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Synthesis of a Library of "Lead-Like" γ-Lactams by a One Pot, Four-Component Reaction

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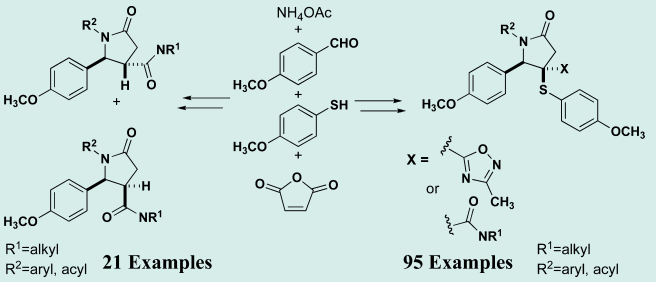
Supporting Information

ABSTRACT: The synthesis of a pilot scale library of 116 structurally diverse γ-lactams is reported. The library core structure emanates from a γ-lactam forming one-pot, four-component reaction of ammonium acetate, *p*-methoxythiophenol, *p*-methoxybenzaldehyde, and maleic anhydride. Structural diversity then arises from amide coupling, thioaryl cleavage, *N*-functionalization, and heterocycle forming reactions on this core structure. Computational analysis reveals that the library contains molecular properties and shape diversity suitable for drug lead and biological probe discovery.



KEYWORDS: *synthesis, γ-lactam, one-pot, four-component reaction, amide coupling, thioaryl cleavage*

INTRODUCTION

γ-Lactams are important structures for the synthesis of natural products and biological probes for drug discovery and development (Figure 1).[1−9] The prevalence of γ-lactams in biologically significant molecules has resulted in the development of many syntheses of this substructure, and has led to the production of diverse libraries of small molecules for biological evaluation.[10−18] It is likely that the use of this substructure in the prospective design of "lead-like" small molecules will be fruitful in the discovery of biological probes and drug leads.

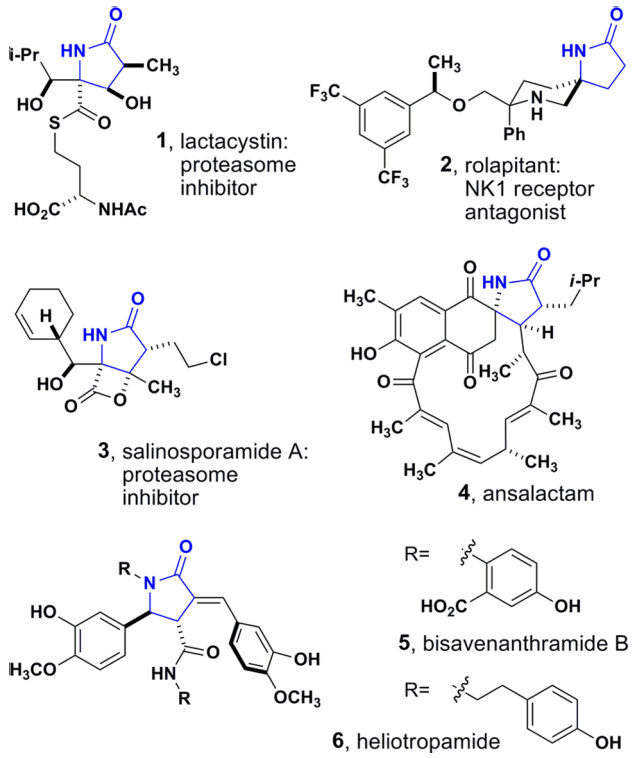


Figure 1. γ-Lactam natural products and lead compounds in drug discovery.

Multi component reactions (MCRs) are powerful transformations that involve the combination of three or more reagents in a one-pot procedure to rapidly generate molecular complexity with minimal effort.[19] Our group reported a novel four-component reaction (4CR) for the synthesis of complex γ-lactams where in a single operation γ-lactams are synthesized in high yield and diastereoselectivity from the combination of an amine **7**, an aldehyde **8**, thiol **9**, and maleic anhydride **10** (Scheme 1A).[12] More recently, we reported a one-pot procedure for the multicomponent assembly of NH γ-lactams **13**, from a 4CR with ammonium acetate **12**, and subsequent *N*-functionalization of the amide nitrogen to generate structures **14** not immediately available for the original 4CR (Scheme 1B).[13] *N*-acylation was achieved using *n*-BuLi as a base followed by addition of an acylating agent, and *N*-arylation was accomplished with an arylboronic acid and stoichiometric amounts of copper(II) acetate (Scheme 1B). This study demonstrated that we could rapidly access complex γ-lactam structures not immediately available from the original 4CR. In our present study we demonstrate the utility of this methodology toward library development by preparing a pilot scale library of 116 structurally diverse γ-lactams for use in high-throughput screening experiments aimed at discovering drug leads and biological probes.

