharmaceuticals.<sup>1</sup> They are frequently used as versatile building blocks for accessing other oxygen-containing heterocycles and carboxylic acid derivatives.<sup>2</sup> Meanwhile, lactams are ubiquitous in drug discovery and medicinal chemistry programs.<sup>3</sup> In addition to their well-studied antibiotic activity,<sup>4</sup> several functionalized lactams act as opioid receptor agonists,<sup>5</sup> HIV-1 integrase inhibitors,<sup>6</sup> anticancer,<sup>7</sup> antidepressant,<sup>8</sup> and anti-inflammatory agents.<sup>9</sup> Importantly,  $sp^3$ -rich fused lactam-lactones are resident in bioactive molecules such as neoxazolomycin and UCS 1025 A (Fig. 1). It has previously been articulated that the presence of carbon stereocenters correlate with success as compounds transition from discovery to drugs.<sup>10</sup> Accordingly, medicinal chemists have become increasingly keen on exploring 3D-structural space, which makes  $sp^3$ -rich fused lactam-lactones important targets for pharmaceutical companies. As depicted in Fig. 2A and B, some reliable tactics for the construction of fused lactam-lactones have been reported by Wee<sup>11</sup> and Burton.<sup>12</sup>

Among existing methods for the construction of common-ring lactones,<sup>13</sup> halogen-initiated cyclization of unsaturated

carboxylic acids is an attractive and direct approach for the stereoselective synthesis of halogenated lactones.<sup>14,15</sup> The transformation is very versatile given that the generated halogen and lactone motifs are versatile linchpins for late-stage diversification. Moreover, over 4700 halogen-containing natural products exist,<sup>16</sup> which has fueled numerous target-oriented synthesis efforts that employ halolactonization protocols. Although the literature is replete with halolactonizations of 5-aryl-4(*E*)-pentenoic acids that predictably afford the 6-*endo* cyclization adducts (mainly due to unsymmetrical build-up of positive charge next to the aryl group in the transition state<sup>17</sup>), the development of methods that reliably alter the innate regioselectivity bias to instead deliver the thermodynamically less favored 5-*exo* cyclization products is still at the incipient stages. For instance, Nicewicz and co-workers expertly


 Fig. 1 Examples of C-fused bioactive  $\gamma$ -lactam- $\gamma$ -lactones.

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 † Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data. See DOI: <https://doi.org/10.1039/d2ra04177d>

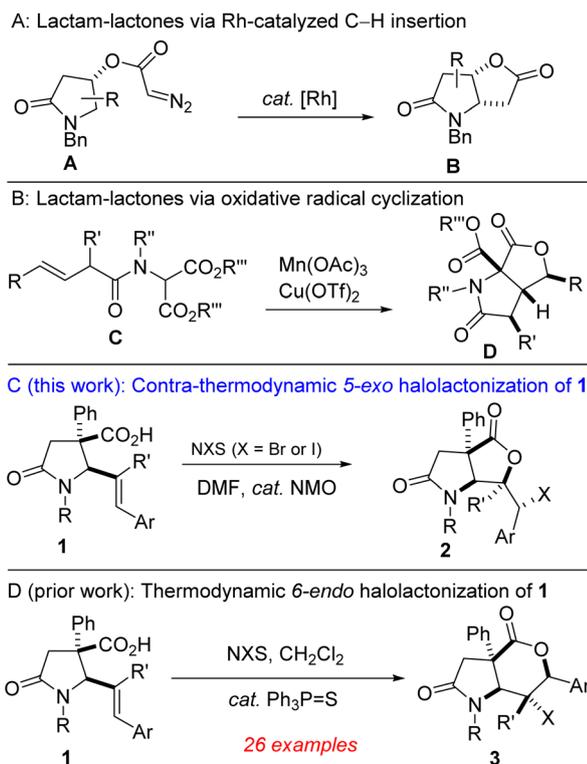



Fig. 2 (A and B) Prior syntheses of fused lactam- $\gamma$ -lactones, (C) our proposed plan for contra-thermodynamic 5-*exo* cyclization of **1**, (D) our recently reported approach for thermodynamic 6-*endo* cyclization of **1**.

developed a synergistic protocol that accomplished halolactonization of 5-aryl-4(*E*)-pentenoic acids with opposite regioselectivity.<sup>18</sup> The authors articulated that even under their photocatalytic conditions, the use of *N*-halosuccinimides failed to override the innate 6-*endo* cyclization pathway.

