S_NAr-Based, Facile Synthesis of a Library of Benzothiaoxazepine-1,1′-dioxides

Alan Rolfe, Thiwanka B. Samarakoon, Sarra V. Klimberg, Marek Brzozowski, Benjamin Neuenswander, Gerald H. Lushington, and Paul R. Hanson*

Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045-7582, and The University of Kansas Center for Chemical Methodologies and Library Development (KU-CMLD), 2034 Becker Drive, Del Shankel Structural Biology Center, Lawrence, Kansas 66047

Received June 15, 2010

The construction of a library of benzothiaoxazepine-1,1′-dioxides utilizing a one-pot, S_NAr diversification−$ODCT_{50}$ scavenging protocol is reported. This protocol combines microwave irradiation to facilitate the reaction, in conjunction with a soluble ROMP-derived scavenger (ODCT) to afford the desired products in good overall purity. Utilizing this protocol, a 78-member library was successfully synthesized and submitted for biological evaluation.

1. Introduction

Advances in high-throughput screening and the need for new pharmaceutical leads have led to the emergence of methods and technologies to access diverse collections of small molecules. This has led to advances of synthetic platforms, such as flow-through, microreactors, microwave, and immobilized reagents/scavengers, and advances in methodology including new efficient synthetic protocols, multicomponent reactions, parallel synthesis, and green chemistry. To this effect, a variety of high-load, soluble immobilized reagents derived from ring-opening metathesis polymerization (ROMP) has emerged. These oligomeric reagents and scavengers have been efficiently utilized in facilitated protocols for the generation of S- and P-heterocycles.[1]

Alongside platform innovation, the advancement of multicomponent cascade protocols to rapidly access core scaffolds in multigram quantities is of high importance. Cascade or domino reactions are highly efficient pathways that allow for the synthesis of complex molecules from simple substrates and encompass a variety of transformations.[2] With such scaffolds in hand, the utilization of facilitated purification-free protocols utilizing immobilized reagents and scavengers, has become a useful method to rapidly access small molecule libraries. In this regard, we herein report the synthesis of a library of benzothiaoxazepine-1,1′-dioxides via a one-pot, S_NAr diversification protocol utilizing a $ODCT_{50}$ scavenger.

Sultams (cyclic sulfonamide analogues) have emerged in recent years as important targets in drug discovery because of their extensive chemical and biological profiles.[3] Though not found in nature, a number of benzofused sultams have recently appeared in the literature, which display potent activity across a variety of biological targets. Such reports include, inhibition of a variety of enzymes, including HIV integrase,[4] COX-2 (Ampiroxicam),[5,6] HCV NS5b RNA-dependent RNA-polymerase,[7] cysteine proteases involved in the progression of malaria,[8] and lipoxygenases.[9] In particular, benzoxazepine-1,1-dioxides have exhibited a wide array of biological activity, including: (1) histone deacetylase inhibition (for treatment of cognitive disorders, such as Alzheimers desease),[10] (2) glucokinase activation,[11] (3) serotonin 5-HT2C activation,[12] (4) modulation of the histamine H3 receptor,[13] (5) inhibition of MDM2-p53,[14] (6) inhibition of sodium-proton exchange, (7) bradykinin B1 receptor antagonism (for treating Alzheimer's disease),[15] (8) AMPA receptor agonism,[16] and (9) inhibition of metalloproteinase.[17]

2. Results and Discussion

We recently reported the development and application of a one-pot cascade protocol for the synthesis of benzothiaoxazepine-1,1′-dioxides and oxathiazepine-1,1′-dioxides.[18] With this method in hand, we envisioned its utilization in the synthesis of a library of benzothiaoxazepine-1,1′-dioxides where-by diversification could be incorporated via S_NAr reaction at the aromatic fluoride position with a variety of nucleophiles (Scheme 1).