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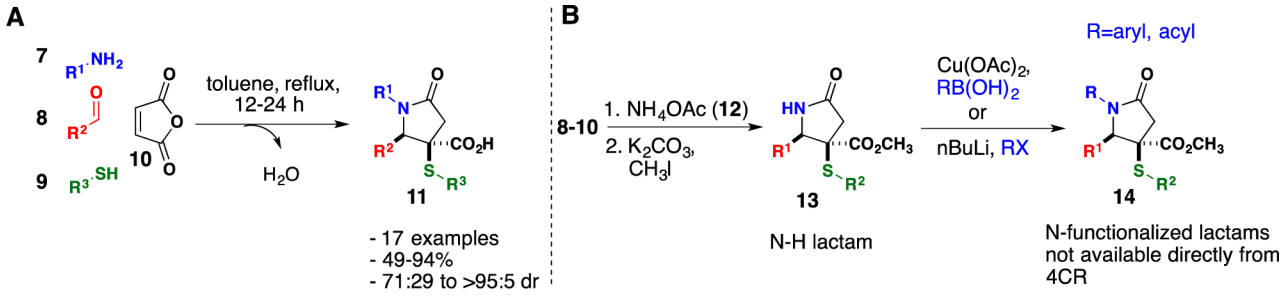
Scheme 1. Assembly of (A) *N*-Substituted and (B) N−H γ-Lactams Using a 4CR



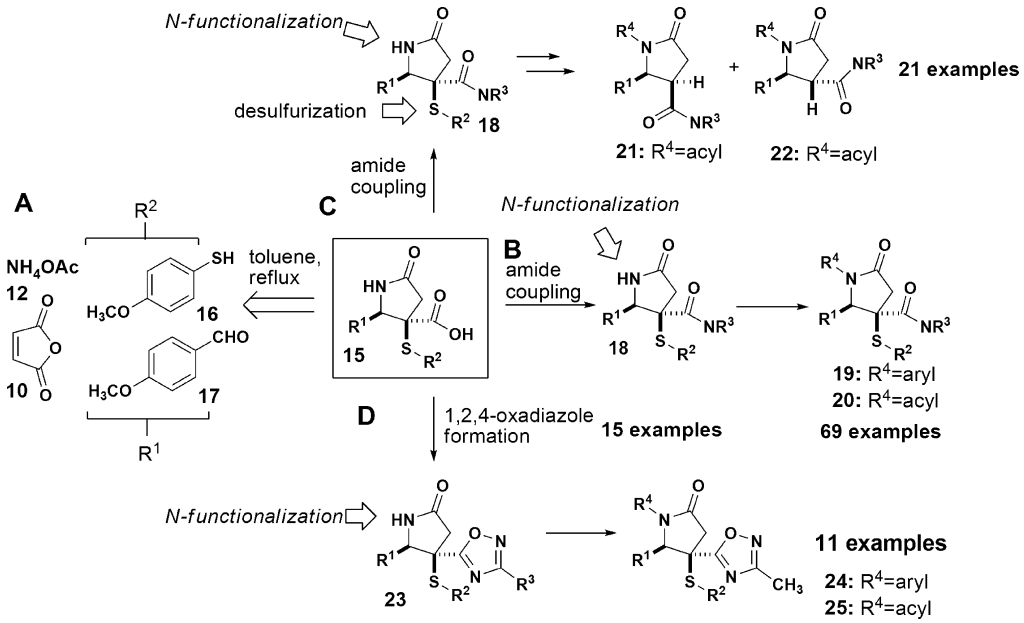


Figure 2. Summary of library strategy based on the one-pot, four-component reaction (4CR).

We envisioned our library would be based on γ-lactam core structure **15**, which emanates from a 4CR with ammonium acetate **12**, maleic anhydride **10**, *p*-methoxythiophenol **16**, and *p*-methoxybenzaldehyde **17** (Figure 2A). Reaction of 15 with primary or secondary amines generated 15 diverse NH γ-lactam products **18** (Figure 2B). Next, a subset of these N−H γ-lactams were *N*-acylated using *n*-BuLi as a base followed by addition of an acylating reagent or *N*-arylated using arylboronic acids and copper(II) acetate to generate 69 γ-lactams **19** and **20** (Figure 2B). The thioaryl group of some N−H γ-lactams **18** was also cleaved and products were *N*-acylated to generate 21 new compounds **21** and **22** (Figure 2C). Finally, we generated 1,2,4-oxadiazoles **23** from the carboxylic acid handle of **15**, and subsequent *N*-functionalization reactions generated 11 additional structures **24** and **25** (Figure 2D). Importantly, syntheses of library chemsets **18**−**22**, **24**, and **25** were conducted in parallel using a Heidolph reaction block, thus allowing for rapid and efficient generation of molecular complexity.

