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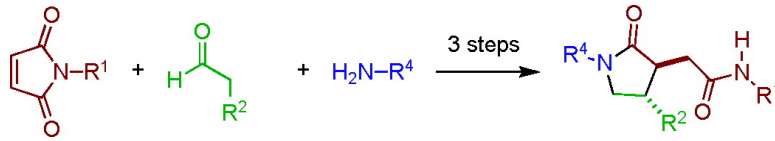

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Efficient Synthesis of γ-Lactams by a Tandem Reductive Amination/Lactamization Sequence

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A three-component method for the synthesis of highly substituted γ-lactams from readily available maleimides, aldehydes, and amines is described. A new reductive amination/intramolecular lactamization sequence provides a straightforward route to the lactam products in a single manipulation. The general utility of this method is demonstrated by the parallel synthesis of a γ-lactam library.

Introduction

The continuing interest surrounding the γ-lactam subunit in medicinal and synthetic chemistry is aptly demonstated by recent research efforts toward efficient methods for their construction.[1] The γ-lactam subunit is widely distributed among biologically interesting natural products,[2] of which (+)-lactacystin,[3] salinosporamide A,[4] and (−)-pramanicin[5] are just a few examples (Figure 1). The γ-lactam subunit also forms the core of the anticonvulsant drug levetiracetam (Keppra)[6] and a series of HIV protease inhibitors developed by GlaxoSmithKline.[7]

Historical methods for the construction of γ-lactams[8] have often required multiple manipulations,[1c,e,i,j,l] high pressure,[1m] or the preparation of reactive precursors, such as α-diazo-α-(phenylsulfonyl)acetamines,[9] α-acetoxy lactams,[1n] or silyl enol ethers.[1b,d] Furthermore, with the exception of a recent report by Shaw and co-workers[1a] and two examples using the Ugi four-component reaction,[1g,h] these historical methods have not been applicable to the parallel synthesis of diverse collections of γ-lactams. Here we present a versatile method for the synthesis of highly substituted γ-lactams from commercially available maleimides, aldehydes, and amines (Scheme 1).

This new method offers two powerful advantages over traditional approaches that could be especially attractive to the medicinal chemistry community. First, the tandem reductive amination/lactamization generates the γ-lactam products in a one-pot process using inexpensive and well-tolerated reaction conditions. Second, the short overall sequence allows for the easy substitution of any of the three commercially available reaction components.

Results and Discussion

The requisite formylmethyl succinimide substrates **2** were readily constructed by the organocatalytic conjugate addition of aldehydes to maleimides **1**. Such organocatalytic enantioselective conjugate addition reactions of carbon nucleophiles to maleimides have recently been investigated by several research groups.[10] We found that a modification of the protocol developed by Córdova and co-workers[10a] to be an efficient and flexible method for the synthesis of the succinimide scaffolds. In our modification, pyrrolidine was substituted for L-proline. This allowed the use of chloroform as solvent in contrast to the less easily removed DMSO. For the purposes of screening, racemic mixtures provide additional diversity and are not considered unfavorable. Nevertheless, one advantage of the present methodology is that it is readily adaptable to enantioselective variation, should the need arise. Table 1 summarizes the results of the conjugate addition trials and the scope of aldehydes and maleimides explored. The conjugate addition was not the focus of this investigation and the reaction conditions remain unoptimized.