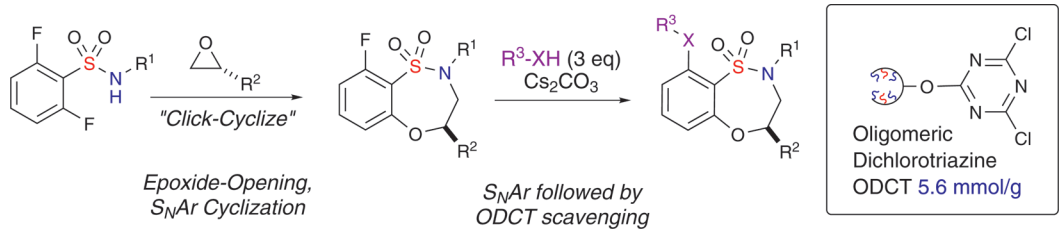
To this effect, a variety of benzothiaoxazepine-1,1′-dioxide scaffolds **1**−**9** were synthesized possessing fluorine substitution at the 6-position with varying functionality at the R^1 and R^2 positions (Scheme 2, Table 1).

With these scaffolds in hand, diversification of the aryl fluoride position utilizing an S_NAr reaction with 4-isopropyl phenol {*6*} was performed on scaffold **1** (Scheme 3, Table 2). Initially, reactions were conducted using conventional thermal heating, followed by screening of a variety of bases, solvent and phenol equivalents to yield the desired product in high conversion (Table 2, entry 1−10). It was found that utilizing 3 equivalents of phenol {*6*} in the presence of

* To whom correspondence should be addressed. E-mail: phanson@ku.edu.

10.1021/cc1001023
Published on Web 09/29/2010

Scheme 1. One-Pot Epoxide Cascade Protocol Library Plan



Scheme 2. Synthesis of Core Benzothiaoxazepine-1,1′-dioxide Scaffolds **1**−**9b**

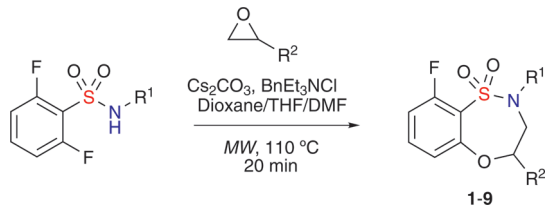


Table 1. Synthesis of Benzothiaoxazepine-1,1′-dioxide Scaffolds via Epoxide Cascade Protocol

entry	R^1	R^2	yield (%)
1	butyl	CH_2OBn	**1** (73%)
2	propargyl	$CH_2O(CH_2)_2CH_3$	**2** (69%)
3	(*R*)-1-phenylethyl	(*S*)-CH_2OBn	**3** (76%)
4	cyclopropane	(*S*)-CH_2OBn	**4** (84%)
5	propargyl	CH_2OPh	**5** (81%)
6	4-methoxybenzyl	$CH_2CH_2CH{=}CH$	**6** (69%)
7	butyl	$CH_2O(CH_2)_2CH_3$	**7** (79%)
8	cyclopentyl	(*R*)-$CH_2OC(O)Pr$	**8** (82%)
9	4-methoxybenzyl	(*R*)-CH_2OBn	**9** (89%)

Scheme 3. Optimization of S_NAr of Phenol {*6*} on Scaffold **1**

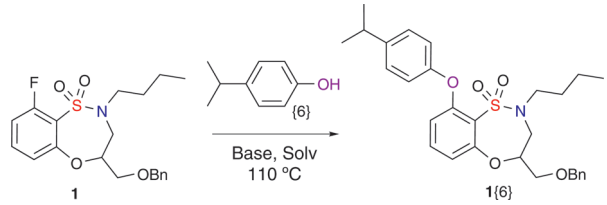


Table 2. Optimization of Intermolecular S_NAr Conditions with a Phenol Nucleophile