RESULTS AND DISCUSSION

Library Synthesis. Multigram scale preparation of **15** was achieved from a 4CR with ammonium acetate **12**, maleic anhydride **10**, *p*-methoxythiophenol **16**, and *p*-methoxybenzaldehyde **17** (Figure 3A). Filtration of the crude reaction mixture followed by washes with cold methanol provided 5 g of **15**, 50% yield, as a single diastereomer which was then used without additional purification. Library diversity based on **15** was then generated from amide-forming reactions with amines **26** (Figure 3B), *N*-functionalization reactions with arylboronic acids **27** and aclyating agents **28** (Figure 3C and D), and hetereocycle forming reactions with oximes **29** (Figure 3E).

Conditions for amide formation were optimized with **15** and *N,N*-dimethylamine **26**{*1*} under a variety of reaction conditions to synthesize amide **18**{*1*} (Scheme 2A). Initial attempts to form amide **18**{*1*} were made using peptide coupling reagents. Treatment of **15** with EDCI and HOBt, or HATU in the presence of *N,N*-dimethylamine **26**{*1*} were unsuccessful and starting material was isolated in all cases (Scheme 2A, entries 1−2). Similarly, amide synthesis via formation of the mixed anhydride by treatment of **15** with ethyl chloroformate followed by addition of **26**{*1*} gave similar results (Scheme 2A, entry 3). We next attempted amide formation through conversion to the acid chloride. Treatment of **15** with oxalyl chloride or thionyl chloride in DCM under a variety of mild reaction conditions failed to produce any amide product **18**{*1*} (Scheme 2A, entries 4−5). ^{13}C NMR and ^{1}H NMR spectra of the presumed acid chloride intermediate revealed acid chloride was not forming under these conditions and thus lead us to investigate harsher reaction conditions for acid chloride synthesis. We ultimately found refluxing **15** in benzene and thionyl chloride initially for 8 h, and then optimized to 2 h, provided the requisite acid chloride, as confirmed by ^{13}C NMR and ^{1}H NMR spectroscopy (data not

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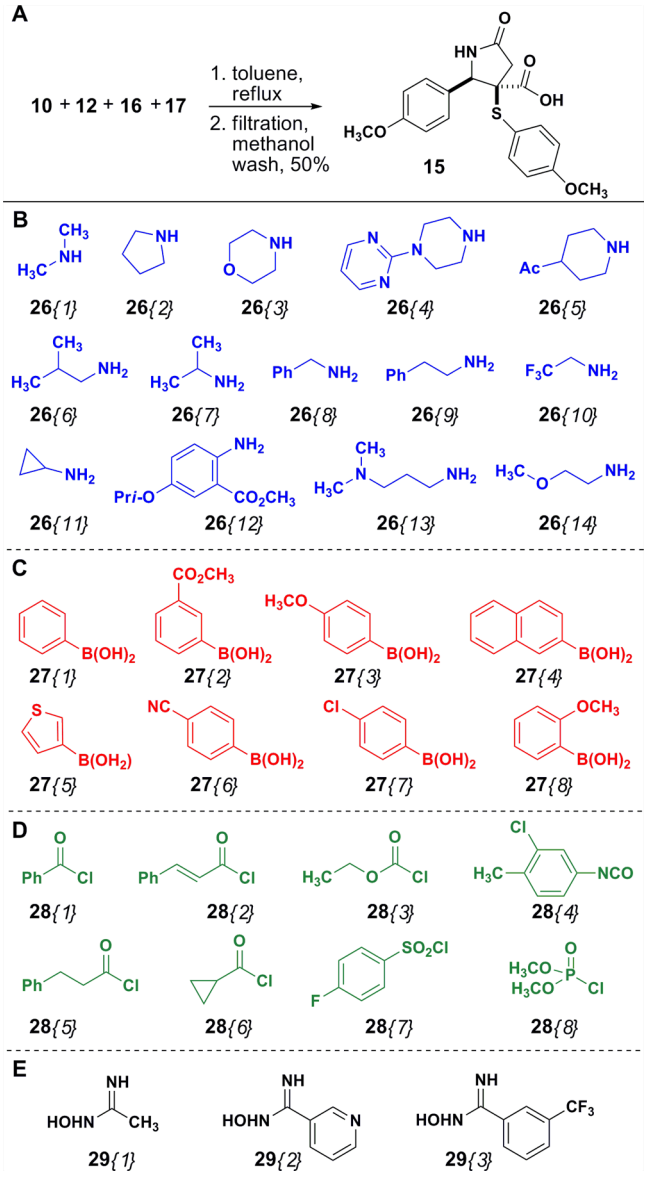
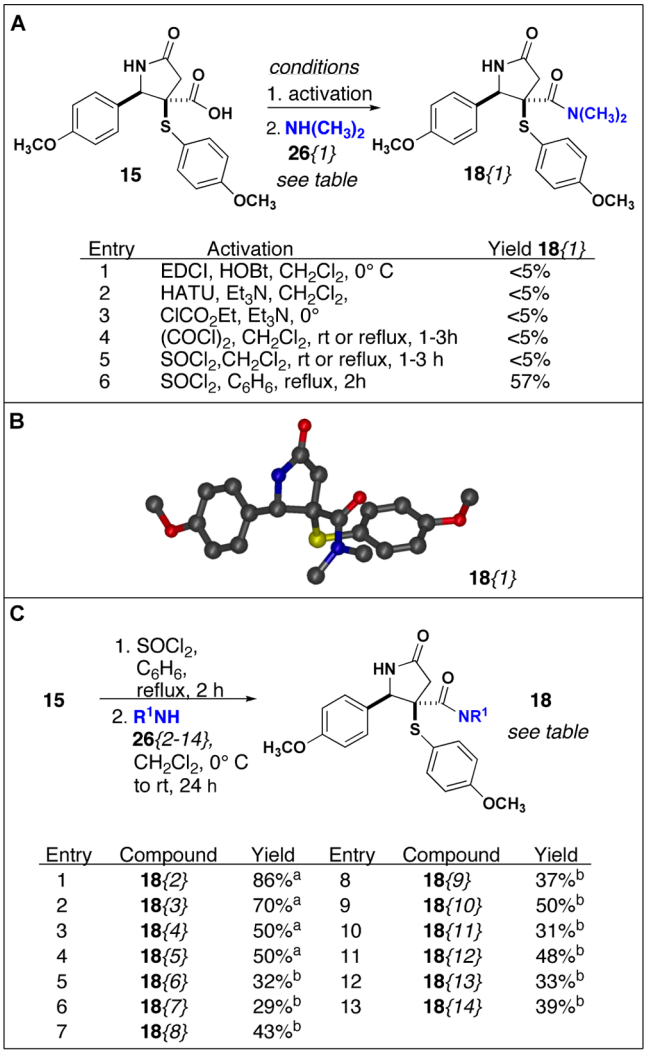


