Published in final edited form as:
ACS Comb Sci. 2013 July 8; 15(7): 356–362. doi:10.1021/co400049f.

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

Kevin S. Martin, **Michael J. Di Maso**, **James C. Fettinger**, and **Jared T. Shaw**
Department of Chemistry, One Shields Ave, University of California, Davis, CA 95616

Jared T. Shaw: jtshaw@ucdavis.edu

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.

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.

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

Correspondence to: Jared T. Shaw, jtshaw@ucdavis.edu.

Supporting information
Detailed experimental procedures, full characterization data, and purification details for all new compounds, representative library members and .cif files 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.

scale library of 116 structurally diverse γ-lactams for use in high-throughput screening experiments aimed at discovering drug leads and biological probes.

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-lactam 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

Multi-gram 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 grams of **15**, 50% yield, as a single diastereomer which was then used without additional purification (Scheme 2A). 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 3B and C), and hetereocycle forming reactions with oximes **29** (Figure 3D).

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}CNMR 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 hours, and then optimized to 2 hours, provided the requisite acid chloride, as confirmed by ^{13}CNMR and ^{1}H NMR spectroscopy (data not 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, 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 tributyltinhydride[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 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}HNMR 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 daltons) 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 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. Due to the propensity for molecules to bind to a biological target in many possible conformations, principle 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the National Science Foundation (CAREER award to JTS) and the National Institutes of Health (NIGMS/P41GM089153). JCF acknowledges support from the NSF (CHE-0840444) for the purchase of the Bruker SMART DUO diffractometer used for X-ray crystallography. The authors thank Patrick Porubsky (University of Kansas) for conducting mass-directed purification of all final library members at the Center for Methodology and Library Development (KU-CMLD), which is funded by the NIH (NIGMS/P50GM069663). Phillip P. Painter (Tantillo research group, UC Davis) is acknowledged for calculating the molecular properties and principle moments of inertia othe library using OpenEye software (www.eyesopen.com).

References

1. Manam RR, Teisan S, White DJ, Nicholson B, Grodberg J, Neuteboom STC, Lam KS, Mosca DA, Lloyd GK, Potts BCM. Lajollamycin, a nitro-tetraene spiro-β-lactone-γ-lactam antibiotic from the marine actinomycete Streptomyces nodosus. J Nat Prod. 2005; 68:240–243. [PubMed: 15730252]
2. Mori T, Takahashi K, Kashiwabara M, Uemura D, Katayama C, Iwadare S, Shizuri Y, Mitomo R, Nakano F, Matsuzaki A. Structure of oxazolomycin, a novel β-lactone antibiotic. Tetrahedron Lett. 1985; 26:1073–6.
3. Feling RH, Buchanan GO, Mincer TJ, Kauffman CA, Jensen PR, Fenical W. Salinosporamide A: a highly cytotoxic proteasome inhibitor from a novel microbial source, a marine bacterium of the new genus Salinospora. Angew Chem Int Ed. 2003; 42:355–357.
4. Fenteany G, Standaert RF, Lane WS, Choi S, Corey EJ, Schreiber SL. Inhibition of proteasome activities and subunit-specific amino-terminal threonine modification by lactacystin. Science (Washington, D C). 1995; 268:726–31.
5. Guntern A, Ioset JR, Queiroz EF, Sandor P, Foggin CM, Hostettmann K. Heliotropamide, a Novel Oxopyrrolidine-3-carboxamide from Heliotropium ovalifolium. J Nat Prod. 2003; 66:1550–1553. [PubMed: 14695794]
6. Okazaki Y, Ishizuka A, Ishihara A, Nishioka T, Iwamura H. New Dimeric Compounds of Avenanthramide Phytoalexin in Oats. J Org Chem. 2007; 72:3830–3839. [PubMed: 17432911]
7. Wilson MC, Nam S-J, Gulder TAM, Kauffman CA, Jensen PR, Fenical W, Moore BS. Structure and biosynthesis of the marine streptomycete ansamycin ansalactam A and its distinctive branched chain polyketide extender unit. J Am Chem Soc. 2011; 133:1971–1977. [PubMed: 21247149]
8. Omura S, Fujimoto T, Otoguro K, Matsuzaki K, Moriguchi R, Tanaka H, Sasaki Y. Lactacystin, a novel microbial metabolite, induces neuritogenesis of neuroblastoma cells. J Antibiot. 1991; 44:113–16. [PubMed: 1848215]
9. Duffy RA, Morgan C, Naylor R, Higgins GA, Varty GB, Lachowicz JE, Parker EM. Rolapitant (SCH 619734): A potent, selective and orally active neurokinin NK1 receptor antagonist with