entry	equiv {*6*}	temp (°C)	solvent	base	time	conversion[a] (%)
1	1	110	DMF	DBU	12 h	19
2	1	110	DMF	K_2CO_3	12 h	40
3	1	110	DMF	Cs_2CO_3	12 h	53
4	1	110	DMSO	Cs_2CO_3	12 h	55
5	3.	110	DMSO	Cs_2CO_3	12 h	>95
6	2	110	DMSO	Cs_2CO_3	12 h	82
7	3	110	DMSO	Cs_2CO_3	4 h	37
8	3	110	DMSO	Cs_2CO_3	8 h	56
9	3	80	DMSO	Cs_2CO_3	12 h	60
10	3	150	DMSO	Cs_2CO_3	8 h	>95
11[b]	3	150	DMSO	Cs_2CO_3	1 h	>95
12[b]	3	150	DMSO	Cs_2CO_3	30 min	>95[c]
13[b]	3	150	DMSO	Cs_2CO_3	10 min	68

[a] Crude conversion determined by ^1H NMR. [b] Reactions carried out under microwave irradiation. [c] Isolated yield after column chromatography 89%.

Cs_2CO_3 and DMSO gave the desired product in >95% conversion after heating at 110 °C for 8 h (Table 2, entry 10). Further optimization of the reaction conditions was investigated with the aim of reducing reaction times via the implementation of microwave irradiation (Table 2, entries 11−13). It was found that reaction times could be reduced to 30 min (Table 2, entry 12), while maintaining conversion at >95%.

Despite isolating the desired product **1**{*6*} in high yield, the utilization of 3 equiv of phenol {*6*} was undesirable for parallel synthesis. When utilizing amines as the nucleophilic species, simple silica SPE was employed efficiently to remove excess amine. However, phenols cannot be removed by simple silica SPE and the application of aqueous workup would require the utilization of a robotic platform. Therefore, it was envisioned that the unreacted nucleophile (phenol, thiophenol, amine, and sulfonamide) could be scavenged utilizing the previously reported high load, soluble scavenger derived from ring-opening metathesis polymerization (ROMP).[19] In this regard, the utilization of oligomeric dichlorotriazine ($ODCT_{50}$) was investigated for the removal of excess phenol {*6*} from the crude reaction mixture (Scheme 4).

Utilizing previously published conditions as a starting point,[19] scavenging of the crude reaction mixture utilizing 3 equiv of $^{2G}ODCT_{50}$ at 110 °C (thermal heating), yielded the desired crude product in >90% purity by ^1H NMR (Table 3, entries 1−3). Despite these results, having to scavenge crude reactions for 10 h in a parallel format was not an optimal protocol for library production. Therefore, we investigated a two-step sequential procedure could be carried out under microwave irradiation to yield the desire product in high yield and purity without the need of conventional purification techniques. The utilization of $^{2G}ODCT_{50}$ under microwave irradiation was investigated (Table 3, entries 4−9), and it was found that reaction conditions could be reduced to 30 min at 50 °C with final crude purity >95% (Table 3, entry 8).[20] Overall, a reaction carried out thermally requiring 8 h of reaction time and 10 h of scavenging (18 h/reaction) has been reduced to 30 min of reaction time and 30 min of scavenging (1 h/reaction) by the utilization of microwave irradiation.

With these optimized procedures in hand, a prototype library was investigated on scaffolds **1** and**7** utilizing a variety of phenols. In addition, a number of amines and sulfonamides were included to probe their potential application as nucleophilic species in the S_NAr diversification (Scheme 5, Table 4).

The successful synthesis of the 16-membered prototype library yielded an average crude purity of 70%, final yield of 59.5% and an average final purity of 98.3% after automated preparative reverse phase HPLC. Taking these results in hand, we proposed the synthesis of a 72-membered library (Scheme 6), with the remaining scaffolds **1**−**9** and the corresponding nucleophilic species {*1*−*21*} (Figure 1).