Figure 3. Diversity reagents for schemes **2**–**6**.

shown). Subsequent addition of *N*,*N*-dimethylamine **26**{*1*} in a second step gave the desired amide product **18**{*1*} in 57% yield (Scheme 2A, entry 6), and crystallization of **18**{*1*} confirmed the relative stereochemistry of **15** (Scheme 2B). Finally, using these optimized conditions, we were able to synthesize NH γ-lactams **18**{*2*–*14*} in 29–86% yields (Scheme 2C).

Next, treatment of NH amides **18**{*1*–*4*} with arylboronic acids **27**{*1*–*8*} and stoichiometric amounts of copper(II) acetate gave amides **19**{*1*–*4, 1*–*8*} in 4.5–69% yield (Scheme 3). As we observed previously,[13] ortho-substituted arylboronic acids were not very reactive, and in the case of *o*-methoxyphenylboronic acid **27**{*8*} we observed slight reactivity with amide **18**{*2*} to yield lactam **19**{*2, 8*}. Then, reaction of NH amides **18**{*1*–*5*} with *n*-BuLi at −78 °C followed by addition of various acylating agents **28**{*1*–*8*} provided lactams **20**{*1*–*5, 1*–*8*} in 12–90% yield (Scheme 4). Acid chlorides tended to provide the best yields while sulfonylation and phosphonylation worked less well. In most cases, yields for arylation and acylation reactions were determined based on material recovered after purification by HPLC. In general,

Scheme 2. (A) Optimization of Amide Coupling Conditions with 26{*1*} (B) Crystal Structure of 18 {*1*}, and (C) Synthesis of 18{*2*–*14*}[a,b]



Entry	Activation	Yield **18**{*1*}
1	EDCI, HOBt, CH_2Cl_2, 0° C	<5%
2	HATU, Et_3N, CH_2Cl_2,	<5%
3	$ClCO_2Et$, Et_3N, 0°	<5%
4	$(COCl)_2$, CH_2Cl_2, rt or reflux, 1-3h	<5%
5	$SOCl_2$,CH_2Cl_2, rt or reflux, 1-3 h	<5%
6	$SOCl_2$, C_6H_6, reflux, 2h	57%

Entry	Compound	Yield	Entry	Compound	Yield
1	**18**{*2*}	86%[a]	8	**18**{*9*}	37%[b]
2	**18**{*3*}	70%[a]	9	**18**{*10*}	50%[b]
3	**18**{*4*}	50%[a]	10	**18**{*11*}	31%[b]
4	**18**{*5*}	50%[a]	11	**18**{*12*}	48%[b]
5	**18**{*6*}	32%[b]	12	**18**{*13*}	33%[b]
6	**18**{*7*}	29%[b]	13	**18**{*14*}	39%[b]
7	**18**{*8*}	43%[b]			

[a](a) Purification by flash chromatography. [b](b) Purification by HPLC.

products were recovered in higher yield from flash chromatography than they were after purification by HPLC.