centrally-mediated antiemetic effects in ferrets. Pharmacol Biochem Behav. 2012; 102:95–100. [PubMed: 22497992]

10. Fenical W, Jensen PR, Palladino MA, Lam KS, Lloyd GK, Potts BC. Discovery and development of the anticancer agent salinosporamide A (NPI-0052). Bioorg Med Chem. 2009; 17:2175–2180. [PubMed: 19022674]
11. Masse CE, Morgan AJ, Adams J, Panek JS. Syntheses and biological evaluation of (+)-lactacystin and analogs. Eur J Org Chem. 2000:2513–2528.
12. Wei J, Shaw JT. Diastereoselective Synthesis of γ-Lactams by a One-Pot, Four-Component Reaction. Org Lett. 2007; 9:4077–4080. [PubMed: 17760458]
13. Tan DQ, Martin KS, Fettinger JC, Shaw JT. Ammonia synthons for the multicomponent assembly of complex γ-lactams. Proc Natl Acad Sci USA. 2011; 108:6781–6786. S6781/1–S6781/91. [PubMed: 21289284]
14. Stuk TL, Assink BK, Bates RC Jr, Erdman DT, Fedij V, Jennings SM, Lassig JA, Smith RJ, Smith TL. An Efficient and Cost-Effective Synthesis of Pagoclone. Org Process Res Dev. 2003; 7:851–855.
15. Ng PY, Tang Y, Knosp WM, Stadler HS, Shaw JT. Synthesis of diverse lactam carboxamides leading to the discovery of a new transcription-factor inhibitor. Angew Chem Int Ed. 2007; 46:5352–5355.
16. Tan DQ, Atherton AL, Smith AJ, Soldi C, Hurley KA, Fettinger JC, Shaw JT. Synthesis of a γ-Lactam Library via Formal Cycloaddition of Imines and Substituted Succinic Anhydrides. ACS Comb Sci. 2012; 14:218–223. [PubMed: 22225535]
17. Raup DEA, Cardinal-David B, Holte D, Scheidt KA. Cooperative catalysis by carbenes and Lewis acids in a highly stereoselective route to γ-lactams. Nat Chem. 2010; 2:766–771. [PubMed: 20729898]
18. Zhao X, DiRocco DA, Rovis T. N-Heterocyclic Carbene and Bronsted Acid Cooperative Catalysis: Asymmetric Synthesis of trans-γ-Lactams. J Am Chem Soc. 2011; 133:12466–12469. [PubMed: 21780842]
19. Biggs-Houck JE, Younai A, Shaw JT. Recent advances in multicomponent reactions for diversity-oriented synthesis. Curr Opin Chem Biol. 2010; 14:371–382. [PubMed: 20392661]
20. Kim MB, Shaw JT. Synthesis of Antimicrobial Natural Products Targeting FtsZ: (+)-Totarol and Related Totarane Diterpenes. Org Lett. 2010; 12:3324–3327. [PubMed: 20597470]
21. Wang Y, Miller RL, Sauer DR, Djuric SW. Rapid and Efficient Synthesis of 1,2,4-Oxadiazoles Utilizing Polymer-Supported Reagents under Microwave Heating. Org Lett. 2005; 7:925–928. [PubMed: 15727476]
22. Zablocki J, Kalla R, Perry T, Palle V, Varkhedkar V, Xiao D, Piscopio A, Maa T, Gimbel A, Hao J, Chu N, Leung K, Zeng D. The discovery of a selective, high affinity A2B adenosine receptor antagonist for the potential treatment of asthma. Bioorg Med Chem Lett. 2005; 15:609–612. [PubMed: 15664822]
23. Lipinski CA. Lead- and drug-like compounds: the rule-of-five revolution. Drug Discovery Today Technol. 2004; 1:337–341.
24. Arkin MR, Wells JA. Small-molecule inhibitors of protein-protein interactions: progressing towards the dream. Nat Rev Drug Discovery. 2004; 3:301–317.
25. Sauer WHB, Schwarz MK. Molecular Shape Diversity of Combinatorial Libraries: A Prerequisite for Broad Bioactivity. J Chem Inf Comput Sci. 2003; 43:987–1003. [PubMed: 12767158]

