# Intramolecular oxa-Michael and Baylis Hillman Strategies towards Sultam Library Production

By

Christopher A Knudtson

Submitted to the Graduate Program in Chemistry and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the degree of Master of Arts.

_____

Chairperson Paul R Hanson

_____

Robert G Carlson

_____

Rich S Givens

Date Defended: 4/19/11

The Thesis Committee for Christopher A Knudtson

Certifies that this is approved version of the following thesis:

# Intramolecular oxa-Michael and Baylis Hillman Strategies towards Sultam Library Production

_____

Chairperson Paul R Hanson

Date Approved: _____

**Abstract**

The utilization of Baylis-Hillman and oxa-Michael methodologies for the synthesis of sultam (cyclic sulfonamides) libraries from chiral non-racemic amino alcohols and epoxides is reported. These strategies employ a divergent synthetic approach utilizing a central vinyl sulfonamide linchpin and a variety of functional group pairing reactions to generate skeletally diverse sultam scaffolds with a variety of functionalizable handles. A variety of 5, 6, 7, and 8-member sultams are accessible through these methods with excellent diastereoselectivity, yields, and purities. In addition, the oxa-Michael protocol has been utilized in a one-pot protocol for the synthesis of alibrary of 4,4-dioxo-1,4,5-oxathiazepines.
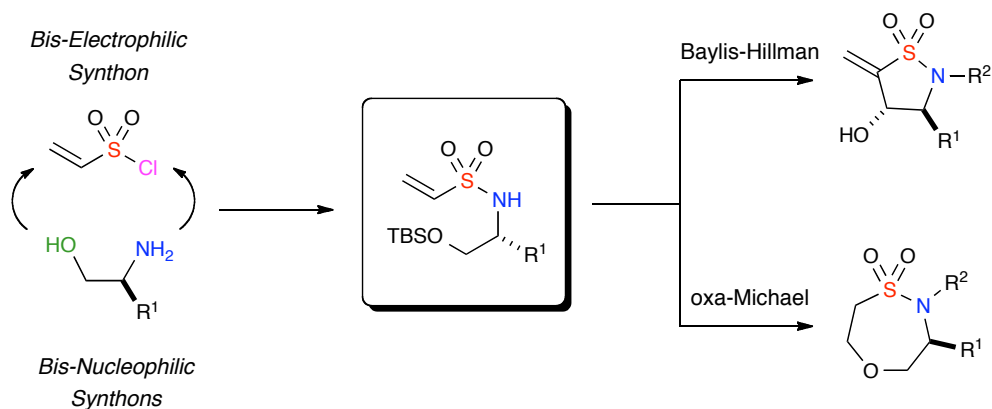
# Chapter 1

# High-Throughput Screening and Diversity-Orientated Synthesis

## 1.1 The Demands of High-Throughput Screening

The current threats to human well-being include many old and new infections, as well as an increasing prevalence of chronic diseases. Among these include cardiac disease, cancer, obesity, autoimmune disorders, and degenerative diseases due to old age. Current medical care must address the challenges in treating these diseases due to their prevalence, mortality rate, healthcare costs, and the patient-to-patient therapy administration. In addition, healthcare providers are expected to provide a high quality of life through non-invasive, easily administered treatments with mild side effects. Although traditional treatments remain popular, the high demands placed on healthcare coupled with the ever-changing environment of human disease prevention requires the development of new chemical entities which better address current and future threats to human health.
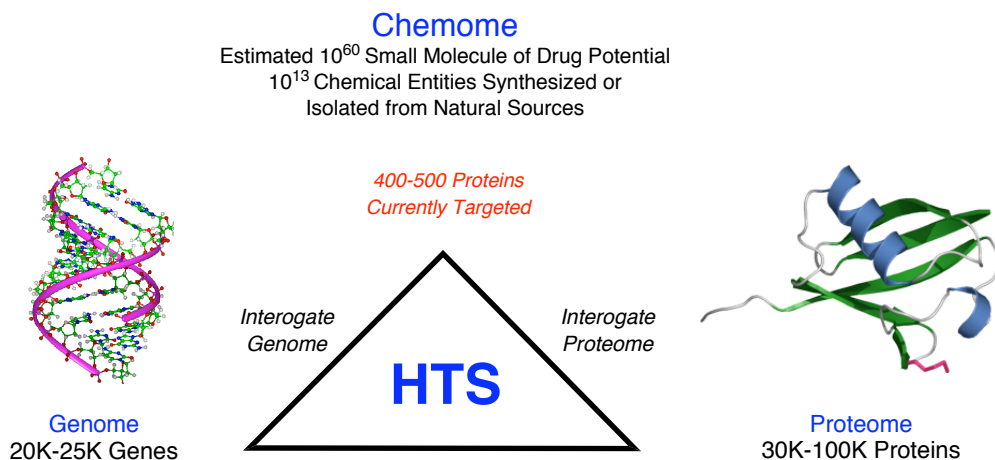
**Figure 1.** *Timeline for Drug Discovery*
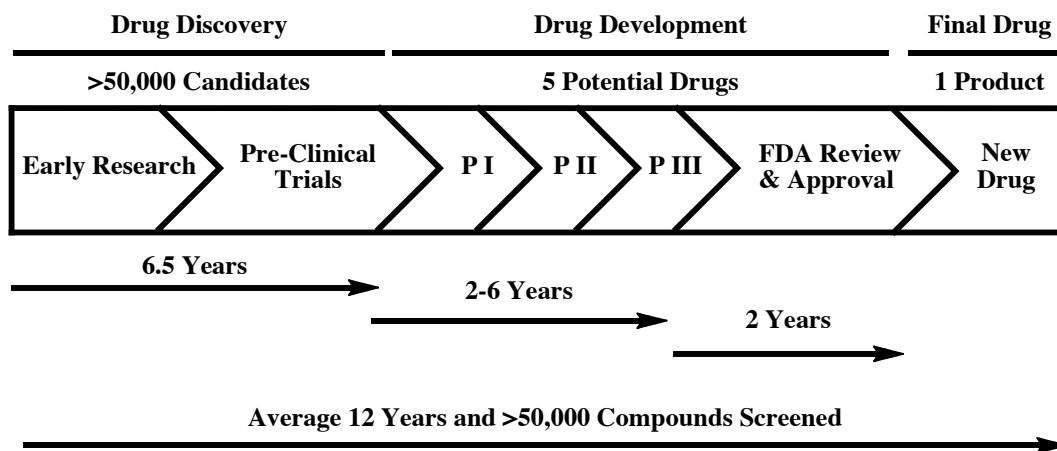


While the demand for new therapeutic agents has existed for many years, the pathway to drug development is a long and complex process (Figure 1).[1] In order to more quickly address the demands for new drugs, enabling technologies have been developed which seek to improve the process. High-throughput screening is one such enabling

technology which allows for the rapid identification of compounds with biological activity[2]. To properly harness this technology, there must be available large collections of potentially druggable molecules in order to screen a diverse set of chemical structures. Thus synthetic chemists are challenged to produce diverse small molecule libraries to address this demand.

## 1.2 Chemical Libraries and Diversity-Orientated Synthesis

The growing demand for diverse small molecule libraries in the development of therapeutic agents requires efficient, innovative methodologies to provide access to these structurally unique molecules. These synthetic routes must address the challenges of rapid library generation including: access to structurally unique molecules, rapid production of compounds, adaptable methodologies, consistent library quality in terms of high yields and purities, and enabling the probing of previously unexplored chemical space. The possible number of synthesizable molecules is estimated to be in the area of $10^{60}$, while the already available synthetic molecules are estimated around $10^{13}$,[3] leaving a vast area unknown (Figure 2).

**Figure 2**: *Known Chemical Space and Drug Targets*



Chemome
Estimated $10^{60}$ Small Molecule of Drug Potential
$10^{13}$ Chemical Entities Synthesized or
Isolated from Natural Sources

*400-500 Proteins*
*Currently Targeted*

*Interogate Genome*     *Interogate Proteome*

HTS

Genome
20K-25K Genes

Proteome
30K-100K Proteins

Due to the expansive size of unexplored chemical space, biomedical research must utilize guided efforts in order to efficiently probe for pharmacologically active structures. Thus, library construction requires a focus on novel scaffolds that not only are skeletally diverse and possess the capability for diversification, but also have display qualities of potentially drug-like molecules. This challenge is met with the utilization of diversity-orientated synthesis (DOS). Pharmacutical research has previously followed a target-orientated synthesis (TOS) rational, seeking to synthesize known biological compounds. Further drug-discovery efforts have in turn focused on producing analogs of these targets through functional-oriented synthesis (FOS)[4] (Figure 3).

**Figure 3:** *Methods for Chemical Probing*
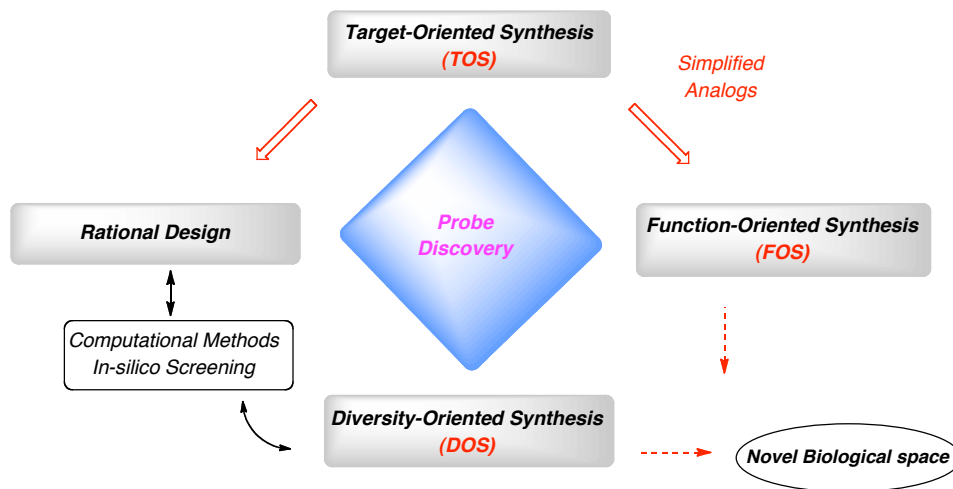


However, in order to explore unknown chemical space, DOS instead uses rationally designed molecules based on known biological data to synthesize libraries of structurally unique compounds.[5] Thus while TOS and FOS are confined to investigating known, although potentially active, chemical space, DOS instead seeks to produce compounds which differ greatly from the known chemone in order to probe for potential

biological activity. Thus, DOS is able to fulfill the demands of high-throughput screening as an efficient, divergent synthetic method which enables the production of a variety of skeletal core structures from a common precursers. These unique skeletal cores define an unknown chemical space and through functionalizing, produce a library capable of defining a wide area of chemical space for bioactive screening (Figure 4).