We next aimed to access *N*-functionalized compounds **21** and **22** through a concise synthetic route requiring only a single *N*-acylation reaction to provide both *syn* **21** and *anti* **22** products (Scheme 5A). We initially envisioned generating **21** and **22** beginning with a stereoselective desulfurization reaction to cleave the thioaryl group of NH γ-lactams **18**{*2*–*3*} (Scheme 5A). Next, *N*-functionalization of **30** would provide *syn* **21**, which could then be epimerized to give *anti* products **22**. Initial attempts to cleave the thioaryl group of **18**{*2*–*3*} using free radical conditions with tristrimethylsilyl silane[12] or tributyltin-hydride[20] were unsuccessful and in both cases a mixture of undesired products were observed (data not shown). Next, we envisioned a similarly concise and efficient route in which thioaryl group cleavage of **18**{*2*–*3*} with Raney Nickel could be used to provide **31** as a 50:50 mixture of *syn* and *anti* diastereomers which could then be *N*-functionalized as a mixture to provide **21** and **22**. Reaction of 18{*2*} with Raney Nickel[12] worked well to a give a 50:50 mixture of *syn* and *anti* **31**{*2*}; however, desulfurization of **18**{*3*} provided **31**{*3*} as

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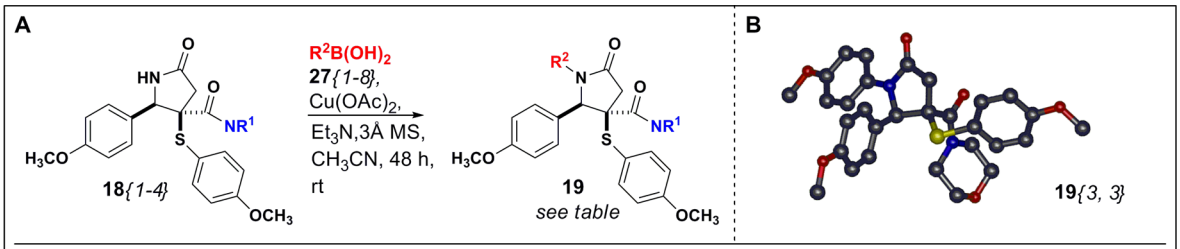
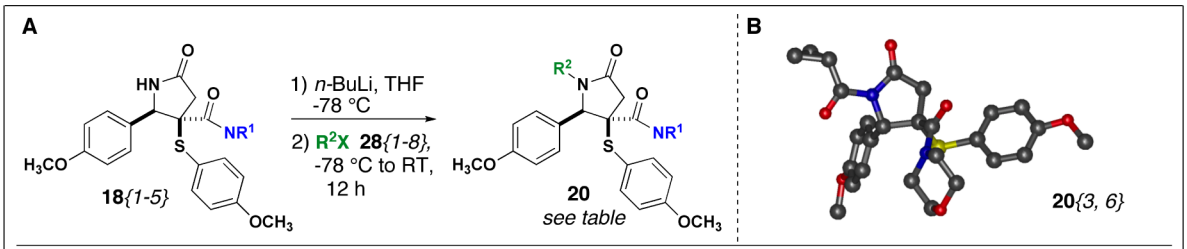
Scheme 3. (A) *N*-Arylation of N−H Amides 18{*1*−*4*} and (B) Crystal Structure of 19{*3,3*}[a,b]



Entry	Compound	Yield	Entry	Compound	Yield	Entry	Compound	Yield	Entry	Compound	Yield
1	**19**{*1, 1*}	26%[b]	9	**19**{*2, 1*}	30%[b]	17	**19**{*3, 1*}	19%[b]	25	**19**{*4, 1*}	38%[b]
2	**19**{*1, 2*}	32%[a]	10	**19**{*2, 2*}	37%[a]	18	**19**{*3, 2*}	43%[a]	26	**19**{*4, 2*}	34%[b]
3	**19**{*1, 3*}	36%[b]	11	**19**{*2, 3*}	69%[a]	19	**19**{*3, 3*}	45%[a]	27	**19**{*4, 3*}	22%[b]
4	**19**{*1, 4*}	24%[b]	12	**19**{*2, 4*}	47%[b]	20	**19**{*3, 4*}	36%[b]	28	**19**{*4, 4*}	22%[a]
5	**19**{*1, 5*}	12%[b]	13	**19**{*2, 5*}	24%[b]	21	**19**{*3, 5*}	12%[b]	29	**19**{*4, 5*}	17%[b]
6	**19**{*1, 6*}	30%[b]	14	**19**{*2, 6*}	39%[b]	22	**19**{*3, 6*}	49%[a]	30	**19**{*4, 6*}	22%[b]
7	**19**{*1, 7*}	45%[b]	15	**19**{*2, 7*}	57%[a]	23	**19**{*3, 7*}	52%[a]	31	**19**{*4, 7*}	52%[a]
8	**19**{*1, 8*}	-	16	**19**{*2, 8*}	5%[b]	24	**19**{*3, 8*}	-	32	**19**{*4, 8*}	-

[a](a) Purification by flash chromatography. [b](b) Purification by HPLC.