Our interest in the synthesis and post-diversification of lactam-tethered alkenoic acids<sup>19</sup> prompted us to explore a practical and flexible route toward  $sp^3$ -rich fused lactam-lactones bearing quaternary and contiguous stereocenters. Toward this end, we sought to interrogate readily available lactam-bearing 5-aryl-4(*E*)-pentenoic acids of type **1**,<sup>20a</sup> in a contra-thermodynamic and catalytic halolactonization protocol (Fig. 2C). Herein, we demonstrate that the natural proclivity of these 5-aryl-4(*E*)-pentenoic acids to undergo 6-*endo* cyclization can be overridden using solvent- and catalyst-controlled reactivity. When DMF is employed as the solvent and *N*-methylmorpholine oxide (NMO) as the catalyst, the 5-*exo* cyclization products are obtained in diastereoselective, chemoselective, modular, and scalable fashions. The method nicely complements our recently developed protocol for accessing the thermodynamic  $\delta$ -lactone-fused lactams (Fig. 2D).<sup>20b</sup>

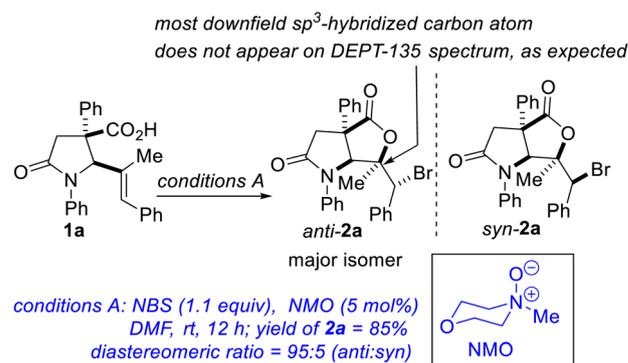
## Results and discussion

During our previous attempts at thermodynamic 6-*endo* cyclization of lactam-bearing 5-aryl-4(*E*)-pentenoic acids of type **1**, we noted that bromolactonization using *N*-bromosuccinimide

(NBS, 1.1 equiv.) and  $Ph_3P=S$  (5 mol%) failed to furnish the desired product when the solvent was switched from dichloromethane to *N,N*-dimethylformamide (DMF).<sup>20b</sup> Instead, the contra-thermodynamic 5-*exo* cyclization product was formed in modest yield. Having previously found an isolated example of catalyst-free regiodivergent bromolactonization on a valerolactam-tethered alkenoic acid,<sup>19f</sup> we set out to explore efficient and general conditions for contra-thermodynamic halolactonization of **1**.

We benchmarked our optimization efforts for bromolactonization of alkenoic acid **1a** with the reaction conditions described in Table 1. Trisubstituted alkenoic acid **1a** was chosen as the model substrate in order to test the power of the methodology since halolactonization reactions of trisubstituted

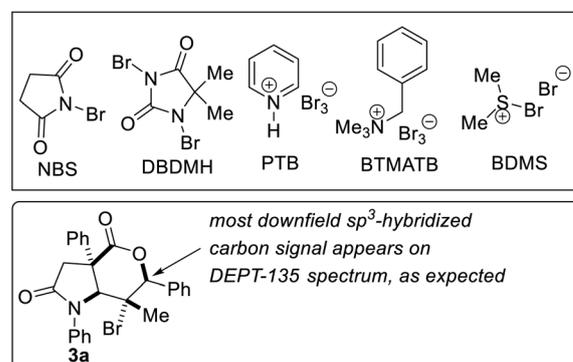
Table 1 Optimization of the bromolactonization of lactam acid **1a**



Entry	Deviation from conditions A	% yield of <b>2a</b> (isolated)
1	1,2-dichloroethane as solvent	0
2	Dichloromethane as solvent	0 <sup>a</sup>
3	Acetonitrile as solvent	0
4	Methanol as solvent	0
5	Br <sub>2</sub> in place of NBS	0
6	DBDMH in place of NBS	61
7	PTB in place of NBS	0
8	BTMATB in place of NBS	0
9	BDMS in place of NBS	0
10	NMO omitted	17 (74) <sup>b</sup>
11	$Ph_3P=S$ in place of NMO	73
12	$Ph_3P=Se$ in place of NMO	77
13	$(PhSe)_2$ in place of NMO	68
14	$Cy_3P=S$ in place of NMO	77
15	<i>n</i> -Bu <sub>3</sub> P=S in place of NMO	73