The earliest precedent for reductive amination/intramolecular lactam formation can be found in a report by Maryanoff and co-workers, who showed that the reductive amination of ketones with ethyl 4-aminobutyrates using sodium triacetoxyborohydride proceeds to spontaneously lactamize, a process they termed reductive lactamization.[11] A similar sequence was observed as an undesired side reaction by Koubeissi et al.[12] The Maryanoff protocol has since been extended to include 4-amino carboxylic acids by Mapes and Mani.[13] While this method is simple and robust, it necessitates the synthesis of the amino carboxylates or carboxylic acids. Recently, Hutton and Bartlett have demonstrated that γ-lactams can be generated from formylmethyloxazolidinones via a reductive amination/cyclization strategy utilizing either *p*-anisidine or various diamines.[1o] Despite this obvious utility, reductive amination followed by lactamization is surprisingly underutilized as a route to γ-lactams. The formylmethyl succinimide scaffolds presented above were constructed with the hope that they would be appropriate substrates for such a process. Indeed, the

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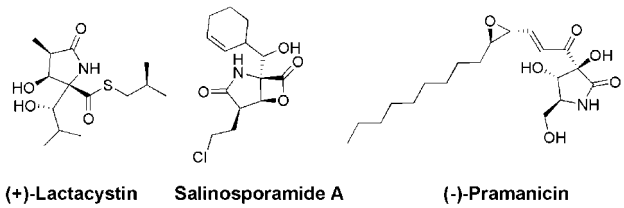


Figure 1. γ-Lactam-based natural products.

Scheme 1

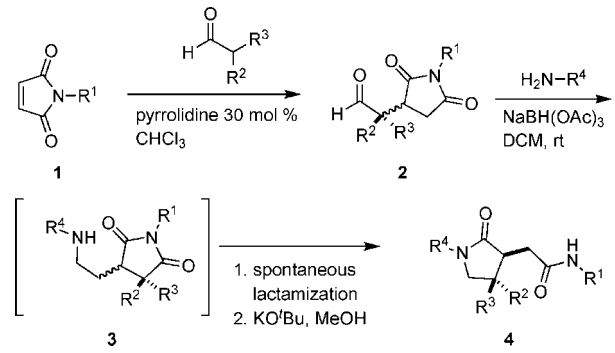
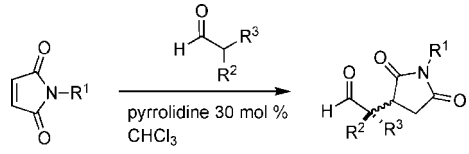


Table 1. Organocatalytic Conjugate Addition of Aldehydes



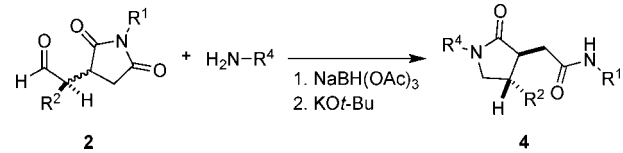
entry	product	R^1	R^2	R^3	yield (%)
1	**2a**	Bn	Me	H	63[a]
2	**2b**	Bn	Bn	H	44
3	**2c**	Bn	*n*-pentyl	H	73
4	**2d**	Bn	Me	Me	8
5	**2e**	*p*-MeOBn	Me	H	74
6	**2f**	*p*-MeOBn	*n*-pentyl	H	54[a]
7	**2g**	*p*-MeOBn	Bn	H	64[a]
8	**2h**	Ph	Bn	H	55[a]
9	**2i**	Ph	Me	Me	20

[a] Experiment performed in parallel using the Bohdan Miniblock synthesis platform.

reductive amination conditions converted the aminosuccinimide intermediate completely to the bisamide product without the need for a second stage or even any additional heat above ambient temperature. The lactam products **4** were obtained as a mixture of cis/trans isomers in the relative configuration of the substituents on the lactam ring, as observed in the ^{1}H and ^{13}C NMR spectra. The mixture could be readily epimerized to afford predominantly the more thermodynamically stable trans isomer using KO*t*-Bu in MeOH (small amounts ($\leq$5%) of peaks presumably corresponding to the cis isomer could be observed in the NMR spectra of some examples). The results of these individual reductive lactamization trials are shown in Table 2.