Scheme 4. (A) *N*-Acylation of N−H Amides 18{*1*−*5*} and (B) Crystal Structure of 20{*3,6*}[a,b]



Entry	Compound	Yield	Entry	Compound	Yield	Entry	Compound	Yield	Entry	Compound	Yield
1	**20**{*1, 1*}	70%[a]	11	**20**{*2, 3*}	74%[b]	21	**20**{*3, 5*}	79%[a]	31	**20**{4, *7*}	47%[b]
2	**20**{*1, 2*}	61%[b]	12	**20**{*2, 4*}	68%[b]	22	**20**{*3, 6*}	90%[a]	32	**20**{4, *8*}	24%[b]
3	**20**{*1, 3*}	63%[b]	13	**20**{*2, 5*}	84%[a]	23	**20**{*3, 7*}	25%[b]	33	**20**{*5, 1*}	54%[b]
4	**20**{*1, 4*}	73%[b]	14	**20**{*2, 6*}	66%[a]	24	**20**{*3, 8*}	20%[b]	34	**20**{*5, 2*}	61%[b]
5	**20**{*1, 5*}	64%[b]	15	**20**{*2, 7*}	50%[b]	25	**20**{*4, 1*}	48%[b]	35	**20**{*5, 3*}	53%[b]
6	**20**{*1, 6*}	50%[b]	16	**20**{*2, 8*}	31%[a]	26	**20**{*4, 2*}	49%[b]	36	**20**{*5, 4*}	56%[b]
7	**20**{*1, 7*}	24%[b]	17	**20**{*3, 1*}	82%[a]	27	**20**{*4, 3*}	90%[b]	37	**20**{*5, 5*}	34%[b]
8	**20**{*1, 8*}	12%[b]	18	**20**{*3, 2*}	90%[a]	28	**20**{*4, 4*}	55%[b]	38	**20**{*5, 6*}	48%[b]
9	**20**{*2,1*}	79%[a]	19	**20**{*3, 3*}	44%[b]	29	**20**{*4, 5*}	27%[b]	39	**20**{*5, 7*}	49%[b]
10	**20**{*2, 2*}	69%[a]	20	**20**{*3, 4*}	68%[b]	30	**20**{*4, 6*}	48%[b]	40	**20**{*5, 8*}	12%[b]

[a](a) Purification by flash chromatography. [b](b) Purification by HPLC.

10:90 mixture of diastereomers (Scheme 5B). We obtained an X-ray crystal structure of the *syn* diastereomer **30**{*3*} which allowed us to identify the *syn* and *anti* products resulting from *N*-acylation of **31** (Scheme 5C). **31**{*2*−*3*} were acylated as a mixture of diastereomers using *n*-BuLi and products were isolated by flash chromatography or HPLC (Scheme 5D). *Syn* products **21**{*3, 1*−*7*} were detectable in the ^{1}H NMR spectra resulting from acylation of **31**{*3*}, yet, we were only able to isolate *anti* products **22**{*3, 1*−*7*} in 17−56% yield (Scheme 5D). Both *syn* **21**{*2, 1*−*8*} and *anti* **22**{*2, 1*−*8*} products resulting from acylation of **31**{*2*} were isolable by flash chromatography or HPLC in 10−27% yield (Scheme 5D).

Finally, we synthesized 1,2,4-oxadiazoles from the carboxylic acid handle of **15** (Scheme 6). We initially attempted a single pot procedure in the microwave with **15**, oxime **29**{*1*}, trichloroacetonitrile and polystyrene bound triphenylphosphine,[21] however, did not observe formation of product **23**{*1*} (data not shown). In a two-step procedure, **15** was first converted to the acid chloride with thionyl chloride and treated with oximes **29**{*1*−*3*}. Subsequent heating in refluxing toluene for one and a half to six hours provided the desired NH γ-lactams **23** in 15−40% yield over two steps (Scheme 6A).[22] Next, *N*-functionalization of **23**{*1*} provided the desired products **24** and **25** in 20 to 58% yield (Scheme 6B).