Scheme 4. Optimization and Utilization of ODCT as an Efficient Scavenger of Phenol {*6*}

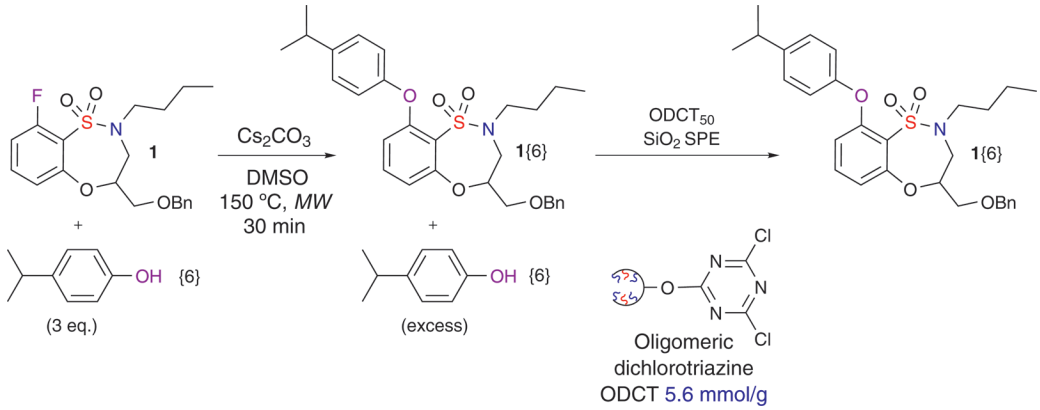


Table 3. Optimization of Scavenging Protocol

entry	^{2G}ODCT$_{50}$ (equiv)	temp (°C)	time	purity[a] (%)
1	1	150	10 h	70
2	3	150	10 h	>90
3	3	110	10 h	>90
4[b]	3	150	1 h	>90
5[b]	3	150	30 min	>95
6[b]	3	150	10 min	80
7[b]	3	100	30 min	>95
8[b]	3	50	30 min	>95
9[b]	3	30	30 min	80

[a] Purity analyzed by ^{1}H NMR spectroscopy (experimental error 5%). [b] Reactions carried out under microwave irradiation (Anton Parr 300 synthesizer).

Scheme 5. Synthesis of the Corresponding Prototype Library from Scaffolds **1** and **7**

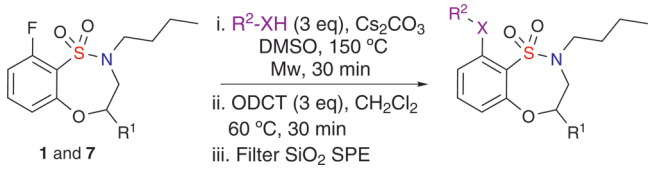


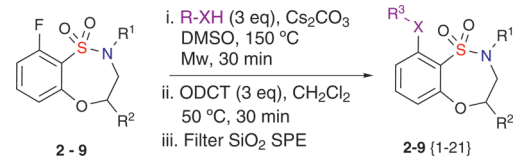
Table 4. Prototype Library Utilizing Scaffold **1**

entry[a]	crude purity[c] (%)	yield[b] (%)	final purity[c] (%)	entry[a]	crude purity[c] (%)	yield[b] (%)	final purity[c] (%)
1{*1*}	73	60	100	**7**{*4*}	70	72	100
1{*3*}	87	60	100	**7**{*5*}	71	66	100
1{*4*}	74	61	91	**7**{*6*}	92	71	92
1{*11*}	77	61	100	**7**{*11*}	77	74	100
1{*15*}	52	49	100	**7**{*16*}	87	67	95
1{*17*}	50	62	97	**7**{*17*}	51	44	100
1{*19*}	45	42	99	**7**{*19*}	60	39	100
7{*1*}	74	61	100	**10**	80	63	100

[a] Reaction conditions: Sultam **1** or 7 (0.136 mmol, 1 equiv), nucleophile (0.408 mmol, 3 equiv), Cs_2CO_3 (4 equiv), dry DMSO (1 M), ODCT$_{50}$ (0.408 mmol, 3 equiv). [b] Purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy). [c] Purity was determined by HPLC with peak area (UV) at 214 nm.