<sup>a</sup>6-*endo* cyclization was predominant (**3a**, 79% yield)

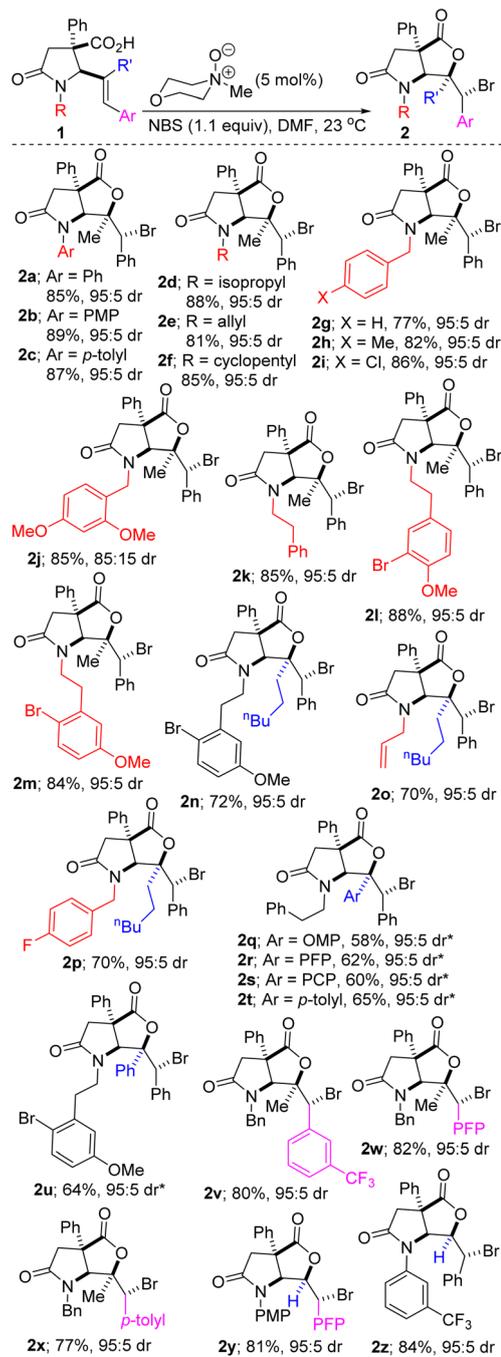
<sup>b</sup>after 72 h at room temperature in the absence of NMO



alkenes are known to be problematic from the standpoints of regioselectivity and stereospecificity.<sup>17</sup> During the optimization studies, DMF indeed emerged as the solvent of choice (entries 1–4). Other electrophilic brominating agents did not perform as well as NBS (entries 5–9). *N*-methylmorpholine oxide (NMO) emerged as the most effective catalyst (entries 11–15). The 5-*exo* cyclization pathway also predominates in the absence of a catalyst, but longer reaction times (~72 h) are required to attain full conversion and the *exo* : *endo* ratio is compromised (3 : 1). Under the optimized conditions, lactam-lactone **2a** was obtained in good yield, high *anti*-stereoselectivity, and in impeccable 5-*exo* selectivity.

The scope of the contra-thermodynamic bromolactonization has been explored by altering the three variables highlighted in alkenoic acid **1** (Scheme 1). Knowing that the nature of the nitrogen substituent present on a nitrogen heterocycle can have a dramatic effect on its biological activity and reactivity,<sup>21</sup> the effect of the *N*-substituent on the sulfenolactonization was first explored. In the event, we find that *N*-aryl-, alkyl-, allyl-, and benzyl-substituted- $\gamma$ -lactam-tethered trisubstituted alkenoic acids undergo successful contra-thermodynamic 5-*exo* bromolactonization (see **2a–m**). The *N*-substituent has an effect on the diastereoselectivity in some cases (see **2j**). The strategic construction of lactam-bromolactones harboring the *N*-phenethyl group (see **2k–n** and **2p–t**) is noteworthy given that the latter is often employed as a precursor to the indolizidine/quinolizidine/tetrahydroisoquinoline scaffolds through Pictet-Spengler-style cyclizations.<sup>22</sup> The transformation displays excellent chemoselectivity given that a lactam-tethered alkenoic acid bearing an *N*-allyl substituent reacts with NBS to afford bicycle **2e**, without complications arising from bromolactonization of the kinetically more accessible allyl group (see **2o** as well). We attribute this chemoselective bromolactonization to conformational constraints and to the more activated nature of the styrenyl double bond.