**Figure 4**: *Probing Chemical Space*
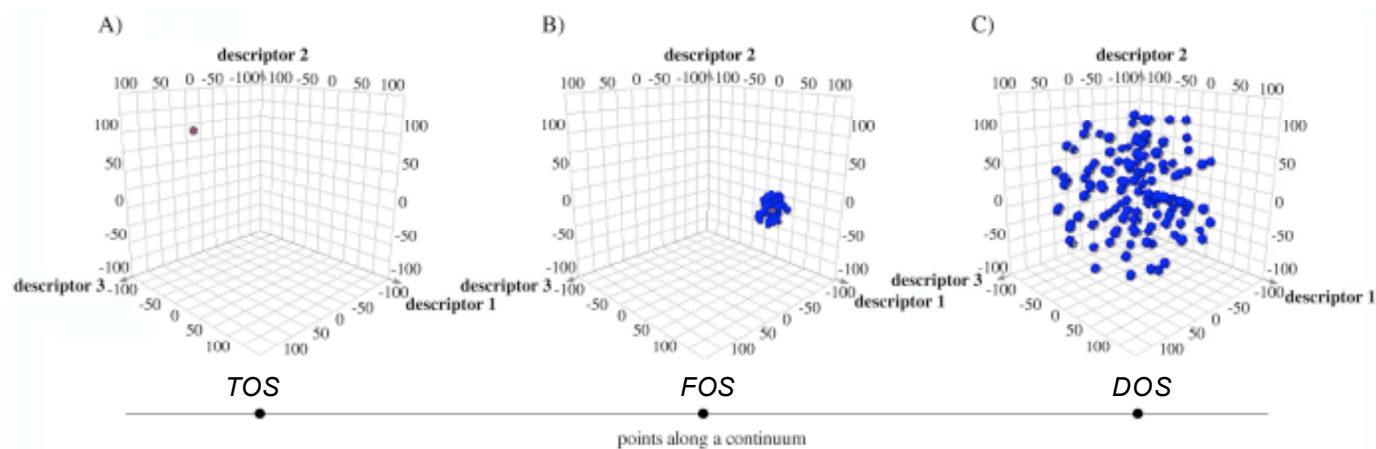


## 1.3 Build-Couple-Pair Strategies and Click Reactions in DOS

This approach to library synthesis involves a "build, couple, pair" (BCP) strategy for the construction of small molecules. Pioneered by Schreiber and co-workers,[6] this strategy has been utilized successfully to produce libraries of macrodiolides,[7] macrolactams,[8] and other complex heterocycles.[9] BCP strategies aim to access acyclic precursors to complex molecules in as few steps as possible from commercially available building blocks utilizing simple, efficient reactions to build the precursors while maximizing atom economy. Cyclization of these intermediates makes use of intramolecular functional group pairing to facilitate the construction of skeletally complex small molecules. Through the use of selective functional group pairing, a variety

of skeletally complex molecules can be constructed from a common linchpin, thus making BCP an enabling strategy for DOS library production (Figure 5). To this end, the linchpins in this library were so designed that they can utilize orthogonal coupling reactions to selectively cyclize into a variety of chemical structures.

**Figure 5:** *Build/Couple/Pair Approach to Small Molecule Synthesis*
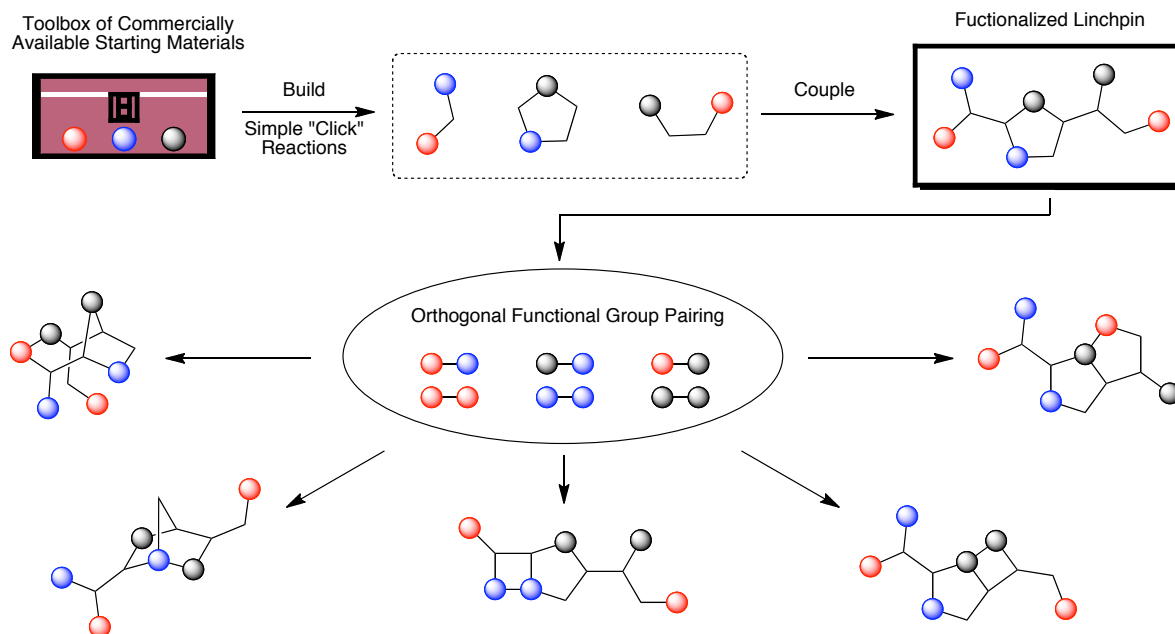


Key to the build phase are simple, efficient reactions that have been termed "click" reaction. Click reaction are characterized as being modular, clean, high-yielding reactions that can utilize commercially available starting materials with simple reaction conditions and a strong thermodynamic driving force (Figure 6).[10] Some of examples of well known click reactions include common carbonyl coupling reactions, nucleophilic additions, and heteroatom-carbon bond forming. Click reactions are integral components of an efficient and reliable route to highly functionalized linchpins in what is termed a "Click, click, cyclize" strategy. Key click reactions in the formation of described sulfonamide linchpins include the ring opening of an epoxide to generate an amino

7

alcohol, sulfonylization of a primary amine, and the diversification of the secondary

sulfonamide as well as the final oxa-Michael and Baylis-Hillman cyclization methods.

**Figure 6:** *Properties of Click Reactions*
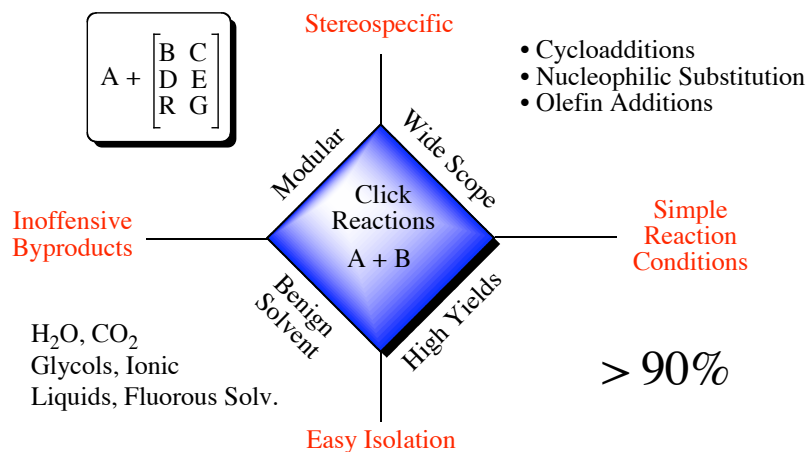


### 1.4 Developing DOS Methodologies towards Library Production

Screening for unique molecules requires a set of metrics as well as an extensive

pool of known molecules to compare against, a task accomplished with computational

aid.[11] The thus termed 'in silico' screening is invaluable in its ability to determine which

molecules represent areas of unexplored space. It is analogous to HTS in that it is a rapid

assaying technique and therefore works best with a library of potential molecular

structures. Candidates that show high diversity scores represent area of chemical space

unpopulated by the chemical database and possible untapped biological properties. By

developing methods that produce such skeletally diverse compounds, untapped chemical

space can effectively be 'mined' for bioactivity.

However, the production of unique molecular structures through traditional, linear

routes is inadequate for the demands of HTS. Therefore, DOS approaches to library

production often rely on diverging methodologies[12], utilizing a forward thinking rational

to design structurally different molecules accessible through common intermediates. In

8

addition, these diverging routes are characterized by simple, efficient coupling reactions which enable easy, rapid construction of molecules, also a hallmark of DOS approaches. A methodology that enables access to a variety of chemical structures is devised by pairing selected coupling reactions and commercially available starting materials from a common toolbox of each (Figure 7). The DOS approach is further expanded through rationally designed molecules with variety of functional groups, capable of undergoing orthogonal pairings to yield differing chemical structures simply by changing reaction conditions. These armed structures, termed linchpins, in combination with the toolbox approach to molecular assembly serve as defining aspects for flexible, modular DOS methodologies.

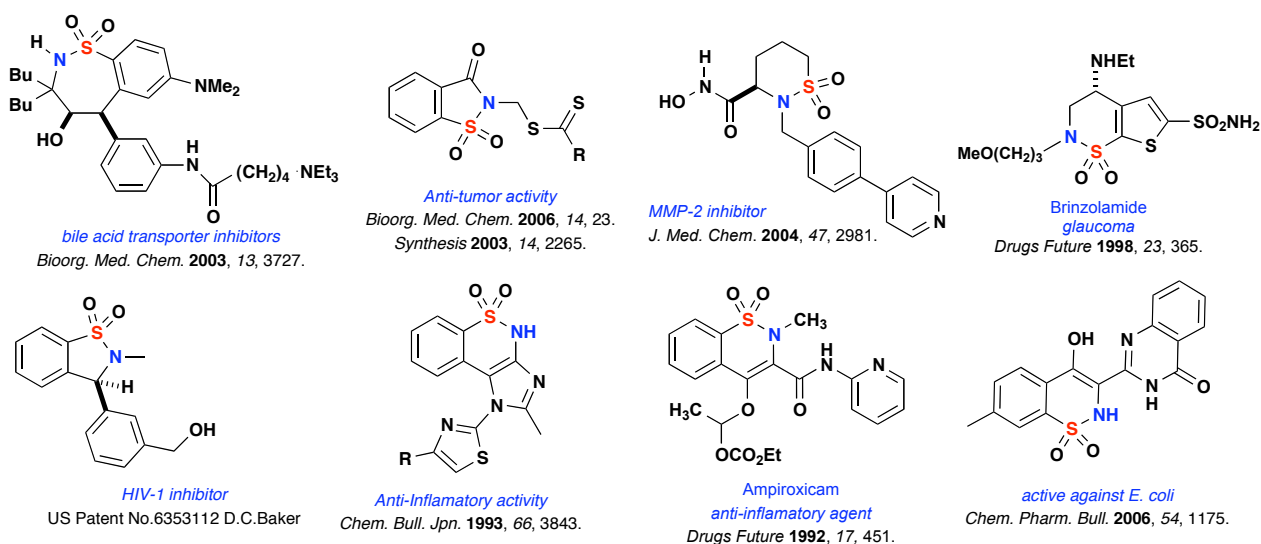**Figure 7:** *Developing DOS Methodologies*
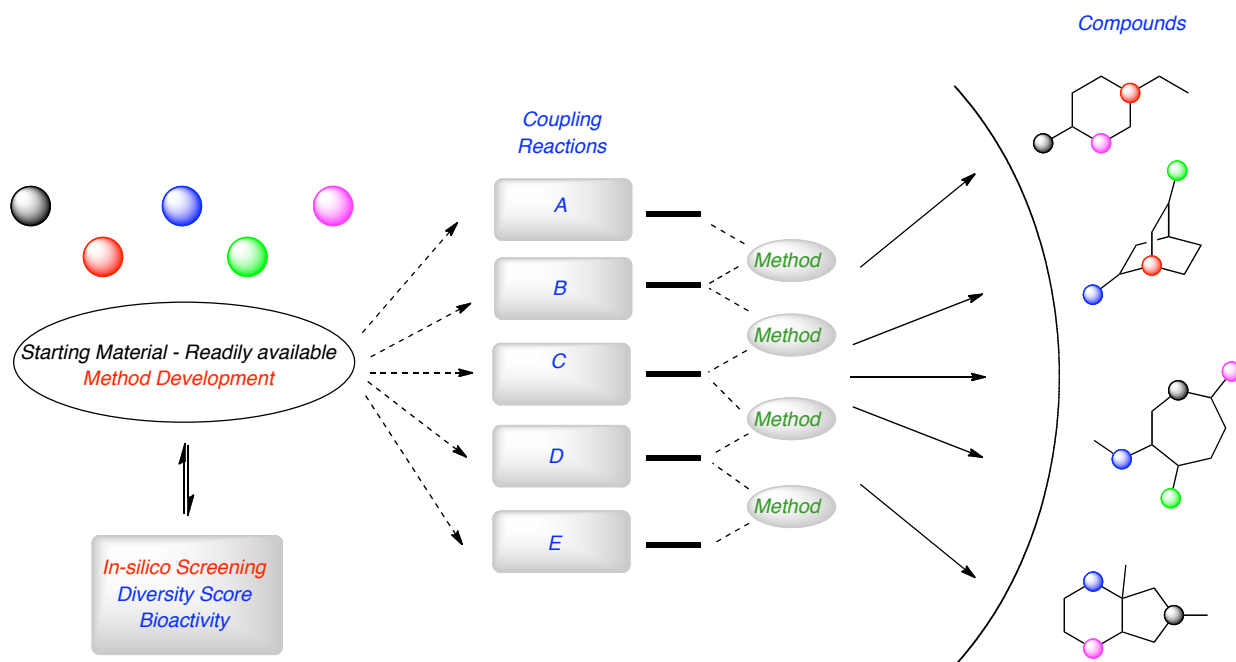