Having validated the reaction sequence in individual reaction trials, we next applied the methodology to the parallel synthesis of a two-dimensional library of γ-lactams generated from the coupling of formylmethyl succinimide scaffolds with a series of primary amines. As in the individual trials, the initial reductive lactamization sequence would be followed by a convergent epimerization step.

Table 2. Individual Reductive Lactamization Trials



entry	product	R^1	R^2	R^4	yield (%)
1	**4a**	Bn	*n*-pentyl	Bn	66
2	**4b**	Bn	Me	cyclohexyl	55
3	**4c**	Bn	*n*-pentyl	*n*-butyl	39
4	**4d**	*p*-MeOBn	*n*-pentyl	$PhCH_2CH_2$-	50
5	**4e**	*p*-MeOBn	Bn	Ph	60
6	**4f**	Ph	Bn	*p*-MeOBn	90

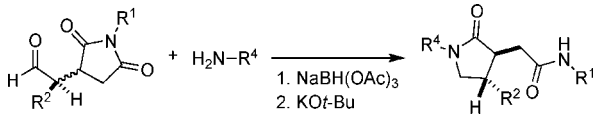
The synthesis of a γ-lactam library was undertaken to serve two purposes. First, it would demonstrate the utility of the methodology by producing compounds for submission to our biological screening collaborations.[14] Second, parallel synthesis would rapidly allow us to survey the suitability of various substrates for this method. We were especially interested in exploring the effect that varying the primary amine component would have on the reaction outcome. Table 3 summarizes the results of these parallel synthesis efforts. From these data, we observed a general trend in the electronegativity of the amine. All attempts to utilize the very electron-poor 3-chloro-4-trifluoromethylaniline failed to give any detectable lactam product (entries 23, 26, and 42). Similarly, the amine 3,4-difluoroaniline typically afforded less than 2% yield of the lactam product (entries 22, 25, 41 and 43), with one exception (entry 5). Even unsubstituted aniline usually afforded lower yields of the lactam product (entries 21, 24, 32, and 40), again with one exception (entry 2). That both exceptions to the trend have R^2 = benzyl suggests that under the right conditions even some electron-poor amines could become adequate substrates for this process, although the effect can be subtle (entry 32). However, the use of an electron-rich aniline such as *p*-hexylaniline restored the activity of the amine component toward the reductive lactamization sequence (entries 6, 14, 15, 35, and 39).

In summary, we have developed a general one-pot method for the synthesis of γ-lactams from formyl methylsuccinimides via a tandem reductive amination reaction sequence. A wide range of amines are well tolerated under identical reaction conditions, with the potential limitation that not all electron-poor anilines will be good participants in the reductive lactamization. The formylmethyl succinimide scaffolds are readily accessible enantiomerically pure in one step by several reported protocols. Future work with this method will focus on the synthesis of additional libraries for high-throughput biological screening and the extension of the reductive lactamization to ketone succinimide scaffolds.

Experimental Section

General Procedure for the Synthesis of the Maleimides 1. The protocol of Robertson and co-workers was employed with slight modification.[15] To a stirred solution of maleic anhydride (4.13 g, 42.0 mmol) in acetic acid (50 mL) was added the amine (35.1 mmol). The reaction mixture was stirred at reflux for 3 h, and then the acetic acid was removed in vacuo. The residue was dissolved in EtOAc (30