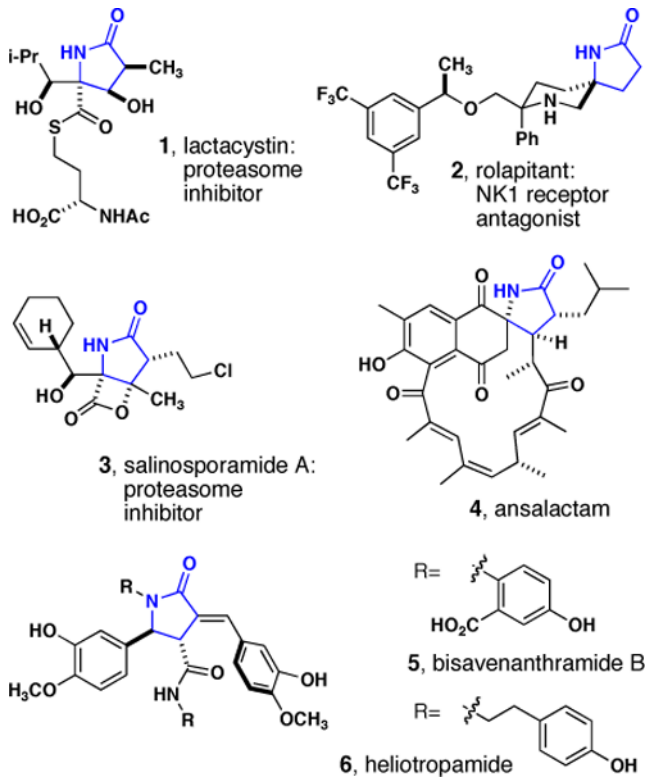


Figure 1.
γ-Lactam natural products and lead compounds in drug discovery.

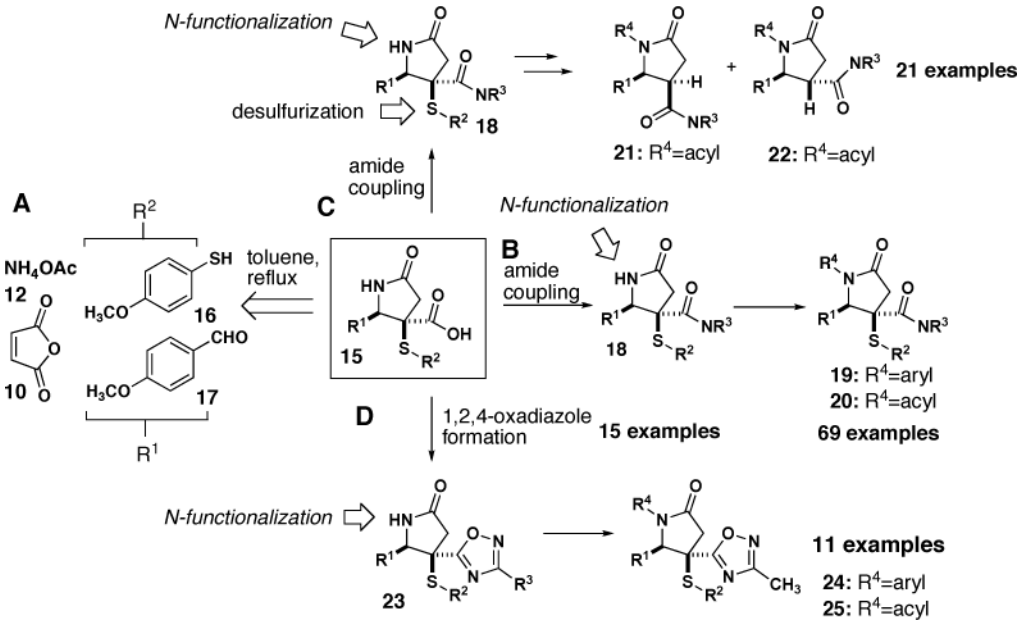


Figure 2.
Summary of Library Strategy Based on the One-Pot, Four-Component Reaction (4CR).