## 1.5 The Potential of Sulfonamides as Library Targets

However, simply producing unique molecules is not enough to effectively explore the vast number of potentially synthesizable compounds. Therefore, along with *in*

*silico* screening, a biological rational is required to provide a metric by which potential drug candidates can be selected. Commonly this entails the incorporation of an established biologically active core structures into the molecular design or constructing small molecules which are analogous to known bioactive structures.

A well-known bioactive motifs is the sulfonamide (Figure 8). Sulfonamides have a history of medicinal applications, dating back to Prontosil in the 1930's, with over 5.400 permutations of the structure in known compounds.[13] Originally only known as antimicrobials, sulfonamides' pharmacological profile has expanded into their use a wide variety of medications. In particular, sulfonamide-containing heterocycles (sultams) have been shown to exhibit wide-ranging, potent biological activity[14] including: the anti-inflammatory agents Ampiroxicam,[15] MMP-2 inhibitor,[16] HIV integrase inhibitor,[17] selective inhibitors of Calpain I,[18] the anti-epileptic agent sulthiame,[19] (Figure 1) and brinzolamide for the treatment of glaucoma.[20]

**Figure 8:** *Bioactive Sulfonamides*



bile acid transporter inhibitors
*Bioorg. Med. Chem.* **2003**, *13*, 3727.

Anti-tumor activity
*Bioorg. Med. Chem.* **2006**, *14*, 23.
*Synthesis* **2003**, *14*, 2265.

MMP-2 inhibitor
*J. Med. Chem.* **2004**, *47*, 2981.

Brinzolamide
glaucoma
*Drugs Future* **1998**, *23*, 365.

HIV-1 inhibitor
US Patent No.6353112 D.C.Baker

Anti-Inflamatory activity
*Chem. Bull. Jpn.* **1993**, *66*, 3843.

Ampiroxicam
anti-inflamatory agent
*Drugs Future* **1992**, *17,* 451.

active against E. coli
*Chem. Pharm. Bull.* **2006**, *54*, 1175.

Compounds containing the sulfonamide moiety are promising candidates in drug discovery[21] due to their similarity to biologically important amides, but being unknown in

nature. Furthermore, these drug-like candidates differ in that they are non-hydrolyzable, display a tetrahedral geometry, and moreover demonstrate their own unique chemical and biological properties (Figure 9)[22]. Moreover, their cyclic analogues sulfonamides (sultams) have also attracted attention recently due to potent biological activity.[23] These structures are easily accessed through the simple coupling of a sulfonyl chloride and an amine, both of which are available in a wide variety, providing easy access to an extensive number of possible combinations. Thus, sultams present attractive targets for the production of small molecule libraries.

**Figure 9:** *Sulfonamide vs Amides*
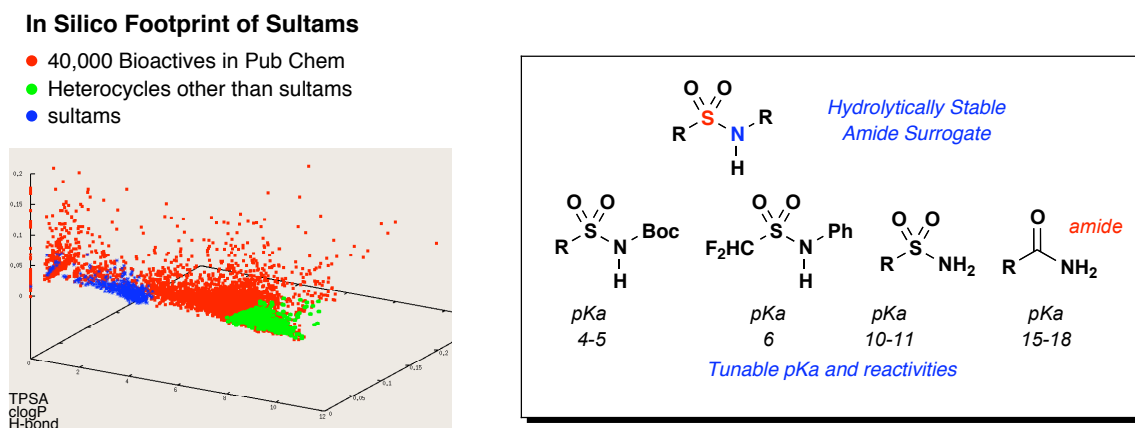


The aforementioned broad-spectrum activity of sulfonamides and their related analogs has prompted investigation of new methods for their synthesis. Among the methods that have recently emerged as powerful methods for the generation of sultams derivatives are Pictet-Spengler,[3a] Friedel-Craft,[24] dianion,[25] cyclization of aminosulfonyl chlorides,[26] [3+2] cycloadditions,[27] Diels-Alder,[28] Heck reaction,[29] RCM[30] and other transition-metal catalyzed reactions.[31] The desire to explore new methods of sultam formation prompted investigation into the reaction profile of the vinyl sulfonamide moiety.[32]

11

**Figure 10**: *A DOS Linchpin Approach to Sultam Synthesis*
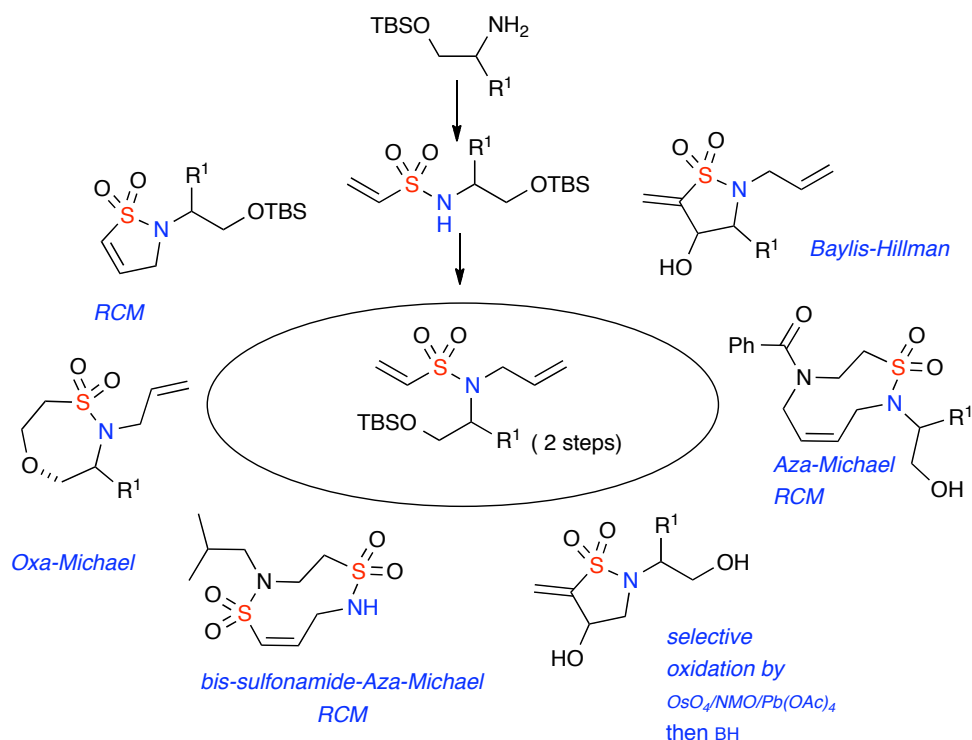


The oxa-Michael[31] and Baylis-Hillman[32] reactions are simple, yet powerful methods for bond formation. Although discovered a long time ago[35], the intramolecular version of the Michael reaction has seen a renaissance and has been extensively utilized in natural product synthesis for over two decades. Although the Michael accepting ability of vinyl sulfones is well documented,[36] their vinyl sulfonamide counterparts have assumed a far less prominent role as viable Michael acceptors.[37] In contrast, the intramolecular version of the Baylis-Hillman reaction has only recently gained favor, where elegant work in this area has elevated the status of this variant.[38] Although the Michael accepting ability of vinyl sulfones is well documented, their vinyl sulfonamide

counterparts have assumed a far less prominent role as viable Michael acceptors. Herein we report the first examples of intramolecular oxa-Michael and Baylis-Hillman reactions on vinyl sulfonamides to afford an array of novel five, six, seven and eight-membered sultam derivatives in good to excellent yields. Good to excellent levels of diastereoselectivity were achieved ultimately yielding a number of interesting sultam scaffolds for library production.

**Literature cited:**

(1) Paul, S. M. Mytelka, D. S. Dunwiddie, C. T. Persinger, C. C. Munos, B. H. Lindborg, S. R. Schacht, A. L. *Nature Rev. Drug Disc.* **2010**, *9*, 203–214.

(2) (a) Schriber, S. L. *Bioorg. Med. Chem.* **1998**, *6*, 1127-1152. (b) Eggert, U. S.; Mitchison, T. J. *Curr. Opin. Chem. Biol.* **2006**, *10*, 232-237. (c) Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74-84. (d) Dobson, C. M. *Nature*, **2004**, *432*, 824-828.

(3) Bohacek et. al., *Med. Res. Rev.* **1996**, *16*, 3-50.

(4) Newman, D. J. Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461–477.

(5) Feher, M. Schmidt, J. M. *J Chem Inf Comput Sci* **2003**, *43*, 218–227.

(6) Schreiber, S. L. *Science* **2000**, *287*, 1964–1969.

(7) Sternson, S. M.; Louca, J. B.; Wong, J. C.; Schreiber, S. L. *J. Am. Chem. Soc.*, **2001**, *123*, 1740–1747

(8) Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, IV, M. D.; Liu, H.; Lowe, J. T.; Marie, J.; Mulrooney, C. A.; Pandya, B. A.; Rowley, B.; Ryba, T. D.; Suh, B.; Wei, J.; Young, D. W.; Akella, L. B.; Ross, N. T.; Zhang, Y.; Fass, D. M.; Reis, S. A.; Zhao, W.; Haggarty, S. J.; Palmer, M.; Foley, M. A. *J. Am. Chem. Soc.*, **2010**, *132*, 16962–16976

(9)    (a)Kubota, H.; Lim J, Depew K. M., Schreiber S. L. Chem Biol. 2002, 9, 265-276.

(b) Zhang, W.; Lu, Y,; Hiu-Tung Chen, C.; Zeng, L.; Kassel, D.B.; J. Comb. Chem. 2006, 8, 687-695.