Table 3. Parallel Synthesis of a 43-Member γ-Lactam Library



2 **4**

entry	product	R^1	R^2	R^4	yield[a] (%)
1	**4**{*1*}	Ph	Bn	Bn	43
2	**4**{*2*}	Ph	Bn	Ph	61
3	**4**{*3*}	Ph	Bn	$PhCH_2CH_2$	78
4	**4**{*4*}	Ph	Bn	*p*-MeOBn	48
5	**4**{*5*}	Ph	Bn	3,4-difluoroPh	40
6	**4**{*6*}	Ph	Bn	*p*-hexylPh	49
7	**4**{*7*}	Ph	Bn	cyclohexyl	71
8	**4**{*8*}	Ph	Bn	*n*-butyl	38
9	**4**{*9*}	Bn	Me	Bn	29
10	**4**{*10*}	Bn	Me	$PhCH_2CH_2$	26
11	**4**{*11*}	Bn	Me	*p*-MeOBn	28
12	**4**{*12*}	Bn	Me	cyclohexyl	17
13	**4**{*13*}	Bn	Me	*n*-butyl	22
14	**4**{*14*}	Bn	Me	*p*-hexylPh	15
15	**4**{*15*}	Bn	*n*-pentyl	*p*-hexylPh	46
16	**4**{*16*}	Bn	*n*-pentyl	Bn	23
17	**4**{*17*}	Bn	*n*-pentyl	$PhCH_2CH_2$	25
18	**4**{*18*}	Bn	*n*-pentyl	*p*-MeOBn	23
19	**4**{*19*}	Bn	*n*-pentyl	cyclohexyl	24
20	**4**{*20*}	Bn	*n*-pentyl	*n*-butyl	17
21	**4**{*21*}	Bn	Me	Ph	2
22	**4**{*22*}	Bn	Me	3,4-difluoroPh	0
23	**4**{*23*}	Bn	Me	3-Cl-4-CF_3Ph	0
24	**4**{*24*}	Bn	*n*-pentyl	Ph	2
25	**4**{*25*}	Bn	*n*-pentyl	3,4-difluoroPh	<1
26	**4**{*26*}	Bn	*n*-pentyl	3-Cl-4-CF_3Ph	0
27	**4**{*27*}	*p*-MeOBn	*n*-pentyl	$PhCH_2CH_2$	30
28	**4**{*28*}	*p*-MeOBn	*n*-pentyl	Bn	23
29	**4**{*29*}	*p*-MeOBn	*n*-pentyl	*p*-MeOBn	27
30	**4**{*30*}	*p*-MeOBn	*n*-pentyl	cyclohexyl	22
31	**4**{*31*}	*p*-MeOBn	Bn	Bn	55
32	**4**{*32*}	*p*-MeOBn	Bn	Ph	16
33	**4**{*33*}	*p*-MeOBn	Bn	*p*-MeOBn	49
34	**4**{*34*}	*p*-MeOBn	Bn	$PhCH_2CH_2$	45
35	**4**{*35*}	*p*-MeOBn	Bn	*p*-hexylPh	37
36	**4**{*36*}	*p*-MeOBn	Bn	cyclohexyl	14
37	**4**{*37*}	*p*-MeOBn	Bn	*n*-butyl	32
38	**4**{*38*}	*p*-MeOBn	*n*-pentyl	*n*-butyl	82
39	**4**{*39*}	*p*-MeOBn	*n*-pentyl	*p*-hexylPh	15
40	**4**{*40*}	*p*-MeOBn	*n*-pentyl	Ph	9
41	**4**{*41*}	*p*-MeOBn	*n*-pentyl	3,4-difluoroPh	<1
42	**4**{*42*}	*p*-MeOBn	*n*-pentyl	3-Cl-4-CF_3Ph	0
43	**4**{*43*}	*p*-MeOBn	Bn	3,4-difluoroPh	2

[a] Yields are for isolated material following mass-directed preparative HPLC purification. All compounds were obtained in greater than 90% purity as measured by UV detection at 214 nm.

mL) and washed with aqueous $NaHCO_3$ (2 × 30 mL), HCl (1 M, 2 × 30 mL), and saturated aqueous NaCl (30 mL). The organic layer was separated and dried (Na_2SO_4), and the solvent was removed in vacuo to afford the maleimides **1** in sufficient purity for further elaboration.