Computational Analysis of Molecular Properties and Shape Diversity. Computational analysis of molecular properties was calculated for this collection of γ-lactams (Figure 4) (see Supporting Information), and average property values are displayed in Table 1. Analysis of molecular properties indicates some compounds may have desirable qualities for drug lead discovery, while others could function more suitably as biological probes (Figure 4 and 5).[23−25] The average molecular weights of **18**, **21**, and **22** fall within the acceptable range (molecular weight less than 500 Da) for drug-like compounds,[23] while higher average molecular weight structures **19**, **20**, **24**, and **25** that also lack hydrogen bond donors may be suitable as biological probes for disrupting protein−protein interactions.[24] Analysis of library molecular shape diversity using the method of Sauer and Schwarz was also performed.[25] This method calculates and plots principal moments of inertia

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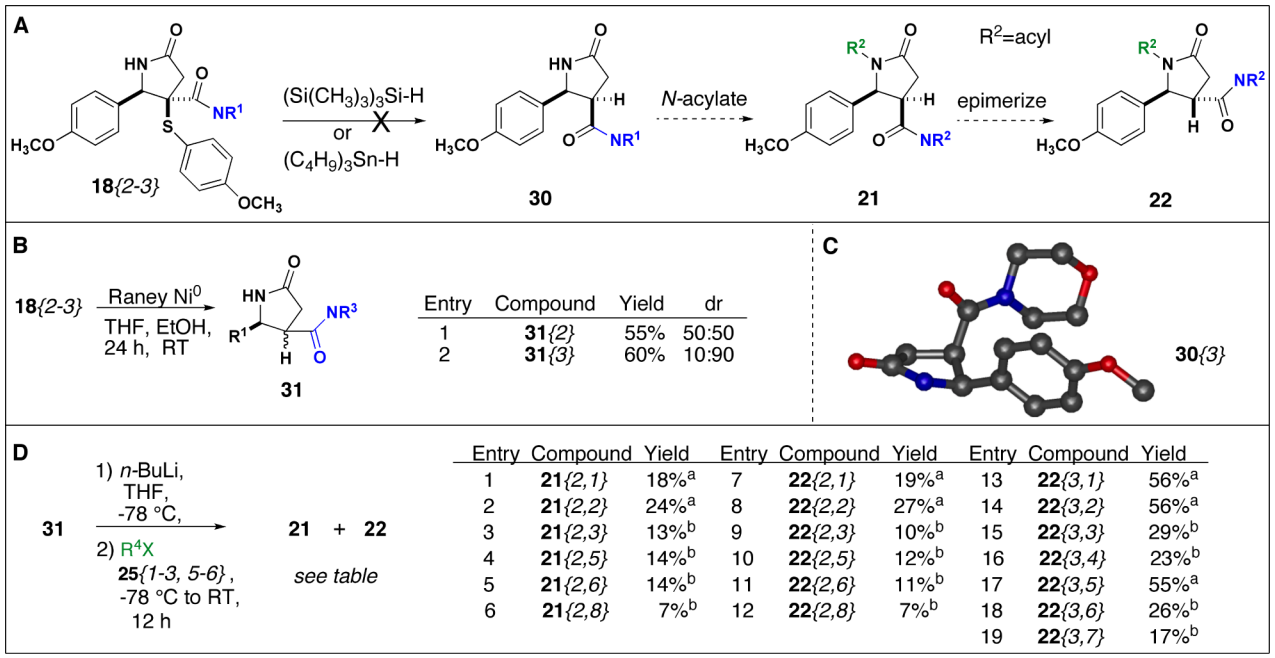
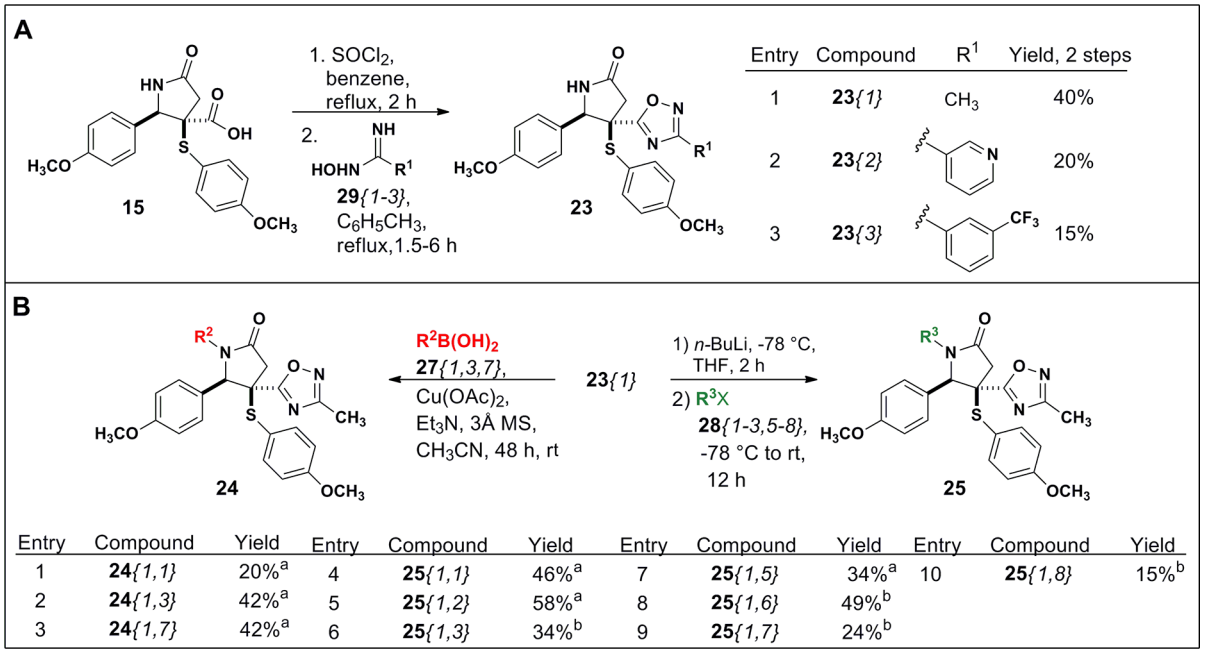
Scheme 5. Desulfurization Reactions[a,b]