(10)   Kolb, H.; Finn, M. G.; Sharpless, K. B *Angew. Chem., Int. Ed.* **2001** *40*, 2004.

(11) (a) Schneider, G.; Fechner, U. *Nat Rev Drug Discov* **2005**, *4*,  649–663. (b) Jorgensen, W. L. *Science* **2004**, *303*, 1813–1818.

(12)   Kumagai, N. Muncipinto, G.; Schreiber S. L. *Angew. Chem. Int. Ed.* **2006** *45*, 3635.

(13)   Hager, T. The Demon Under the Microscope: From Battlefield Hospitals to Nazi Labs, One Doctor's Heroic Search for the World's First Miracle Drug. Harmony Books: New York City, 2006.

(14) (a) Drews, J. Science **2000**, *287*, 1960-1964. (b) Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. *Curr. Med. Chem.* **2003**, *10*, 925-953.

(15) (a) Silvestri, R.; Marfè, G.; Artico, M.; La Regina, G.; Lavecchia, A.; Novellino, E.; Morgante, M.; Di Stefano, C.; Catalano, G.; Filomeni, G.; Abruzzese, E.; Ciriolo, M. R.; Russo, M. A.; Amadori, S.; Cirilli, R.; La Torre, F.; Salimei, P. S. *J. Med. Chem.* **2006**, *49*, 5840-5844. (b) Lebegue, N.; Gallet, S.; Flouquet, N.; Carato, P.; Pfeiffer, B.; Renard, P.; Léonce, S.; Pierré, A.; Chavatte, P.; Berthelot, P. *J. Med. Chem.* **2005**, *48*, 7363-7373.

(16) Rabasseda, X.; Hopkins, S. J. Ampiroxicam : A prodrug of piroxicam devoid of gastrointestinal toxicity. *Drugs of Today* **1994**, *30*, 557-563.

(17) Cherney, R. J.; Mo, R.; Meyer, D. T.; Hardman, K. D.; Liu, R. Q.; Covington, M. B.; Qian, M.; Wasserman, Z. R.; Christ, D. D.; Trzaskos, J. M.; Newton, R. C.; Decicco, C. P. Sultam Hydroxamates as Novel Matrix Metalloproteinase Inhibitors. *J. Med. Chem.* **2004**, *47*, 2981-2983.

(18) Brzozowski, Z.; Saczewski, F.; Neamati, N. Synthesis and anti-HIV-1 activity of a novel series of 1,4,2-benzodithiazine-dioxides. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5298-5302.

(19) Wells, G. J.; Tao, M.; Josef, K. A.; Bihovsky, R. 1,2-Benzothiazine 1,1-dioxide P2-P3 peptide mimetic aldehyde calpain I inhibitors. *J. Med. Chem.* **2001**, *44*, 3488-3503.

(20) Tanimukai, H.; Inui, M.; Harigushi, S.; Kaneko, J. Antiepileptic property of inhibitors of carbonic anhydrase. *Biochem. Pharmacol.* **1965**, *14*, 961-970.

(21) (a) Drews, J. *Science* **2000**, *287*, 1960–1964. (b) Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. *Curr. Med. Chem.* **2003**, *10*, 925–953.

(22) (a) Drews, J. Science **2000**, *287*, 1960-1964. (b) Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. *Curr. Med. Chem.* **2003**, *10*, 925-953.

(23) ( a) Silvestri, R.; Marfè, G.; Artico, M.; La Regina, G.; Lavecchia, A.; Novellino, E.; Morgante, M.; Di Stefano, C.; Catalano, G.; Filomeni, G.; Abruzzese, E.; Ciriolo, M. R.; Russo, M. A.; Amadori, S.; Cirilli, R.; La Torre, F.; Salimei, P. S.

*J. Med. Chem.* **2006**, *49*, 5840-5844. (b) Lebegue, N.; Gallet, S.; Flouquet, N.; Carato, P.; Pfeiffer, B.; Renard, P.; Léonce, S.; Pierré, A.; Chavatte, P.; Berthelot, P. *J. Med. Chem.* **2005**, *48*, 7363-7373)

(24) Wroblewski, T.; Graul, A.; Castaner, J. Brinzolamide. *Drugs Future* **1998**, *23*, 365-369.

(25) Silvestri, R.; Marfè, G.; Artico, M.; La Regina, G.; Lavecchia, A.; Novellino, E.; Morgante, M.; Di Stefano, C.; Catalano, G.; Filomeni, G.; Abruzzese, E.; Ciriolo, M. R.; Russo, M. A.; Amadori, S.; Cirilli, R.; La Torre, F.; Salimei, P. S. *J. Med. Chem.* **2006**, *49*, 5840-5844.

(26) (a) Bravo, R. D.; Cánepa, A. S. *Syn. Comm.* **2002**, *32,* 3675-3680. (b) Orazi, O.O.; Corral, R. A.; Bravo, R. *J. Het. Chem.* **1986**, *23,* 1701-1708. (c) Katritzky, A. R.; Wu, J.; Rachwal, S.; Rachwal, B.; Macomber, D. W.; Smith, T. P. *Org. Prep. Proced. Int.* **1992**, *24*, 463-467.

(27) Lee, J.; Zhong, Y.-L.; Reamer, R. A.; Askin, D. *Org. Lett.* **2003**, *5,* 4175-4177.

(28) Enders, D.; Moll, A.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, 1271-1274.

(29) Chiacchio, U.; Corsaro, A.; Rescifina, A.; Bkaithan, M.; Grassi, G.; Piperno, A.; *Tetrahedron* **2001**, *57*, 3425-3433.

(30) (a) Metz, P.; Seng, D.; Fröhlich, R. *Synlett* **1996**, 741-742. (b) Plietker, B.; Seng, D.; Fröhlich, R.; Metz, P. *Tetrahedron* **2000**, *56*, 873-879. (c) Rogatchov, V. O.; Bernsmann, H.; Schwab, P.; Fröhlich, R.; Wibbeling, B.; Metz, P. *Tetrahedron*

*Lett.* **2002**, *43*, 4753-4756. (d) Greig, I. R.; Trozer, M. J.; Wright, P. T. *Org. Lett.* **2001**, *3*, 369-371. (e) Wanner, J.; Harned, A. M.; Probst, D. A.; Poon, K. W. C.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R. *Tetrahedron Lett.* **2002**, *43*, 917-921.

(31) (a) Merten, S.; Fröhlich, R.; Kataeva, O. *Adv. Synth. Catal.* **2005**, *347*, 754-758. (b) Vasudevan, A.; Tseng, P-S.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 8591-8593.

(32) (a) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239-2258. (b) Moriggi, J.-M.; Brown, L. J.; Castro, J. L.; Brown, R. C. D. *Org. Biomol. Chem.* **2004**, *2*, 835-844. (c) Freitag, D.; Schwab, P.; Metz, P. *Tetrahedron Lett.* **2004**, *45*, 3589-3592. (d) Karsch, S.; Freitag, D.; Schwab, P.; Metz, P. *Synthesis* **2004**, *10*, 1696-1712.

(33) Zhou, A; Hanson, P. R. *Org. Lett.* **2008**, *10*, 2951-2954.

(34) (a) Loydl, F. *Justus Liebigs Ann. C* **1878**, *192*, 80-89. (b) Berkessel, A. *Methods of Organic Chemistry (Hueben-Weyl) 4$^{th}$ ed.* **1952,** Vol. E21e **1995** pp 4818-4856 and references cited therein. (c) Enders, D; Haertwig, A. Raabe, G.; Runsink, J. *Angew. Chem. Int. Ed.* **1996**, *35*, 2388-2390 and references cited therein. (d) Shi, Y-L.; Shi, M. *Org. Biomol. Chem.* **2007**, *5*, 1499-1504.

(35) (a) Baylis, A. B.; Hillman, M. E. D. German Patent 2155113, 1972; *Chem. Abstr.* 1972, *77*, 34174q. (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811-891.

(36)  (a) Roth, F.; Gygax, P.; Frater, G. *Tetrahedron Lett.* **1992***, 33*, 1045-1048. (b) Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002***, 124*, 2402-2403. (c) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404-2405. (d) Keck, G. E.; Welch, D. S. *Org. Lett.* **2002**, *4*, 3687-3690. (e) Huddleston, R. R.; Krische, M. J. *Synlett.* **2003**, 12-21.  (f) Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230-6231. (g) Yeo, J. E.; Yang, X.; Kim, H. J.; Koo, S. *Chem. Commun.* **2004**, 236-237. (h) Aroyan, C. E.; Vasbinder, M. M.; Miller, S. J. *Org. Lett.* **2005**, 7, 3849-3851. (i) Shi, M.; Chen, L. H.; Li, C. Q. *J. Am. Chem. Soc.* **2005**, *127*, 3790-3800. (j) Krafft, M. E.; Haxell, T. F. N.; Seibert, K. A.; Abboud, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4174-4175. (k) Teng, W.-D.; Huang, R.; Kwong, C. K.-W.; Shi, M.; Toy, P. H. *J. Org. Chem.* **2006**, *71*, 368-371. (l) Nakano, A.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2006**, *8*, 5357-5360.

(37) (a) Truce, W. E.; Wellisch, E. *J. Am. Chem. Soc.* **1952**, *74,* 2881-2884.  (b) Luis, A.-L.; Krische, M. J. *Synthesis* **2004**, 2579-2585. (c) Meadows, D. C.; Gervay-Hague, J. *Med. Res. Rev.* **2006**, *26*, 793-814. (d) Oh, K. *Org. Lett.* **2007**, *9,* 2973-2975. (e) Esteves, A. P.; Silva, M. E.; Rodrigues, L. M.; Oliveira-Campos, A. M. F.; Hrdina, R. *Tetrahedron Lett.* **2007**, *48*, 9040-9043. (f) Das, I.; Pal, T. K.; Pathak, T. *J. Org. Chem.* **2007**, *72*, 9181-9189.

(38) (a) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E. *J. Am. Chem. Soc.* **1989**, *111*, 6682-6690. (b) Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446-2453. (c) Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 6087-6090. (d) Ahmed, M. M.; Mortensen, M. S.; O'Doherty, G. A. *J. Org. Chem.* **2006**, *71*, 7741-7746. (e)

Chandrasekhar, S.; Rambabu, C.; Shyamsunder, T. *Tetrahedron Lett.* **2007**, *48*, 4683-4685.

**Chapter 2**

**Development of Oxa-Michael and Baylis-Hillman Methodologies**

## 2.1 Rationale For Sultam Library Design

In order to produce libraries of compounds sufficient to meet the demands of HTS, a DOS approach to sultam synthesis was developed. To this end the aforementioned "build, couple, pair" strategy was utilized as a core principle in the methodology design. A strategy for DOS sultam production focused on the use of easily accessed acyclic sulfonamide linchpins and orthogonal coupling pathways to access a variety of unique structures (Figure 1).