General Procedure A: The Synthesis of Carboxysuccinimides 2. The organocatalytic conjugate addition of aldehydes to maleimides was carried out using a modified version of the procedure by Córdova and co-workers.[16] To a stirred solution of the maleimide (1 g, 1 equiv) in $CHCl_3$ (25 mL) was added pyrrolidine (30 mol%) and the aldehyde (2 equiv). The reaction mixture was heated at 65 °C for 4 h. After it was cooled to room temperature, the reaction mixture was diluted with water (20 mL), and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic layer was separated and dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by silica chromatography to afford the succinimides **2** as mixtures of isomers.

General Procedure B: The Synthesis of Carboxysuccinimides 2 Performed in Parallel. The reactions were performed using a 6-position Bohdan MiniBlock XT solution phase synthesizer obtained from Mettler-Toledo Auto Chem. The purification was carried individually as described above. To a stirred solution of the maleimide (16.03 mmol, 1 equiv) in $CHCl_3$ (50 mL) was added pyrrolidine (0.4 mL, 4.81 mmol, 30 mol%) and the aldehyde (32.05 mmol, 2 equiv). The reaction mixture was stirred at 65 °C for 4 h. After it was cooled to room temperature, the reaction mixture was diluted with water (40 mL). The organic layer was separated and dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by column chromatography (eluted with a gradient of EtOAc in hexanes 0−100%) using the CombiFlash Companion automated chromatography system to obtain the succinimides **2** as diastereomeric mixtures of isomers.

General Procedure for the Individual Synthesis of γ-Lactams 4 (Table 2) by Tandem Reductive Amination/Lactam Formation Followed by Epimerization. To a stirred solution of the succinimide **2** (1 g, 2.9–4.1 mmol) in CH_2Cl_2 (30 mL) was added the amine (5.8–8.2 mmol, 2 equiv), followed by $NaBH(OAc)_3$ (7.1–10.3 mmol, 2.5 equiv). The reaction mixture was stirred at rt for 12 h and then stirred at 40 °C for 2 h. Unreacted $NaBH(OAc)_3$ was quenched by the addition of aqueous NaOH (1 M, 30 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over $NaSO_4$. The solvent was removed in vacuo to obtain the crude lactams which were used without further purification in the epimerization step. The crude product was dissolved in MeOH (15 mL). KO*t*-Bu (5.7–8.2 mmol, 2 equiv) was added, and the reaction mixture was stirred at RT for 12 h. The solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 and filtered through neutral aluminum oxide and eluted with EtOAc. Evaporation of the solvent gave the pure lactams **4**.

General Procedure for the Parallel Synthesis of γ-Lactams 4 (Table 3). The reactions were performed in a 24-position Bohdan MiniBlock XT solution phase synthesizer obtained from Mettler-Toledo Auto Chem. To a stirred solution of the succinimide (60 mg, 0.17–0.24 mmol, 1 equiv) in CH_2Cl_2 (2 mL) was added the amine (0.34–0.48 mmol, 2 equiv), followed by $NaBH(OAc)_3$ (0.43–0.60 mmol, 2.5 equiv). The reaction mixture was stirred at rt for approximately 12 h and then at 40 °C for 2 h. The reaction was quenched by the addition of aqueous NaOH (1 M, 2 mL). The organic phase was separated in parallel using phase-separation tubes containing a hydrophobic frit. The organic layer was collected, and the solvent was removed using a GeneVac EZ2 plus evaporator. The crude lactams thus obtained were used without further purification in the epimerization step. The crude lactam was dissolved in MeOH (1 mL) and KO*t*-Bu (0.36–0.48 mmol, 2 equiv) was added while stirring. The reaction mixture was stirred at rt for 12 h, and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 and filtered through neutral aluminum

oxide and eluted with EtOAc. The solvent was removed in parallel using a GeneVac EZ2 plus evaporator, and the residue was purified by mass directed HPLC to give the pure lactams **4**.

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Supporting Information Available. Experimental details and full characterization data for all new compounds successfully synthesized, HPLC purification data for all library compounds, and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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