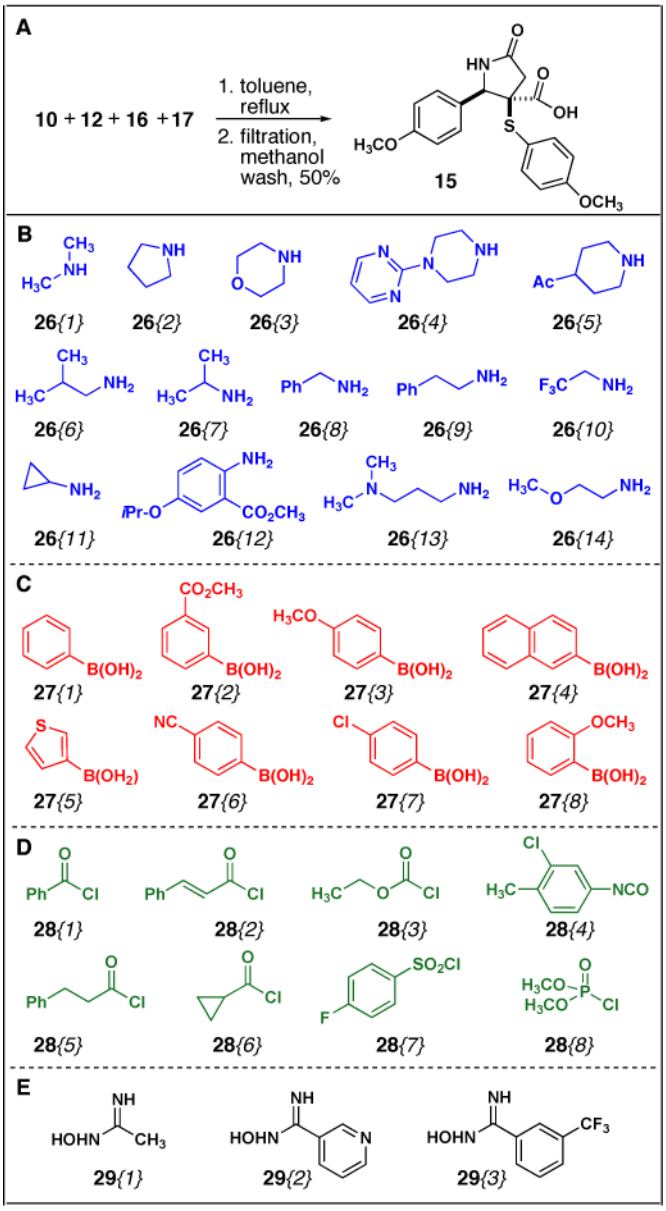


Figure 3.
Diversity reagents for schemes 2–6.