We have also explored the scope of the transformation with respect to the alkene portion resident in **1**. Starting with the internal substituent on the alkene (*i.e.*, R'), we find that this 5-*exo-trig* cyclization is quite sensitive to the steric environment given that the replacement of the internal methyl substituent with an unbranched hexyl group leads to a compromise in the efficiency of the annulation (**2e** vs. **2o** or **2m** vs. **2n**). The situation is unsurprisingly exacerbated when the methyl group is replaced by more sterically imposing aryl groups (**2k** vs. **2q–t** or **2m** vs. **2u**), thus, necessitating an increase in the temperature to 60 °C. Of note, products **2q–u** are indeed the thermodynamic products since they result from the unsymmetrical build-up of positive charge on the tertiary benzylic position. Efforts to explore the effect of external aryl substituent on the alkene (*i.e.*, the Ar group in **1**) have revealed that lactam-tethered 5-aryl-4(*E*)-pentenoic acids bearing electron-rich aryl groups are as competent as their electron-deficient congeners (**2v/x** vs. **2w**). The successful deployment of these lactam-tethered trisubstituted alkenoic acids has facilitated the stereocontrolled construction of lactam- $\gamma$ -lactones bearing two tetrasubstituted stereocenters, which is noteworthy since, as noted previously, halolactonization reactions of trisubstituted alkenes are not



Performed on 1.0 mmol scale using 1 mL DMF.  
 Reaction times ranged from 4 to 18 h.  
 \*Performed at 60 °C for 2 h. Isolated yields reported.  
 PMP = *para*-methoxyphenyl, OMP = *para*-methoxyphenyl.  
 PFP = *para*-fluorophenyl, PCP = *para*-chlorophenyl.  
 Diastereomeric ratios were determined by GC-MS, <sup>1</sup>H NMR, or <sup>19</sup>F NMR (where applicable) analyses of the crude mixture.  
 Relative configurations were established using NOESY analysis of selected compounds. The others were ascribed by analogy.

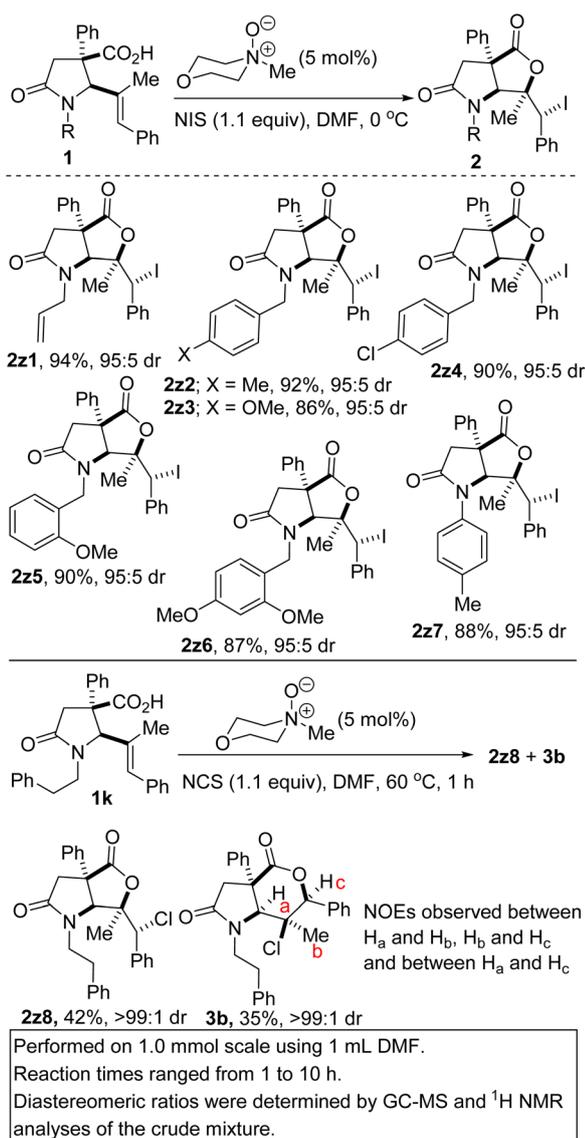
Scheme 1 5-*exo*-bromolactonization of  $\gamma$ -lactam-tethered alkenoic acids.

often stereospecific.<sup>17</sup> Finally, sterically less imposing 1,2-disubstituted styrenic acids are competent substrates for the bromolactonization (see **2y/z**).