[a](a) Purification by flash chromatography. [b](b) Purification by HPLC.

Scheme 6. (A) Synthesis of 1,2,4-Oxadiazoles 23 and (B) *N*-Functionalization of 23{1}[a,b]



[a](a) Purification by flash chromatography. [b](b) Purification by HPLC.

for each library member and characterizes molecular shape as rod- (e.g., acetylene), sphere- (e.g., adamantane), or disc-like (e.g., benzene). Greater shape diversity of a library correlates with increased likelihood of the library containing bioactive molecules. Because of the propensity for molecules to bind to a biological target in many possible conformations, principal moments of inertia were calculated and plotted for all conformers ≤3 kcal/mol in energy from the minimum energy conformer. The shape diversity of our library indicates an increase in the odds of a compound binding to a biological target.

CONCLUSION

The diversity-oriented synthesis of a "pilot scale" library of complex γ-lactams has been achieved. Large scale preparation of library core structure **15** and use of a reaction block for parallel synthesis allowed for library production with minimal effort. Computational analysis indicates molecular properties suitable for drug lead and biological probe discovery.

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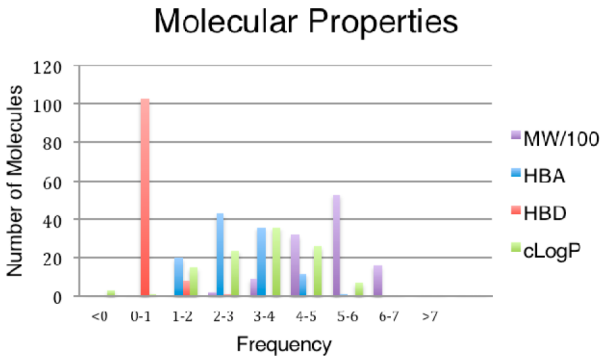

Figure 4. Molecular properties of the library.

Table 1. Average Molecular Property Values

	Chemset				
property	**18** (*n* = 18)	**19** (*n* = 29)	**20** (*n* = 40)	**21 + 22** (*n* = 15)	**24 + 25** (*n* = 10)
MW	437	552	572	395	518
HBD	2	0	0	0	0
HBA	3	3	4	3	4
cLogP	3	4	3	2	5

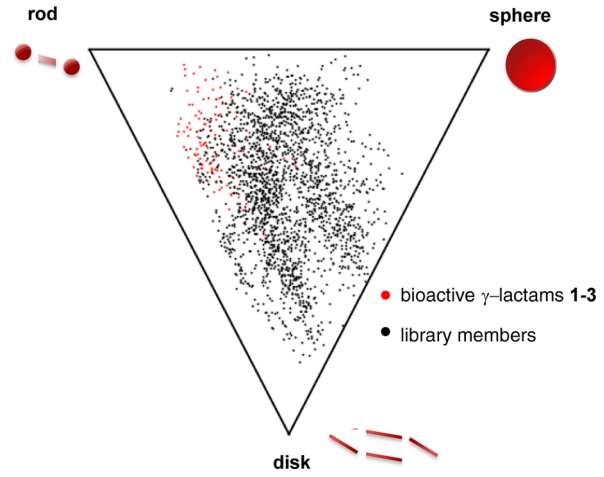

Figure 5. Scatter plot with principal moments of inertia (PMI) ratios plotted to compare molecular shape diversity of γ-lactam library. Ratios were calculated for all conformers ≤3 kcal/mol from the minimum energy conformer. Bioactive γ-lactams **1**−**3** are in red, and library members are in black.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, full characterization data, and purification details for all new compounds, representative library members for compounds **18**{*1*}, **19**{*3,3*}, **20**{*3,6*}, and **30**{*3*} are reported. This material is available free of charge via the Internet at http://pubs.acs.org. In addition, all library members have been submitted to the National Small Molecule Repository where they will be made available for high-throughput screening.

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Notes

The authors declare no competing financial interest.

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