**Figure 1:** *Functional Group Pairing on a Sulfonamide Linchpin*
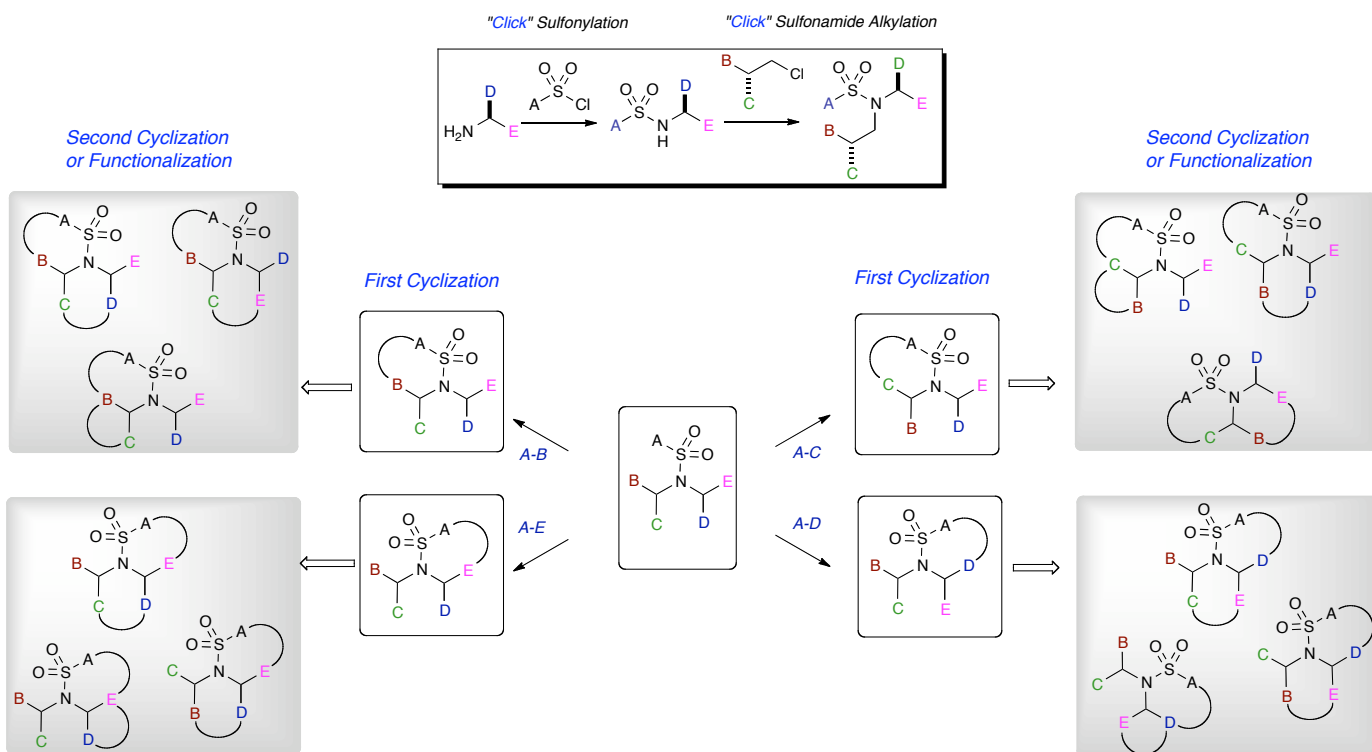


The vinyl sulfonamide moiety is an attractive lynchpin component as it exhibits unique chemical properties and special reactivities (Figure 2). The conjugated olefin has both nucleophilic and electrophilic components due to the electron-withdrawing nature of the sulfonyl group, enabling the use of a variety of novel cyclization methods through generally mild conditions.[1] In addition, the electronegativity of the oxygen in the sulfonyl group results in an acidic –NH, demonstrating a lower pKa than corresponding amides,

and making sulfonamide alkylation relatively less demanding[2]. The sulfur's size in combination with the longer C-S bond length is expected cause angle compressing of the sulfonamide's functionalized arms, allowing ring closures usually deemed inaccessible according to Baldwin's rules[3]. Furthermore, the *gem*-dioxa groups are also believed to restrict rotation around the sulfur atom, affecting reactions in a manner similar to the Thorpe-Ingold effect,[4] as seen in ring-closing metathesis of sulfonamides.[5] Thus sulfonamide cyclizations are expected to proceed at increased reaction rates and milder conditions due to functional groups being brought closer together.

**Figure 2:** *Properties of Vinyl Sulfonamides*
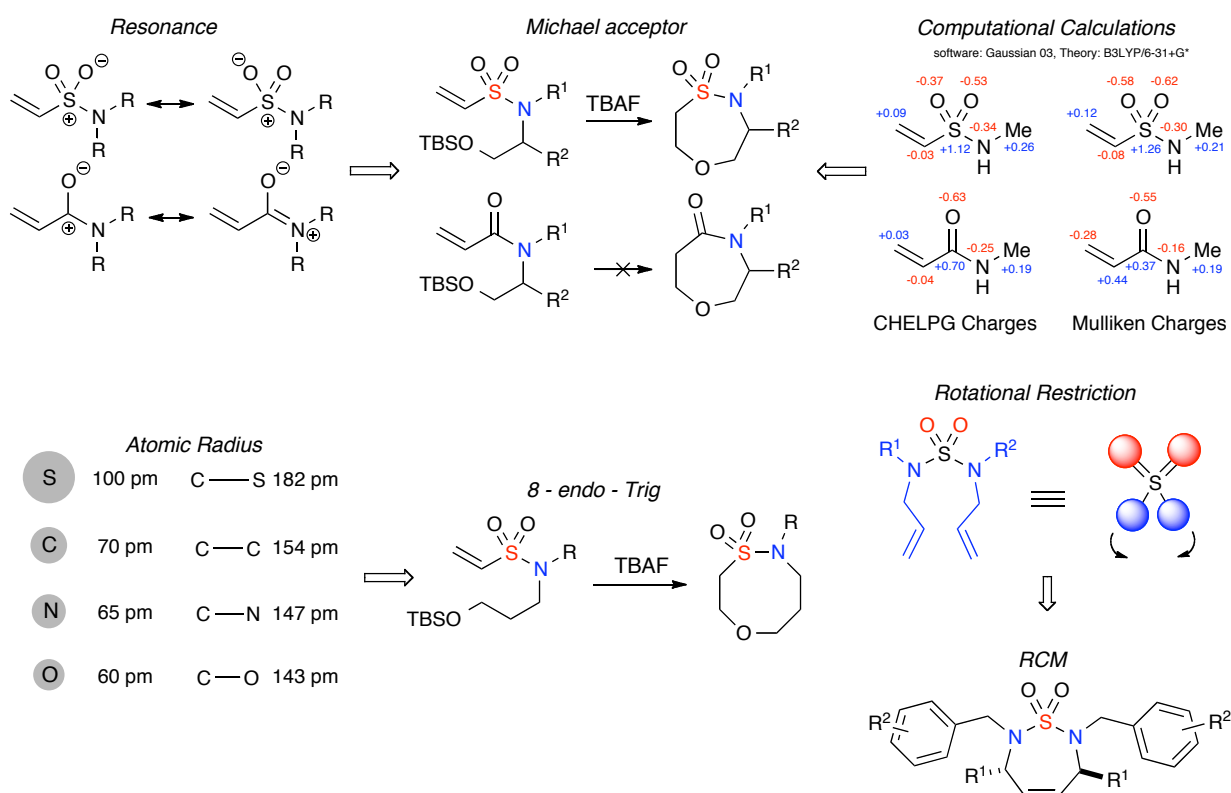


This wide range of chemical properties allows this moiety participate in a variety of coupling reactions. In addition, there is a wide availability of building blocks able to incorporate diversity elements into the sulfonamide, including benzyl bromides, amines,

and benzoyl chlorides. Literature gives evidence of the wide-ranging reaction profile of sulfonamides in Diels-Alder[6], Heck[7], indium-initiated radical addition, and [3 + 2] cycloaddition reactions[8]. Further work has shown their feasibility in ring-closing metathesis (RCM)[9], intramolecular oxa-Michael, and Baylis-Hillman[10] cyclizations to generate sultams. This makes investigation into sulfonamide library production a particularity fruitful endeavor, with a large number of possible synthetic routes to explore (Figure 3).

**Figure 3**: *Sultams Accessible from the Vinyl Sulfonamide Linchpin*
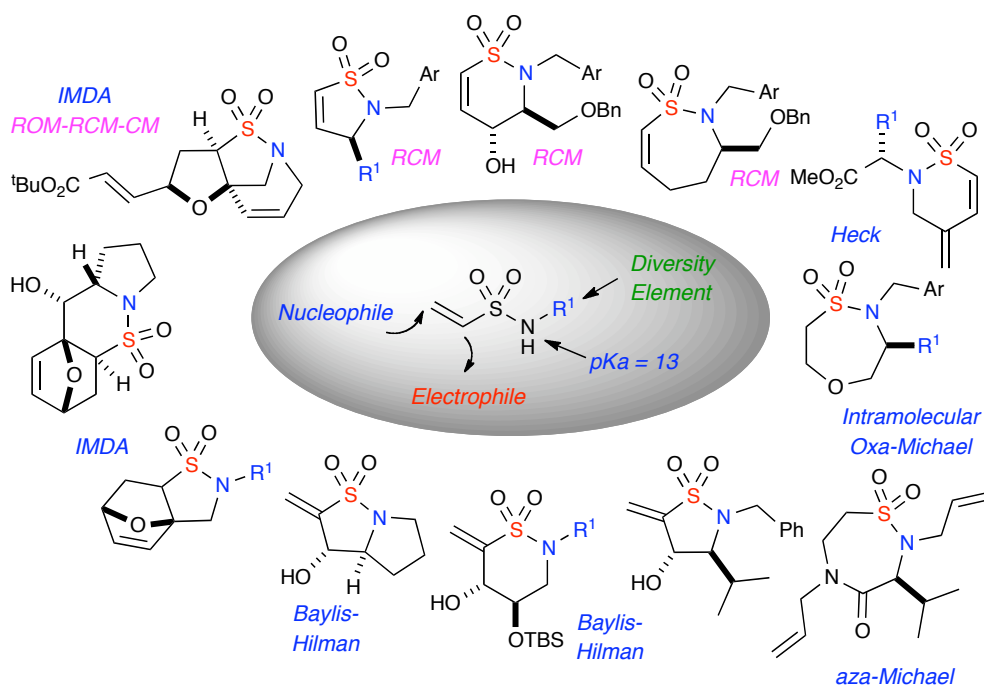


The first BCP strategy sought to make use of the excellent Michael-acceptor properties of the vinyl sulfonamide for an intramolecular cyclization. To this end, it was envisioned that a deprotonated hydroxy group would be ideal, thus allowing for the construction of the sultam from commercially available amino alcohols. While previous oxa-Michael reactions have demonstrated issues with selectivity and reactivity[11], it was thought that the intramolecular nature of the cyclization combined with the reactivity of

the activated olefin would overcome this. In addition, a second strategy would make use of the presence of a terminal hydroxy group in the oxidation to an aldehyde, followed by a Baylis-Hillman cyclization to the nucleophilic carbon of the vinyl sulfonamide. This would form a highly functionalized sultam conserving both the vinyl sulfonamide and hydroxy groups, and enabling further diversification steps. Further cyclization methods were also envisioned with this linchpin, including ring-closing metathesis (RCM), but not explored at this time (Figure 4).