In comparison to the prototype library, crude purity was on average lower because of the presence of either starting material or unknown byproduct. Overall, 59 of 78 members in this library yielded the desired products in 12−82% yield with 47 in 90% purity or greater after automated preparative reverse phase HPLC. It was found that submission of scaffolds **2** and **5** to the library reaction conditions gave poor yield and in most cases reaction failed (12 examples) because of the formation of unidentified byproduct. Additionally it is proposed that the failure of nucleophile {2} was due to unfavorable steric interactions.

Scheme 6. Proposed 72-Member Library of Benzothiaoxazepine-1,1′-dioxides



Conclusion

In conclusion, we have developed an efficient protocol for the diversification of benzothiaoxazepine-1,1′-dioxides via intermolecular diversification with a variety of nucleophilic species. A ROMP-derived oligomeric scavenger ODCT$_{50}$ was

Table 5. Successful Run of 62 Members of the 78-Member Proposed Library

entry[a]	yield[b] (%)	purity[c] (%)	entry[a]	yield[b] (%)	purity[c] (%)
2{*1*}	28	83	**4**{*21*}	29	92
2{*2*}	NA	NA	**5**{*1*}	32	100
2{*3*}	12	50	**5**{*3*}	28	78
2{*4*}	31	72	**5**{*5*}	35	100
2{*5*}	26	77	**5**{*6*}	40	92
2{*6*}	28	80	**5**{*16*}	22	100
2{*7*}	18	89	**5**{*17*}	24	97
2{*8*}	19	83	**5**{*18*}	28	92
2{*9*}	25	92	**6**{*1*}	52	99
2{*10*}	22	92	**6**{*3*}	46	100
3{*1*}	41	100	**6**{*4*}	87	79
3{*2*}	NA	NA	**6**{*5*}	62	100
3{*4*}	51	95	**6**{*6*}	35	100
3{*5*}	31	100	**6**{*9*}	52	99
3{*6*}	77	99	**6**{*16*}	56	94
3{*7*}	47	100	**6**{*17*}	52	98
3{*8*}	39	100	**6**{*18*}	29	100
3{*9*}	49	100	**6**{*19*}	31	97
3{*11*}	51	100	**7**{*3*}	82	78
3{*13*}	44	91	**7**{*9*}	41	74
3{*16*}	34	93	**7**{*14*}	64	94
3{*17*}	42	100	**7**{*15*}	48	99
3{*20*}	33	100	**8**{*1*}	55	100
3{*21*}	31	100	**8**{*3*}	34	97
4{*1*}	59	100	**8**{*5*}	35	100
4{*2*}	NA	NA	**8**{*6*}	28	100
4{*3*}	53	100	**8**{*7*}	40	100
4{*4*}	58	99	**8**{*8*}	32	95
4{*15*}	34	100	**8**{*11*}	24	100
4{*16*}	41	92	**9**{*6*}	50	100
4{*17*}	57	100	**9**{*16*}	57	95

[a] Reaction conditions: Sulfonamide (0.136 mmol, 1 equiv), nucleophile (0.408 mmol, 3 equiv), Cs_2CO_3 (4 equiv), and dry DMSO (1M), ODCT$_{50}$ (0.408 mmol, 3 equiv). [b] Purified by an automated preparative reverse-phase HPLC (detected by mass spectroscopy). [c] Purity was determined by HPLC with peak area (UV) at 214 nm.