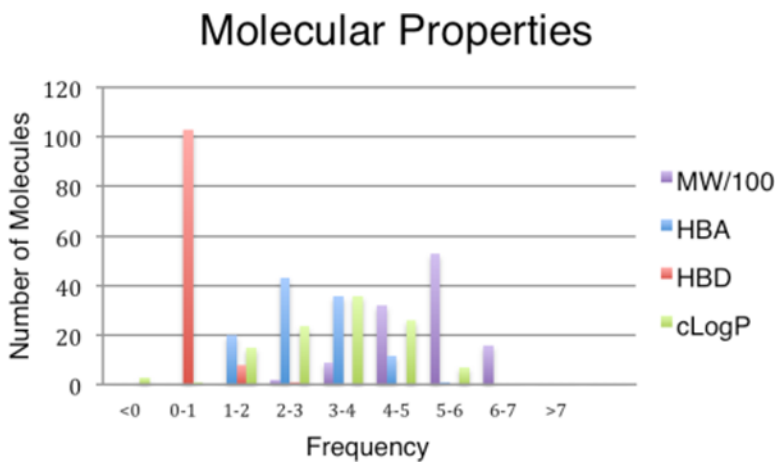


Figure 4.
Molecular properties of library

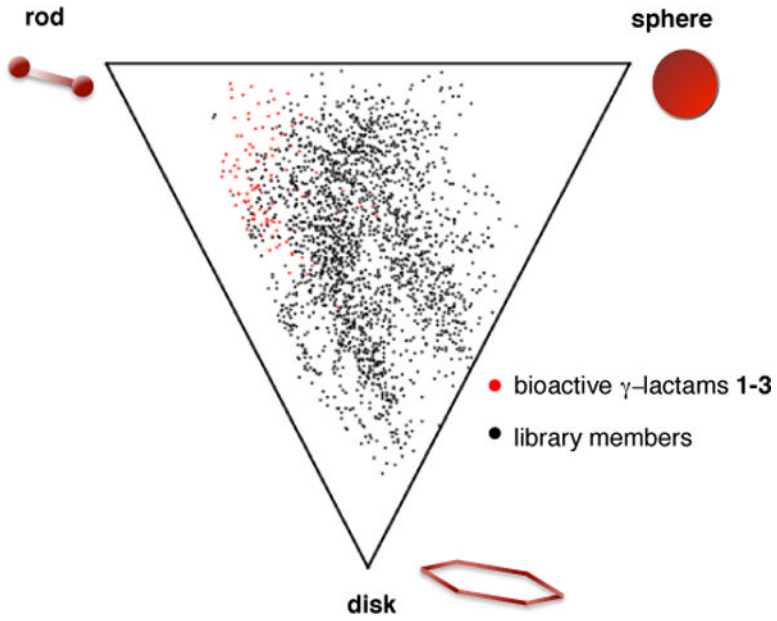
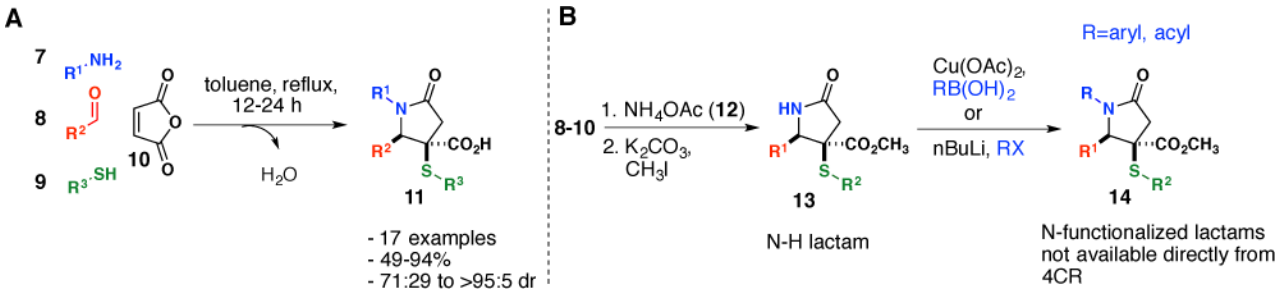
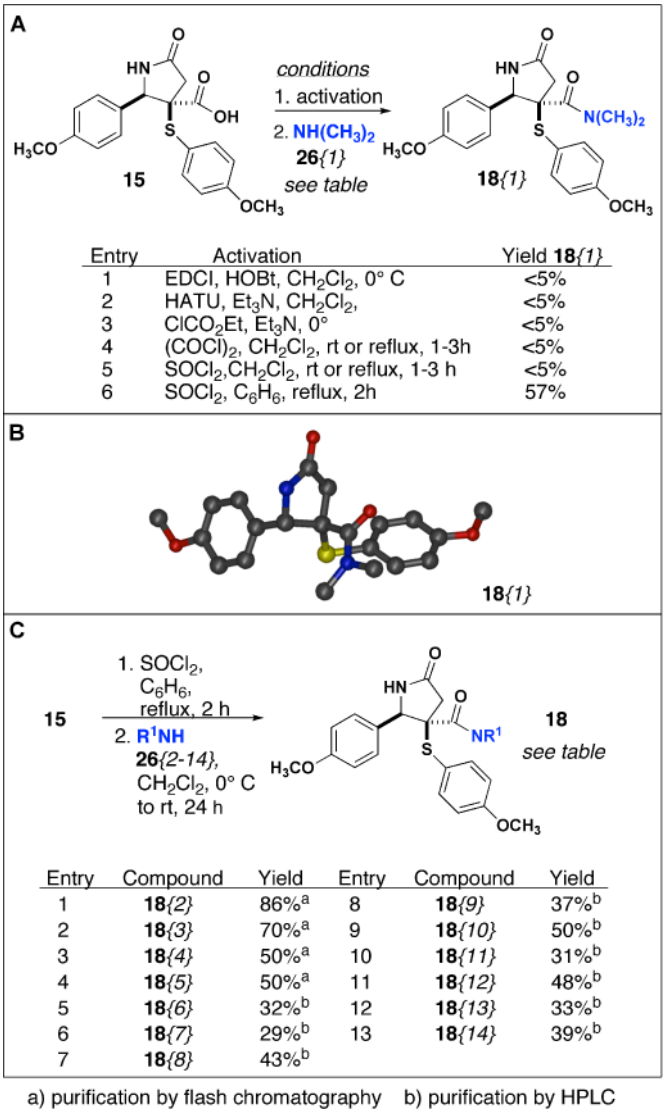