**Figure 4**: *Oxa-Michael and Baylis-Hillman Pathways*
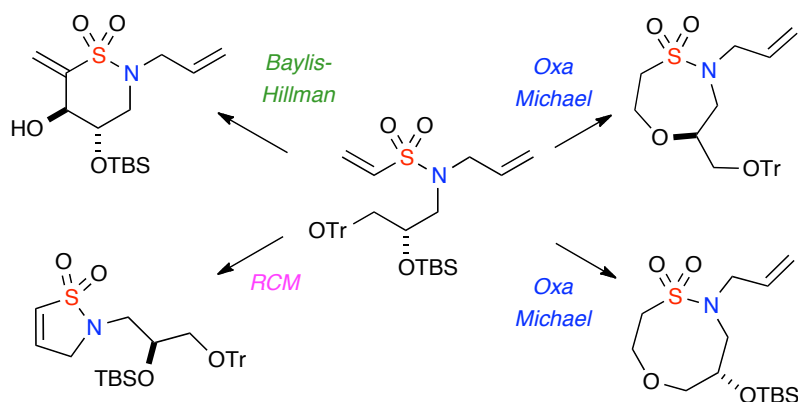


The amino alcohol represents a highly desirable starting material. They are available in a wide variety of forms, with different substitutions, chirality, and chain lengths (Figure 5).[12] This allows for the development of differing skeletal structures from the same methodology simply by changing a single component of the synthesis. Furthermore, the presence of a stereogenic center in many amino alcohols allows for the easy incorporation of chirality in a molecule. Thus the amino alcohol moiety offers access to a variety of chiral 7- and 8-member oxa-Michael products through the simple incorporation of a commercially available building block. In addition, the amino alcohol moiety is present in a number of natural products, including amino sugars, nucleosides, and nucleotides.[13]

**Figure 5**: *Commercially Available Amino Alcohols*



R = 2-Me, 3-Me, 4-Me, 3-F,
4-F, 3-Cl, 2-Cl, 4-OH,
4-NO2, 3,4-OMe, 4-OMe
2-OMe, 4OBn, 4-Cl

R = 2-F, 3-F, 4-F, 4CN,
3-I, 3,4-F, 4-CF3,
4-OBn, 2-OMe

R = Me, Et, Ph, Bn, iPr,
OBn,
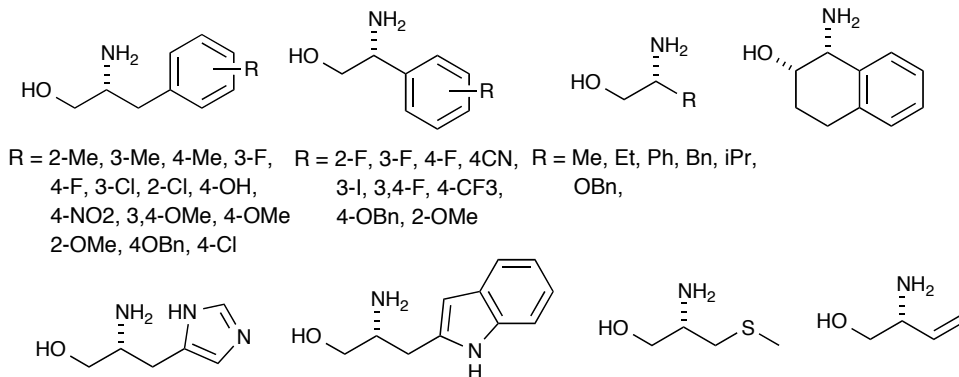
In order to evaluate how unique the proposed compounds are compared to other known structures, they were submitted for *in silico* screening. The diversity model utilized at KU utilizes an algorithm to compare structures to known molecules within the database. The algorithm utilizes 5 properties called diversity elements (high positive charge, high negative charge, high polizerability, low polizerability, and number of H-bonding atoms) scaled in 10 degree increments to compare structures, thus creating a matrix of $10^5$ or 100,000 cells[14] (Figure 6). Proposed molecules are assigned to cells based on how the algorithm utilizes these diversity elements to interpet their structure. Compound diversity scores are calculated based on the number of known compounds populating their assigned cells relative to the average cell population, which is weighted relative to the compound population of individual cells rather than a straight average.

**Figure 6:** *Calculating Diversity Scores*



Diversity Model: 5 diversity elements
10 increments
100,000 possible cells
~6,000 occupied
Ave. weighted population per cell: 24,123
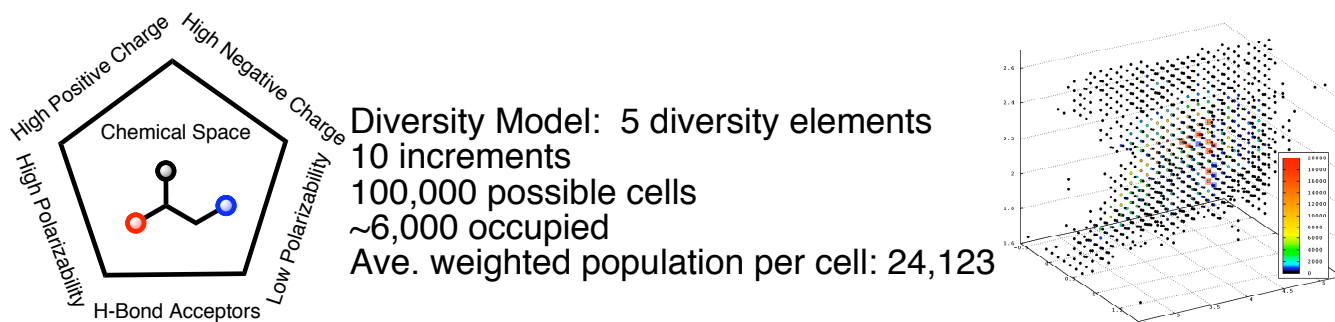
Therefore in a matrix with an average cell population of 98.1, a compound in a cell with a population of 98 is assigned a diversity score of 1, as its diversity is relatively equal to the average population of the matrix. A compound in a cell with half the average population would have a score of 0.5, being twice as unique as the average compound, just as a compound in a cell with twice the average population would be half as diverse, receiving a score of 2. Ideally, compounds screened as possible candidates for DOS should have a diversity score of 0.5 or less to ensure compound libraries represent less populated areas chemical space and are relatively dissimilar to klnown chemical compounds. The submitted structures showed relatively low diversity scores, (Figure 7) indicating good target structures for DOS.

**Figure 7:** *Diversity Scores of Selected Sultams*



| 0.912103536 | 0.260590594 | 0.387130879 | 0.387130879 |
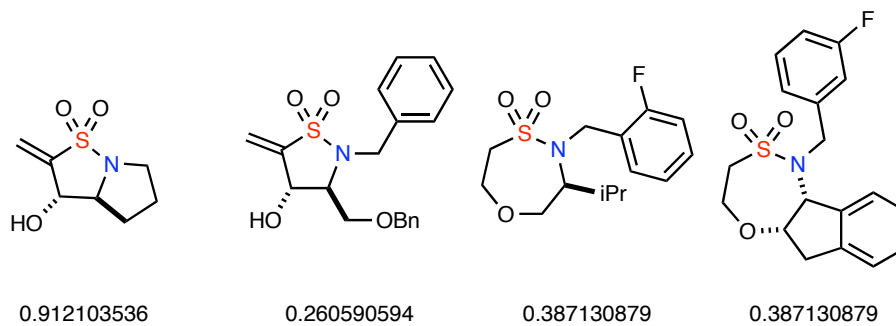
## 2.2 Oxa-Michael Strategies for Sultam Synthesis

In order to ensure that the sulfonylation would chemoselectivly target the amine under reaction conditions, the hydroxy group would have to be protected. For this, a silyl ether was chosen due to the mild conditions of protection and deprotection,[15] and its selectivity for the alcohol over the amine[16]. Furthermore the following reaction steps and workup were devoid of conditions that would deprotect the silyl ether. The protection proceeded easily by the addition of a slight excess of TBSCl to a stirring solution of the amino alcohol and triethylamine in DCM with a catalytic amount of imidazole. The

27

reaction was allowed to stir overnight, during which it formed a thick slurry from precipitated salts. Workup involved extraction 3x with DCM, a brine wash, addition of sodium sulfate to remove excess moisture, filtration and rotary evaporation. This workup would be followed for all procedures unless otherwise noted. Following workup, the TBS-protected amino alcohols were isolated as a viscous, off-white, semi-crystalline liquid.

The assembly of the vinyl sulfonamide linchpins began with the reaction of 2-chloroethanesulfonyl chloride with various *TBS*-protected amino alcohols **1**. The sulfonyl chloride was added dropwise to a stirring solution of the TBS-protected alcohol and triethylamine in DCM. Due to the extremely exothermic nature of the sulfonylation, it was performed in an ice bath with the sulfonyl chloride added slowly to the reaction. A yellow color was noted during the addition of the sulfonyl chloride, most likely from the presence of the free sulfonamide base. The reaction proceeded rapidly and was complete in less than 2 hrs. Workup and isolation produced the products as yellow oils.

Diversification of the vinyl sulfonamides **2** proceeded through either benzylation or allylation methodologies. An excess (1.5 eq) of the diversification reagents were added in solution of the vinyl sulfonamide in acetonitrile with $K_2CO_3$ to maintain a basic environment.[17] The reaction mixture was refluxed at 80 ºC until complete (usually about 4 hrs). The increased nucleophilicity of the nitrogen allowed for smooth transformation, with all of the starting material converted to the vinyl sulfonamide linchpin **3**.

It was anticipated that following TBAF-initiated TBS-deprotection of the alcohol, a NaH-initiated Michael addition would have to be performed. However, it was found that TBAF addition led to the formation of oxygen anion, which subsequently underwent

oxa-Michael reactions in a single step to afford the unique seven-membered sultams **4** via 7-*endo* Trig ring closure pathways in excellent yields (Scheme 1). Thus, the reaction proceeded by the simple addition of 1 eq. of TBAF in THF to a stirring solution of the sulfonamide linchpin in THF. The reaction was complete in under 30 min, yielding thiooxaazepines in good yields and purities. The final products were purified by flash chromatography and Mass-Directed Fractionation (MDF) process and submitted for biological screening.

**Scheme 1**: *Oxa-Michael Synthesis of Sultams via 7-*endo-*Trig Ring Closure Pathway*
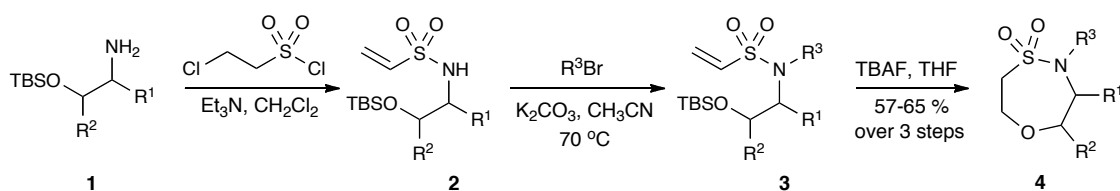


The high yields, mild reaction conditions, and little need for chromatography between steps led to interest in developing this procedure for a one-pot protocol. To achieve this, the TBS-protected amino alcohols were added to a sealed reaction tube and submitted to sulfonylation conditions. Following completion, the reaction solution was divided into separate reaction tubes for diversification. To each tube was added a separate diversification reagent and all tubes underwent the benzylation reaction conditions. Upon complete conversion, TBAF was added to the stirring reaction to initiate oxa-Michael cyclization. The crude reaction mixture was purified using chromatography to yield the products in good yields over 3 steps. Using this one-pot protocol it was possible to synthesize 5 compounds a day from a common starting material.

While the commercially available amino alcohols offer a wide variety of diversification, the synthesis of designed amino alcohols would expand the number of

compounds accessible through this synthetic route and possibly enable the incorporation of additional functionalities not available through commercial building blocks. To this end, the opening of trityl glycidyl ethers **5** with primary amines was investigated as a method for the production of amino alcohols (Scheme 2). In a minimum amount of methanol as a solvent, the amine, ether, and a catalytic amount of $Zn(ClO_4)_2 \cdot H_2O$ was allowed to stir overnight. The yellowish oil was immediately subjected to previously described TBS protection procedure to yield the double-protected amino alcohols **6** in excellent yields and purities. The synthesized amino alcohols were submitted to the oxa-Michael methodology, followed by a final deprotection of the trityl group to yield the thiaoxaazepines **8** in moderate yields.