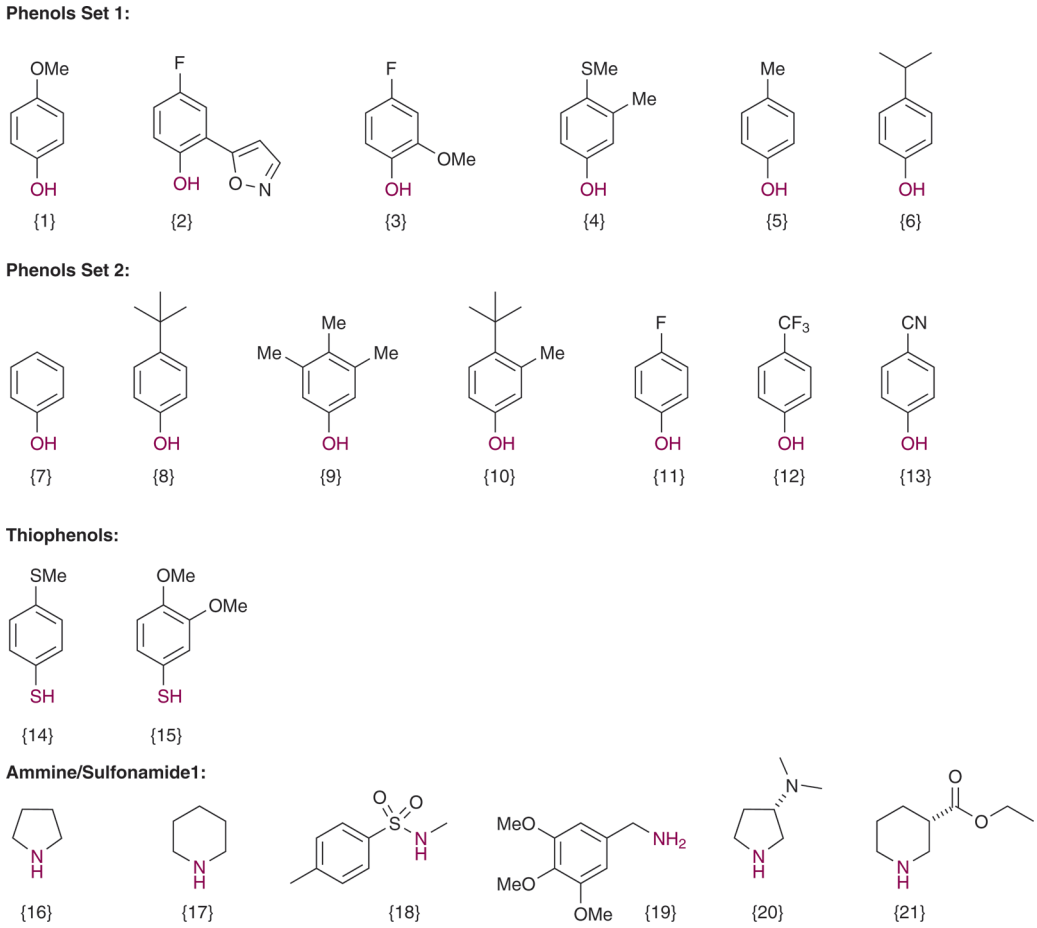


Figure 1. Phenols, amines, and sulfonamide nucleophiles for library synthesis.

successfully utilized to scavenge excess nucleophilic species yielding the desired compounds in good crude purity. A total of 76 compounds were synthesized utilizing this protocol and evaluation of the biological activity of these compounds in high-throughput screens is currently underway.