Figure 5.
Scatter plot with principle moments of inertia (PMI) ratios plotted to compare molecular shape diversity of γ-lactam library. Ratios were calculated for all conformers ≤3 kcal/mol from the minimum energy conformer. Bioactive γ-lactams **1**–**3** are in red and library members are in black.



Scheme 1.

Assembly of (**A**)*N*-substituted and (**B**) N-H γ-lactams using a 4CR.



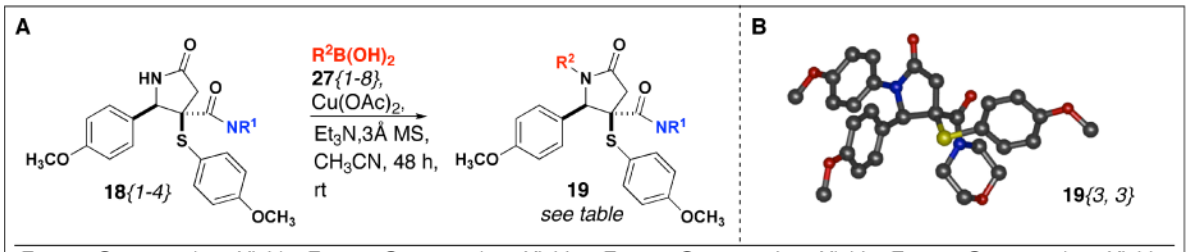
Entry	Activation	Yield **18**{1}
1	EDCI, HOBt, CH_2Cl_2, 0° C	<5%
2	HATU, Et_3N, CH_2Cl_2,	<5%
3	$ClCO_2Et$, Et_3N, 0°	<5%
4	$(COCl)_2$, CH_2Cl_2, rt or reflux, 1-3h	<5%
5	$SOCl_2$,CH_2Cl_2, rt or reflux, 1-3 h	<5%
6	$SOCl_2$, C_6H_6, reflux, 2h	57%

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) purification by flash chromatography b) purification by HPLC

Scheme 2.

(**A**) Optimization of amide coupling conditions with **26**{1}(**B**) crystal structure of **18**{1}, and (**C**) synthesis of **18**{2–14}.