Iodolactonization of **1** using *N*-iodosuccinimide (NIS) proceeded regioselectively (see **2z1–2z7**). In these cases, the reactions were conducted at 0 °C due to the enhanced reactivity of NIS. When lactam-tethered alkenoic acid **1k** was subjected to chlorolactonization using *N*-chlorosuccinimide (NCS), no conversion was observed after 48 h at room temperature. After warming to 60 °C for 1 h, complete conversion was observed. However, both the contra-thermodynamic (*5-exo-trig* cyclization) and thermodynamic (*6-endo-trig* cyclization) products were isolated (see **2z8** and **3b**, respectively). NOESY experiments (see ESI† for details) revealed that in the case of the *6-endo* cyclization product, the *syn*-diastereomer is the exclusive stereoisomer.

The appreciable stability of the bicycles depicted in Schemes 1 and 2 is commendable since they harbor a benzylic halide, which is typically prone to hydrolysis.<sup>23</sup> It is worth emphasizing

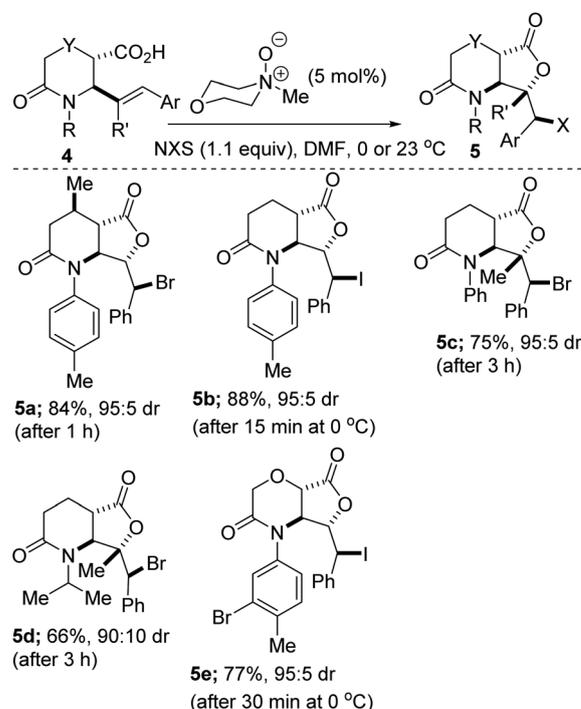


Scheme 2 Contra-thermodynamic *5-exo*-iodolactonization and unselective chlorolactonization of lactam-tethered alkenoic acids.

that molecules containing all-carbon quaternary stereocenters and  $\alpha$ -alkoxy quaternary stereocenters such as those depicted in Schemes 1 and 2 have the propensity to mitigate a spectrum of structural diversity issues in medicinal chemistry. Indeed, of the top 120 chiral small-molecule pharmaceuticals by retail sales in the United States in 2018, 13% contained a quaternary stereocenter.<sup>24</sup>

Extending reactivity trends from one *N*-heterocycle to another can be daunting and at times foolhardy. Nevertheless, as a testament to the modularity of this methodology, our studies have revealed that the contra-thermodynamic and catalytic halolactonization protocol described herein is not limited to  $\gamma$ -lactam-tethered alkenoic acids. For instance, 2-piperidinone-tethered alkenoic acids<sup>19a,f</sup> also undergo productive *5-exo* cyclization to afford the 6,5-bicycles depicted in Scheme 3 (see **5a–d**). These allylic valerolactam acids react significantly faster than the sterically encumbered  $\gamma$ -lactam congeners depicted in Schemes 1 and 2. The rate enhancement in the presence of the NMO catalyst is quite evident given that our previous synthesis of **5a** under catalyst-free conditions required 48 h.<sup>19f</sup> Furthermore, iodolactonization of a morpholinone-tethered alkenoic acid<sup>19a</sup> proceeds satisfactorily and affords bicycle **5e**.