**Scheme 2**: *Epoxide Ring Opening in Sultam Synthesis*
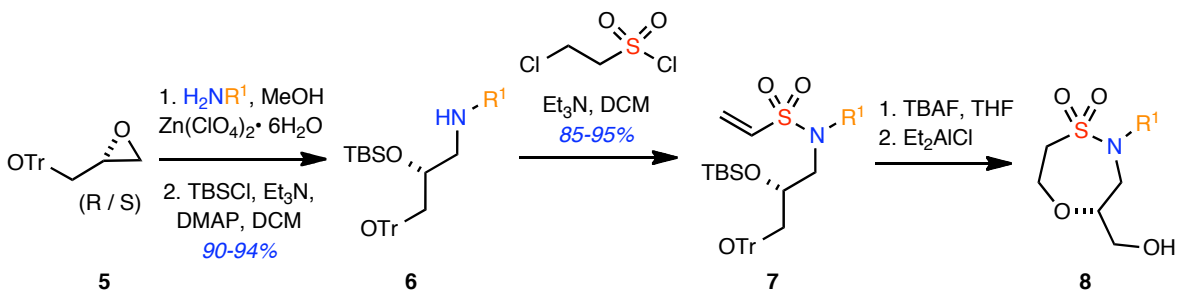


## 2.3 Baylis-Hillman Strategies for Sultam Synthesis

The Baylis-Hillman (BH) reaction is a powerful C-C bond-forming reaction, enabling the production of heterocycles and other cyclic structures containing allylic alcohol functional groups. It is catalyzed by the nucleophilic addition of an amine to an election deficient alkene, forming a zwitterion which then attacks an electrophilic aldehyde, finally eliminating the amine catalyst to form the allylic alcohol. Therefore the same electron-deficient nature of the vinyl sulfonamides that makes them excellent Michael acceptors and also makes the moiety suitable for BH cyclization.

The investigation of methodologies for the formation of the Baylis-Hillman precursor has led to the development of two differing synthetic routes toward BH-cyclized sultams. The first route makes use of a chemoselective oxidation of the terminal olefin to generate the corresponding aldehyde in the presence of the vinyl sulfonamide. The second pathway took the previously described vinyl sulfonamide lynchpin through a two-step deprotection and oxidation methodology to generate the reactive aldehyde. Both routes made use of the same BH cyclization conditions to synthesize highly functionalized 5 and 6-membered sultam derivatives.

The first methodology involved a key oxidation step that chemoselectivly targeted a terminal alkene over the vinyl sulfonamide to produce precursors for BH cyclizations (Scheme 3). To this extent, ozonolysis was selected, as it is a well-established method for the conversion of olefins to aldehydes. It was predicted that the electron-deficient vinyl sulfonamide would be resistant to ozonolysis, allowing for chemoselective oxidation of the terminal olefin.

**Scheme 3**: *Chemoselective Ozonolysis/Baylis-Hillman pathway*
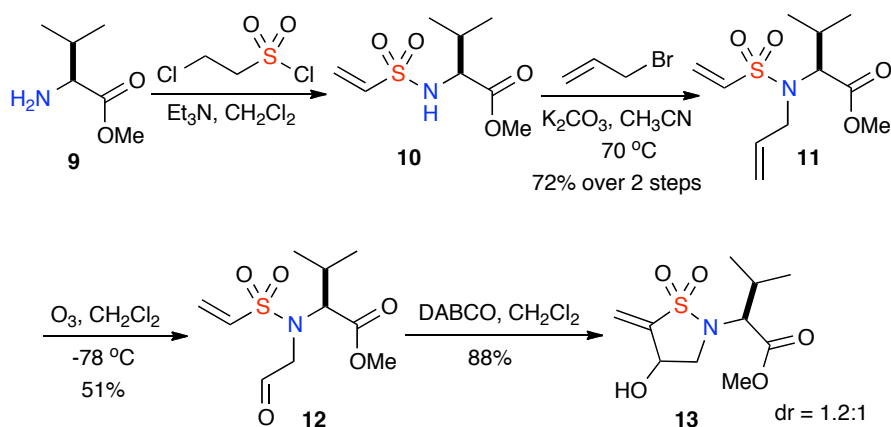


The synthesis began using primary amines **9** for the construction of the vinyl sulfonamides **10** from via previously described methods. Instead of benzylation, all

compounds were allylated to yield linchpins **11** with terminal olefins. Selective oxidation of the vinyl sulfonamides by ozonolysis proceeded by bubbling ozone through a solution of the sulfonamide in methyl sulfide spiked with Sudan III until the indicator's color faded. The vinyl sulfonamide aldehydes **12** were isolated in moderate yields and high purity. Intramolecular Baylis-Hillman proceeded rapidly to produce the 5-member cyclized products **13** in excellent yields. It was notable that unlike most intermolecular Baylis-Hillman reactions, which normally take a long time to complete, this Baylis-Hillman reaction proceeds in 2 to 4 h.

This chemoselective oxidation/Baylis-Hillman protocol was further extended to a chiral starting material (Scheme 4). The synthesis began with (*S*)-glycidyl ether **14** whereby treatment with trimethyl sulfonium iodide and butyl lithium at low temperature (-30 ºC) generated chiral allyl alcohol **15**.[28] Following Mitsunobu reaction of **15** with phthalimide and hydrazine,[29] chiral allyl amine **16** was obtained in 61% yield over 3 steps. Sulfonylation to **17**, followed by benzylation afforded **18**, which underwent chemoselective oxidation to generate aldehyde **19**. Baylis-Hillman cyclization of **19** afforded sultam **20** as an inseparable 4:1 diastereomer mixture in 86% yield.

**Scheme 4**: *Chemoselective Oxidation of Chiral Allyl Vinyl Sulfonamide to Make Baylis-Hillman Sultam Derivatives.*
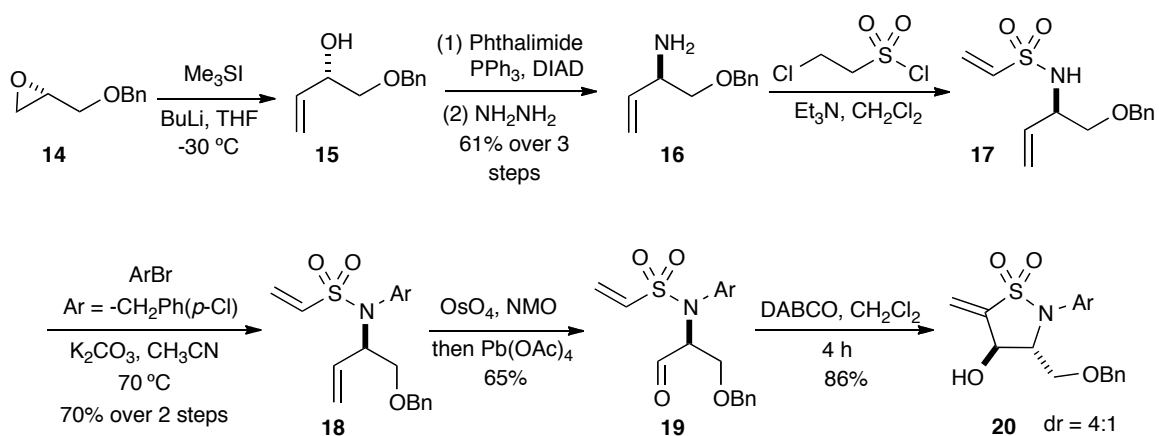
An alternative to the chemoselective oxidation of vinyl sulfonamides towards Baylis-Hillman precursors is the use of *TBS*-protected amino alcohols as starting materials. Using the same procedure as with the OM method, vinyl lynchpins were prepared as precursors for the BH cyclization. It was found aqueous HCl promotes *TBS*-deprotection without initiating the intramolecular oxa-Michael reaction, resulting in the formation of corresponding alcohol. This pathway is more attractive than the former chemoselective oxidation/Baylis-Hillman pathway due the ease of production from commercially available amino alcohols, the milder reaction conditions, and the utilization of a common synthetic route with the OM method, demonstrating the vinyl sulfonamide linchpin as a single molecular structure armed for differing intramolecular cyclization methods.

Investigation of the second pathway began with sulfonylation of chiral amino alcohols **21** (Table 3) to afford vinyl sulfonamides **22**. Following benzylation, vinyl sulfonamides **23** were obtained in excellent yields. Removal of *TBS*-protection by acid (10 mol% HCl) generated vinyl sulfonamide alcohols, which underwent oxidation by Dess-Martin periodate to yield vinyl sulfonamide aldehydes 30. Baylis-Hillman reactions of **24** produced five-membered sultams **25/26** in excellent yields with moderate to good

diastereoselectivity. Other organocatalysts such as brucine, quinine and quinidine were also used (Table 1) but proved less efficient than DABCO, resulting low yield and moderate selectivity.

**Scheme 5**: *Intramolecular Baylis-Hillman Protocol via Chiral Amino Alcohols*
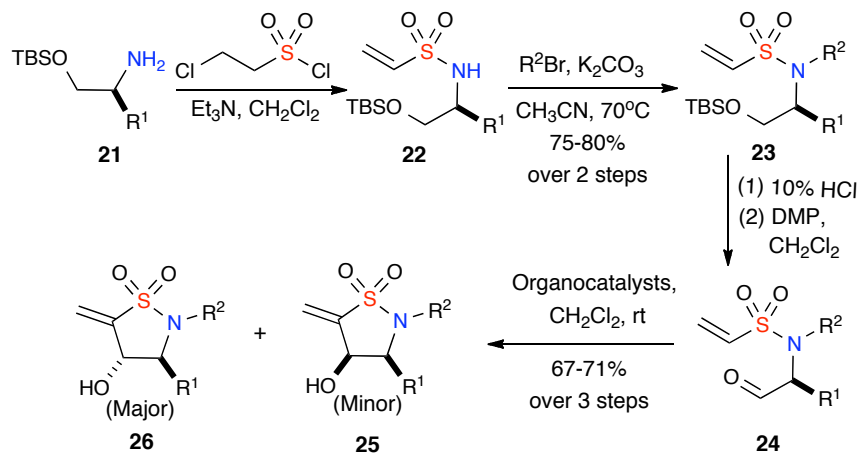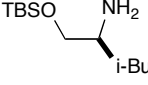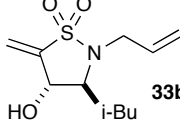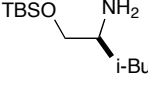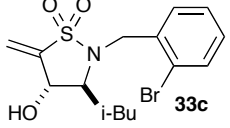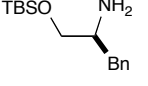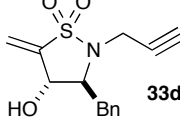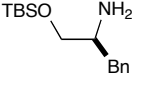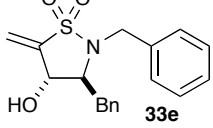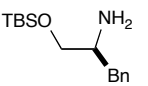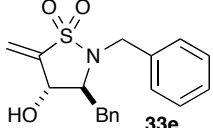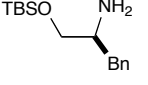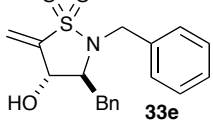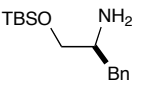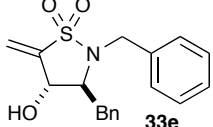


**Table 1:** *Catalysts for Baylis-Hillman Cyclization*

| Entry | Catalyst | Amino alcohol | Product | Yield (%)[a] | dr ratio |
|-------|----------|---------------|---------|-------------|----------|
| 1 | DABCO |  |  33a | 69 | 1.7:1 |

34

| | | | | | |
|---|---|---|---|---|---|
| 2 | DABCO | TBSO–CH(NH₂)(i-Bu) |  **33b** | 67 | 3.2:1 |
| 3 | DABCO | TBSO–CH(NH₂)(i-Bu) |  **33c** | 71 | 1.6:1 |
| 4 | DABCO | TBSO–CH(NH₂)(Bn) |  **33d** | 69 | 3.3:1 |
| 5 | DABCO | TBSO–CH(NH₂)(Bn) |  **33e** | 71 | 9.0:1 |
| 6 | Brucine | TBSO–CH(NH₂)(Bn) |  **33e** | 46 (72 h) | 10:1 |
| 7 | Quinine | TBSO–CH(NH₂)(Bn) |  **33e** | 45 (72 h) | 9.2:1 |
| 8 | Quinidine | TBSO–CH(NH₂)(Bn) |  **33e** | 42 (72 h) | 8.5:1 |

[a] Isolated yields from **23** to **25/26**.