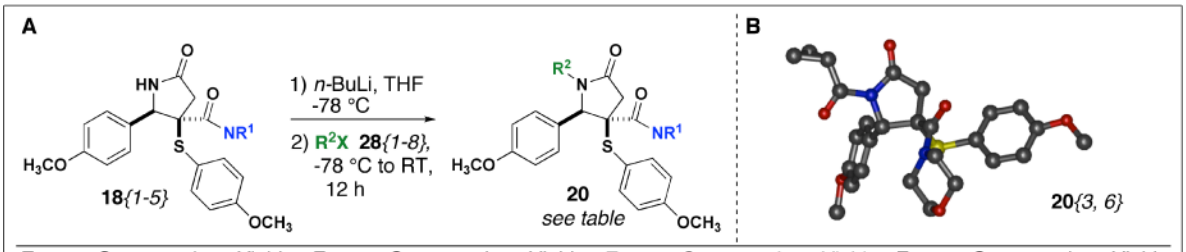


Entry	Compound	Yield	Entry	Compound	Yield	Entry	Compound	Yield	Entry	Compound	Yield
1	**19**{1, 1}	26%[b]	9	**19**{2, 1}	30%[b]	17	**19**{3, 1}	19%[b]	25	**19**{4, 1}	38%[b]
2	**19**{1, 2}	32%[a]	10	**19**{2, 2}	37%[a]	18	**19**{3, 2}	43%[a]	26	**19**{4, 2}	34%[b]
3	**19**{1, 3}	36%[b]	11	**19**{2, 3}	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) purification by flash chromatography b) purification by HPLC

Scheme 3.

(**A**)*N*-arylation of N-H amides **18**{*1–4*} and (**B**) crystal structure of **19**{*3,3*}.

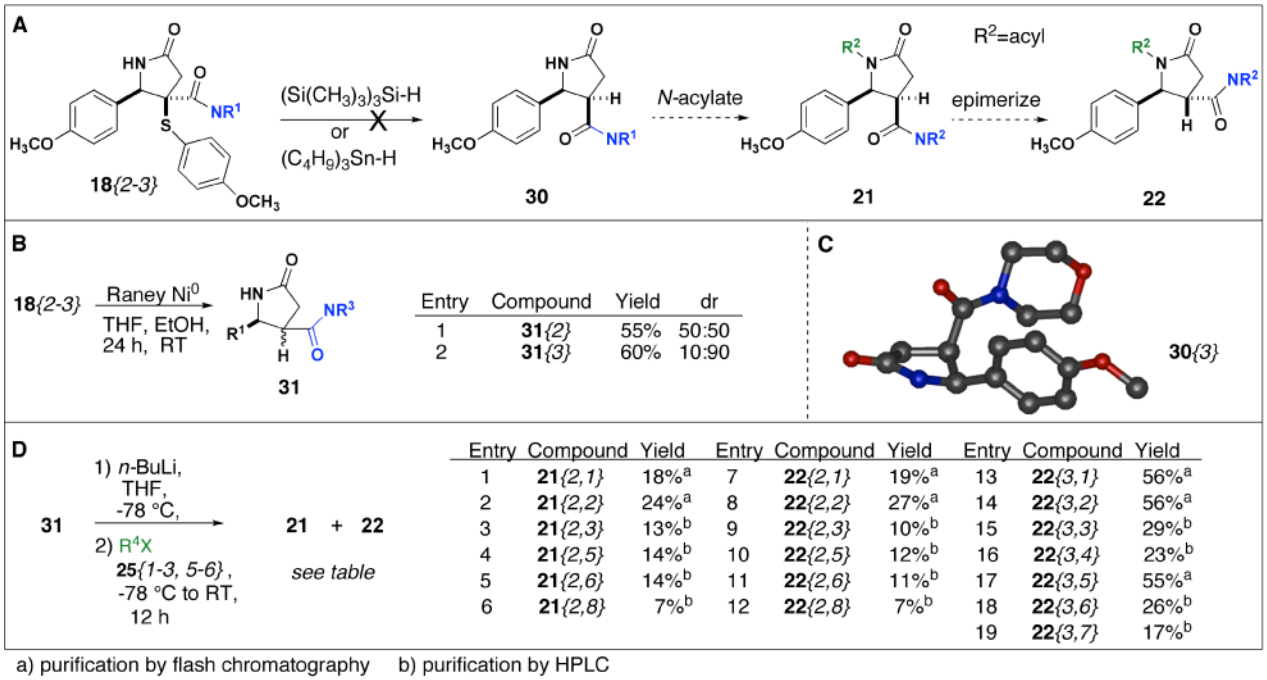


Entry	Compound	Yield	Entry	Compound	Yield	Entry	Compound	Yield	Entry	Compound	Yield
1	**20**{1, 1}	70%[a]	11	**20**{2, 3}	74%[b]	21	**20**{3, 5}	79%[a]	31	**20**{4, 7}	47%[b]
2	**20**{1, 2}	61%[b]	12	**20**{2, 4}	68%[b]	22	**20**{3, 6}	90%[a]	32	**20**{4, 8}	24%[b]
3	**20**{1, 3}	63%[b]	13	**20**{2, 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]