A widely accepted mechanism for 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. Regarding the mechanistic underpinnings of the *N*-oxide catalyzed bromolactonization of **1**, congruent with Moriyama's insightful findings,<sup>15e</sup> we surmise that the halogen bonding interaction



Scheme 3 *5-exo*-cyclization of piperidinone- and morpholinone-tethered alkenoic acids.<sup>19a,f</sup>



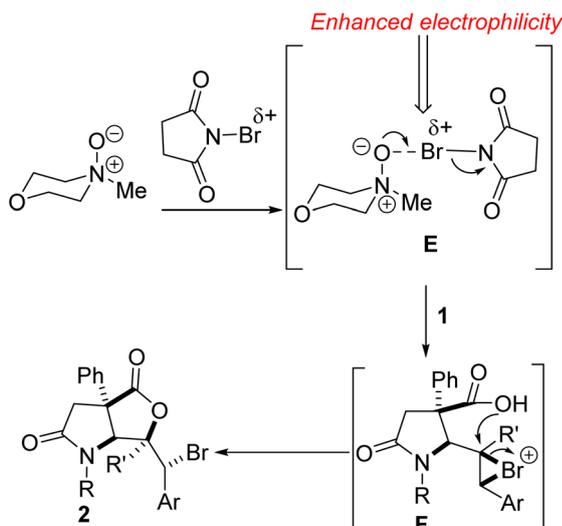


Fig. 3 Plausible mechanism for *N*-oxide catalyzed bromolactonization of lactam-tethered alkenoic acids of type 1.

between the bromine atom in NBS and the axial *N*-oxide in NMO enhances the electrophilicity of the bromine atom in NBS (Fig. 3, see E), thus, facilitating cleavage of the N–Br bond in NBS. Subsequent attack of the electrophilic bromine on the alkene furnishes bromonium ion F, which is then engaged by the pendant carboxylic acid, giving rise to lactam-lactone 2. It is unclear at this point how the solvent (*i.e.*, DMF) alters the site-selectivity of the reaction.

## Conclusions

In summary, the site-selective, efficient, and stereocontrolled synthesis of halogenated fused  $\gamma$ -lactone-lactams has been accomplished through the catalytic and contra-thermodynamic halolactonization of readily available allylic lactam acids. The innate tendency of these lactam-tethered-5-aryl-4(*E*)-pentenoic acids to undergo 6-*endo* cyclization is overridden in favor of 5-*exo* cyclization by catalyst- and solvent-controlled reactivity. Several trisubstituted alkenoic acids undergo regioselective and diastereocontrolled halolactonization, leading to the construction of  $sp^3$ -rich fused lactam-lactones bearing medicinally relevant quaternary and contiguous stereocenters. We anticipate that this efficient strategy would expand the 3D-structural space for the discovery of new lactam- $\gamma$ -lactones with medicinal value. Computational studies geared toward gaining a better understanding of the role of DMF and NMO in controlling the regioselectivity, are ongoing.

## Experimental

All experiments involving air and moisture sensitive reagents were carried out under an inert atmosphere of nitrogen and using freshly distilled solvents. Column chromatography was performed on silica gel (230–400 mesh). Thin-layer chromatography (TLC) was performed using Silicycle Siliplate<sup>TM</sup> glass backed plates (250  $\mu$ m thickness, 60 Å porosity, F-254 indicator)

and visualized using UV (254 nm) or  $KMnO_4$  stain. Unless otherwise indicated,  $^1H$ ,  $^{13}C$ , and DEPT-135 NMR, and NOESY spectra were acquired using  $CDCl_3$  solvent at room temperature. Chemical shifts are quoted in parts per million (ppm). HRMS-EI<sup>+</sup> data were obtained using either electrospray ionization (ESI) or electron impact (EI) techniques. High-resolution ESI was obtained on an LTQ-FT (ion trap; analyzed using Excalibur). High resolution EI was obtained on an Autospec (magnetic sector; analyzed using MassLynx). Brine solutions are saturated solutions of aqueous sodium chloride. Representative GC-MS traces are provided.

### General procedure A: bromolactonization of lactam acid 1

To an oven-dried 10 mL screw-cap vial, equipped with a stir bar, was added lactam-tethered alkenoic acid 1 (1.0 mmol), dissolved in DMF (1 mL). Then, NBS (196 mg, 1.1 mmol, 1.1 equiv.) and *N*-methylmorpholine oxide (5.9 mg, 5 mol%) were added. The reaction mixture was stirred at room temperature until TLC and GC-MS showed full conversion. The reaction mixture was then diluted with DCM (20 mL) and quenched with 10% aqueous sodium sulfite (10 mL). The layers were separated and the aqueous layer was extracted once with DCM. The combined organic extracts were washed with brine, dried over  $MgSO_4$  and concentrated *in vacuo* to give the desired lactam-lactone, which was purified by flash chromatography on silica.