Experimental Section

General Procedures. All air and moisture sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere using standard gastight syringes, cannula, and septa. Stirring was achieved with oven-dried, magnetic stir bars. CH_2Cl_2 was purified by passage through the Solv-Tek purification system employing activated Al_2O_3.[21] Et_3N was purified by passage over basic alumina and stored over KOH. Flash column chromatography was performed with SiO_2 from Sorbent Technology (30930M-25, Silica Gel 60A, 40−63 um). Thin layer chromatography was performed on silica gel 60F254 plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance operating at 500 and 126 MHz, respectively. High-resolution mass spectrometry (HRMS) and FAB spectra were obtained in one of two manners: (i) on a VG Instrument ZAB double-focusing mass spectrometer and (ii) on a LCT Premier Spectrometer (Micromass UK Limited) operating on ESI (MeOH). All library syntheses was carried out in 1 dram vials utilizing Anton Parr Synthon 3000 microwave platform. Parallel evaporations were performed using a GeneVac EZ-2 plus evaporator. Automated preparative reverse-phase HPLC purification was performed using an Agilent 1200 Mass-Directed Fractionation system (Prep Pump G1361 w/gradient extension, Make-up pump G1311A, pH modification pump G1311A, HTS PAL autosampler, UV-DAD detection G1315D, Fraction Collector G1364B, and Agilent 6120 quadrapole spectrometer G6120A). The preparative chromatography conditions included a Waters X-Bridge C18 column (19 × 150 mm, 5um, w/19 × 10 mm guard column), elution with a water and CH_3CN gradient which increases 20% in CH_3CN content over 4 min at a flow rate of 20 mL/min (modified to pH 9.8 through addition of NH_4OH by using an auxiliary pump), and sample dilution in DMSO. The preparative gradient, triggering thresholds, and UV wavelength were selected based on the HPLC analysis of each crude sample. The analytical method employed an Agilent 1200 RRLC system with UV detection (Agilent 1200 DAD SL) and mass detection (Agilent 6224 TOF). The analytical method conditions included a Waters Aquity BEH C18 column (2.1 × 50 mm, 1.7 μm) and elution with a linear gradient of 5% CH_3CN in pH 9.8 buffered aqueous NH_4HCO_3 to 100% CH_3CN at 0.4 mL/min flow rate. The purity was determined using UV peak area at 214 nm.

General Procedure A for the Synthesis of Benzothiaoxazepine-1,1′-dioxide Scaffolds 1−9. Into a microwave vial (0.5−2.0 mL) was added 2,6-difluorobenzene sulfonamide (2 mmol), anhydrous Cs_2CO_3 (6 mmol), $BnEt_3NCl$ (0.2 mmol), epoxide (2 mmol) and dry dioxane/DMF (1:1,

1M). The microwave vial was heated at 110 °C for 20 min, after such time the reaction was purified (directly loading of crude reaction mixture) by flash chromatography (8:2 hexane/EtOAc) to afford the desired sultam.

General Procedure B for the Synthesis of Library Members. Into a 1-dram vial was added Cs_2CO_3 (0.17 g, 0.54 mmol, 3 equiv), a stock solution of corresponding sultam (0.136 mmol) in dry DMSO (70 μL) (stock solution A) and nucleophile (0.40 mmol, 3 equiv). The reaction was heated in microwave at 110 °C for 30 min, followed by cooling to RT. To the crude reaction mixture was added a stock solution of $ODCT_{50}$ (70 mg) in dry CH_2Cl_2 (1 mL), and the crude reaction mixture was heated at 60 °C for an additional 30 min in the microwave. After such time, the crude reaction mixture was diluted (hexane:EtOAc, 1 mL) and filtered through a silica SPE, flushing with solvent (hexane:EtOAc, 5 mL). The resulting organic filtrate was concentrated and analyzed by HPLC (UV 214 nm). Crude material with purity below 90% was submitted to purification by mass-directed fractionation (MDF).

Acknowledgment. This research was made possible by generous funds provided by the National Institute of General Medical Sciences [Pilot-Scale Libraries Program (P41 GM076302)], and The University of Kansas Center for Chemical Methodologies and Library Development (KU-CMLD) (P50 GM069663). Undergraduate funding was provided by the NIH K-INBRE award and KU Center for Research (S.V.K and M.B).

Supporting Information Available. Experimental procedures, tabulated results for all libraries, and full characterization data for representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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