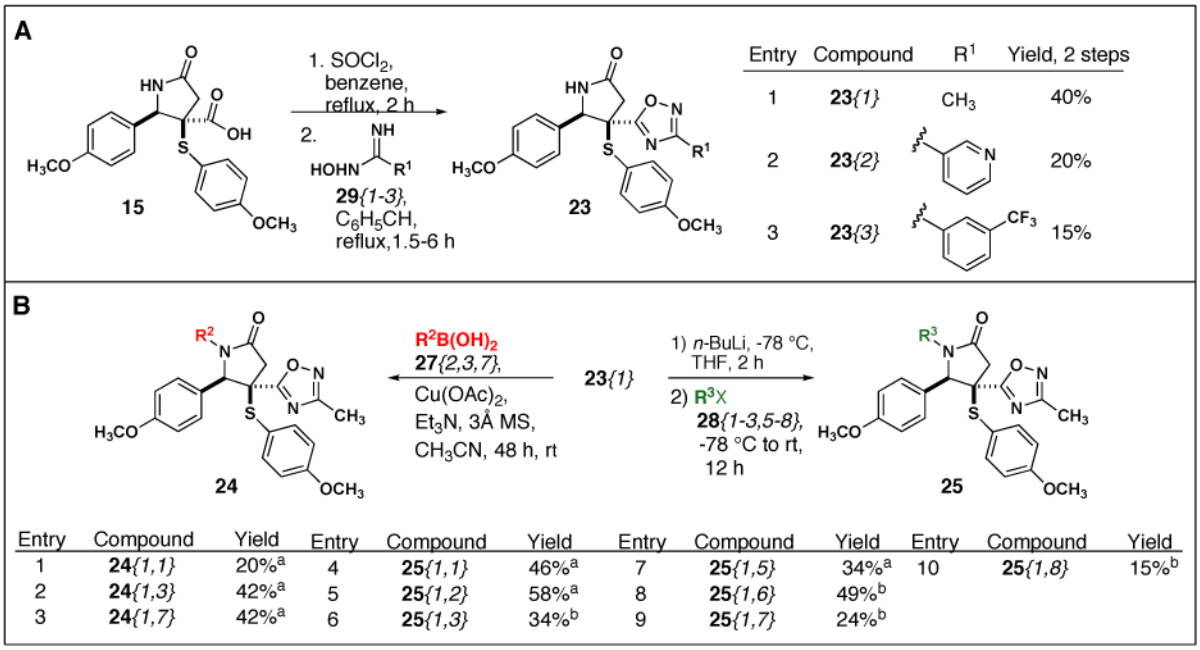
a) purification by flash chromatography b) purification by HPLC

Scheme 4.

(**A**)*N*-acylation of N-H amides **18***{1–5}* and (**B**) crystal structure of **20***{3,6}*.



Scheme 5.
Desulfurization reactions



Entry	Compound	Yield	Entry	Compound	Yield	Entry	Compound	Yield	Entry	Compound	Yield
1	**24**{1,1}	20%[a]	4	**25**{1,1}	46%[a]	7	**25**{1,5}	34%[a]	10	**25**{1,8}	15%[b]
2	**24**{1,3}	42%[a]	5	**25**{1,2}	58%[a]	8	**25**{1,6}	49%[b]			
3	**24**{1,7}	42%[a]	6	**25**{1,3}	34%[b]	9	**25**{1,7}	24%[b]			

a) purification by flash chromatography b) purification by HPLC

Scheme 6.

(**A**) Synthesis of 1,2,4-oxadiazoles **23** and (**B**)*N*-functionalization of **23**{*1*}.

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