### General procedure B: iodolactonization of lactam acid 1

To an oven-dried 10 mL screw-cap vial equipped with a stir bar was added lactam-tethered alkenoic acid 1 (1.0 mmol), dissolved in DMF (1 mL). NIS (247.5 mg, 1.1 mmol, 1.1 equiv.) and *N*-methylmorpholine oxide (5.9 mg, 5 mol%) were then added. The reaction mixture was stirred at 0 °C until TLC and GC-MS showed full conversion. The reaction mixture was then diluted with DCM (20 mL) and quenched with 10% aqueous sodium sulfite (10 mL). The layers were separated and the aqueous layer was extracted once with DCM. The combined organic extracts were washed with brine, dried over  $MgSO_4$  and concentrated *in vacuo* to give the desired lactam-lactone, which was purified by flash chromatography on silica.

**Synthesis of lactam-bromolactone 2a.** Prepared in 1.0 mmol scale using General Procedure A. Purification: Flash chromatography on silica eluting with hexane/EtOAc (70 : 30). Yellowish oil. Yield = 404.6 mg, 85%, 95 : 5 dr (*anti* : *syn*).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.46–7.20 (m, 15H), 5.33 (s, 1H), 4.67 (s, 1H), 3.40–3.29 (m, 2H), 1.41 (s, 3H).  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  175.2, 174.6, 138.9, 135.1, 132.0, 128.7, 128.6, 128.4, 128.1, 127.4, 127.0, 126.5, 125.6, 124.1, 89.0, 71.5, 58.5, 52.3, 44.4, 21.0. FTIR (KBr): 2965.4, 1727.5, 1696.3, 1604.9, 1511.0, 1448.5, 1414.7, 1384.9, 1357.4, 1298.7, 1247.5, 1179.3, 1135.9, 1031.8, 905.8, 839.0. HRMS-EI<sup>+</sup> (*m/z*): calc for  $C_{26}H_{22}BrNO_3$  [ $M$ ]<sup>+</sup> 475.0783, found 475.0789.

Note: All other lactam-bromolactones depicted in Scheme 1 were prepared as described above. Spectroscopic data can be found in the ESI.

**Synthesis of lactam-iodolactone 2z1.** Prepared in 1.0 mmol scale using General Procedure B. Purification: Flash



chromatography on silica eluting with hexane/EtOAc (50 : 50). Pale-yellowish oil. Yield = 457.8 mg, 94%, 95 : 5 dr (*anti* : *syn*). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.40–7.28 (m, 8H), 7.09–7.07 (m, 2H), 5.68 (dddd, *J* = 17.5, 10.2, 7.5, 4.6 Hz, 1H), 5.33–5.19 (m, 2H), 5.08 (s, 1H), 4.56–4.50 (m, 2H), 3.17–3.12 (m, 2H), 2.94 (d, 1H), 1.64 (s, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 174.3, 171.9, 138.7, 137.5, 131.4, 130.3, 129.1, 128.8, 128.1, 125.5, 119.6, 88.0, 68.5, 52.8, 45.1, 43.6, 39.5, 23.7. HRMS-ESI<sup>+</sup> (*m/z*): calc for C<sub>23</sub>H<sub>22</sub>INO<sub>3</sub> [M]<sup>+</sup> 487.0644, found 487.0649.

Note: All other lactam-iodolactones depicted in Scheme 2 were prepared as described above. Spectroscopic data can be found in the ESI.

## Author contributions

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

## Conflicts of interest

There are no conflicts of interest to declare.

## Acknowledgements

We are grateful to Central Washington University for financial support through startup funds. We thank the Office of Undergraduate Studies and Provost DenBeste for research fellowships to C. B. The school of graduate studies is thanked for research fellowships to T. K. B. and M. J. R. We are grateful to Mr Daniel Hall and Miss Lisa Stowe for timely ordering and delivery of chemicals and supplies during challenging times. Miss Cindy White is thanked for help with instrument and acquisition of 2D NMR data.

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