Further investigation of the method to generate larger sultam rings utilized *TBS*-protected 3-amino-1-propanol **27** as a starting material. Sulfonylation with 2-chloroethanesulfonyl chloride to generate **28**, followed by allylation yielded vinyl sulfonamide **29** (Scheme 6). From here, the vinyl sulfonamide could either undergo

TBAF deprotection to the 8-membered oxa-Michael sultam **30** or acidic *TBS*-deprotection followed by the Dess-Martin oxidation to aldehyde **31**, which readily underwent Baylis-Hillman cyclization to afford 6-membered sultam **32** in 68% yield over 3 steps. However, attempts at producing corresponding 7-member sultams proved unsuccessful.

**Scheme 6**: *Intramolecular Baylis-Hillman Protocol for Six-Membered Sultam Synthesis*
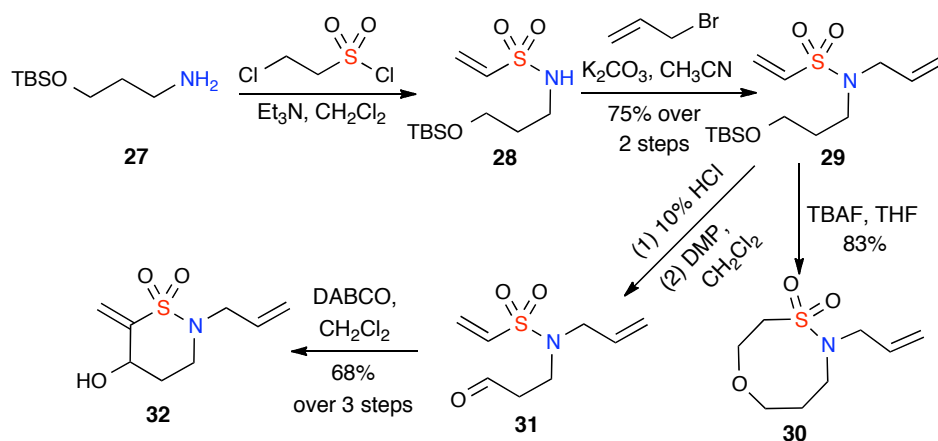


The combination of the oxa-Micahel and Baylis Hillman approaches into a single, divergent methodology was investigated utilizing chiral amino alcohol starting materials, synthesized from glycidyl trityl ethers **31** (Scheme 10). The epoxide ring was opened by *iso*-butyl amine,[30] to afford the amino alcohols **32** followed by subsequent *TBS*-protection to yield the silyl-protected amino alcohol **33**. Sulfonylation of **33** with 2-chloroethanesulfonyl chloride afforded vinyl sulfonamide linchpin **34**. From here, the Baylis-Hillman pathway was initiated by use of a selective, orthogonal deprotection of trityl ether **34** affording vinyl sulfonamide **35**. The resulting alcohol **35** was oxidized to aldehyde **36** using Dess-Martin periodinate. Treatment of **36** with DABCO afforded the sultam **37** in excellent yield with >95:5 diastereoselectivity. Intramolecular oxa-Michael pathways were then pursued through selective deprotection of the alcohols. The first oxa-

Michael cyclization utilized TBAF to selectively deprotect and cyclize the *TBS-*
deprotection alcohol to afford 7-member sultams **38**. An alternative utilized the
terminally deprotected alcohol **35**, but through a NaH-initiated oxa-Michael cyclization
of **35** to afford an 8-membered sultam **39**. Both reactions proceeded quickly and provided
sultams in excellent yields.

**Scheme 10.**   Functional group pairing through oxa-Michael and Baylis-Hillman
Cyclizations
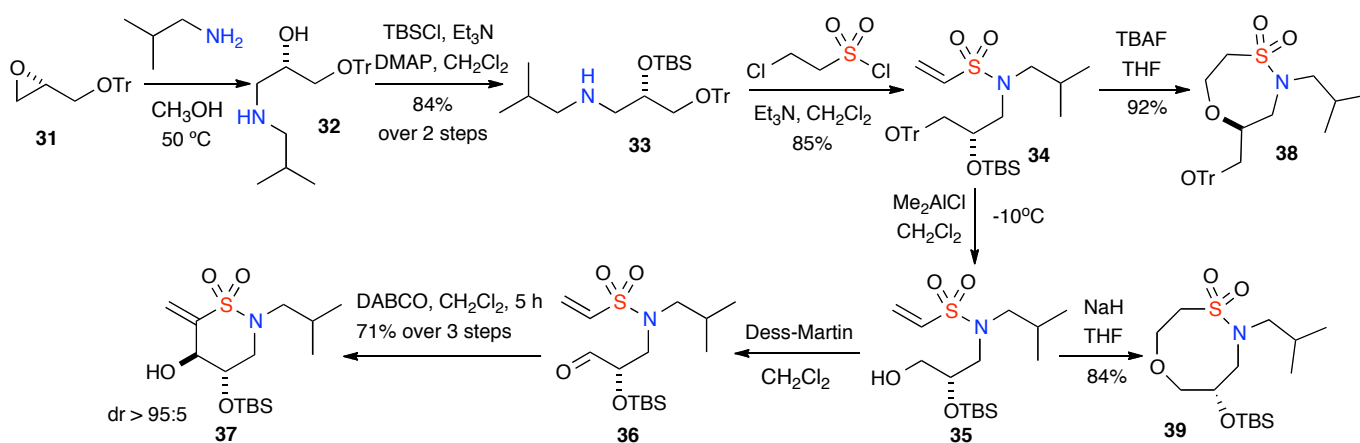


## 2.4 Future Work

The vinyl sulfonamide moiety continues to present potential for the application of
new cyclization methods to access sultam compounds. Continued work by Qin Zang in
the Hanson group has given evidence for thio-Michael, aza-Michael, and bis-aza-Michael
methodologies, as well as continued exploration of the oxa-Michael pathways (Scheme
11). In addition, the highly-functionalized Baylis-Hillman adducts are an attractive
structure for diversification that has yet to be explored. Further investigation into
cyclization methods, possible building blocks, and orthogonal reactions are expected to
expand the reaction profile and compounds accessible through this moiety.

**Scheme 11:** *Further Work in Hetero-Michael Pathways*
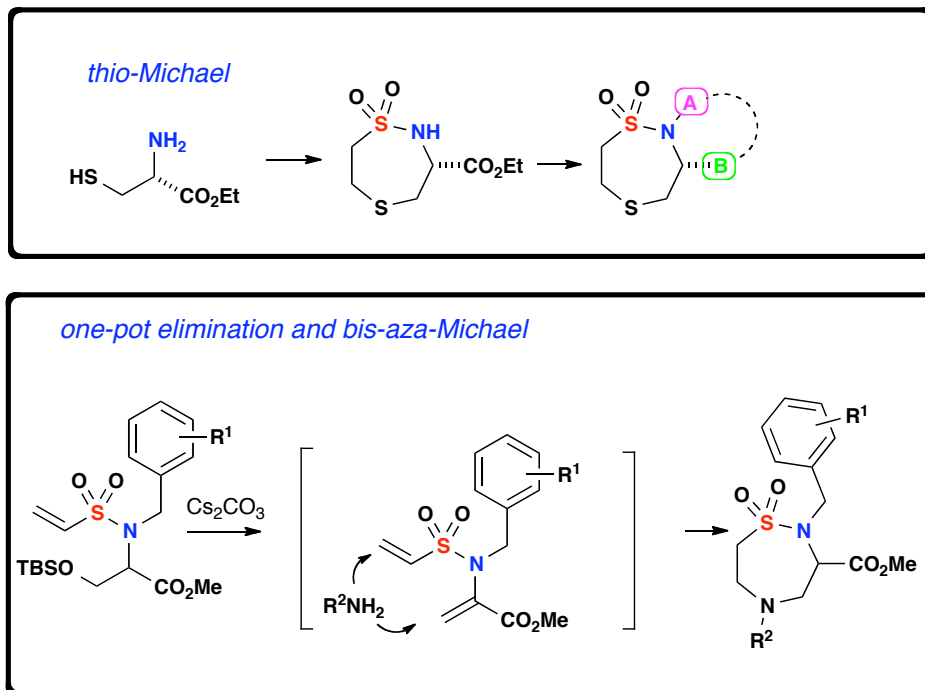


## 2.5 Conclusions

In summary, two protocols involving intramolecular oxa-Michael and Baylis-Hillman reactions to generate 5, 6, 7 and 8-membered sultam derivatives have been reported. Empirical evidence validating 8-*endo* Trig cyclization pathway in oxa-Michael reactions has been presented which enriched Baldwin rules for ring closure. The oxa-Michael method has been shown to be a rapids production method, easily implemented in a one-pot procedure. For Baylis-Hillman protocol, two pathways were demonstrated: (I) a chemoselective oxidation/Baylis-Hillman and (II) use of a vinyl sulfonamide alcohol. Both pathways were completed within short order and occurred with good to excellent yields. In addition, good to excellent levels of diastereoselectivity were achieved. Overall, these two reactions can be conveniently combined into one synthetic route to produce skeletally diverse scaffolds from a single precursor in excellent yields. Finally,

these methods are highly amenable to library generation and current efforts are currently engaged in this endeavor, with additional potential for expanding the scope of these methodologies. Libraries are currently in progress and some of sultam the compounds are currently undergoing biological screening through the NIH Molecular Library Screening Network (NIH-MLSCN).

**Literature Cited:**

(1)   (a) Synthesis. (b) Zhou, A.; Hanson, P. R. *Org. Lett*. **2008**, *10*, 2951–2954.

(2)   The pKa of $RSO_2NH_2$ is around 10-11, while pKa of $RCONH_2$ is typically 15-18.

(3)   (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun*. **1976**, 734–736. (b) Rolfe, A.; Lushington, G. H.; Hanson, P. R. *Org. Biomol. Chem*. **2010**, *8*, 2198–2203.

(4)   Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans*. **1915**, *107*, 1080–1106.

(5)   (a) Jun, J. H.; Dougherty, J. M.; Jimenez, M. S.; Hanson, P. R. Tetrahedron **2003**, *59*, 8901-8912. (b) McReynolds, M. D.; Sprott, K. T.; Hanson, P. R. *Org. Lett*. **2002**, *4*, 4673-4676.

(6)   Chiacchio, U.; Corsaro, A.; Rescifina, A.; Bkaithan, M.; Grassi, G.; Piperno, A.; *Tetrahedron* **2001**, *57*, 3425-3433.

(7)   (a) Metz, P.; Seng, D.; Fröhlich, R. *Synlett* **1996**, 741-742. (b) Plietker, B.; Seng, D.; Fröhlich, R.; Metz, P. *Tetrahedron* **2000**, *56*, 873-879. (c) Rogatchov, V. O.; Bernsmann, H.; Schwab, P.; Fröhlich, R.; Wibbeling, B.; Metz, P. *Tetrahedron Lett*. **2002**, *43*, 4753-4756. (d) Greig, I. R.; Trozer, M. J.; Wright, P. T. *Org. Lett*. **2001**, *3*, 369-371. (e) Wanner, J.; Harned, A. M.; Probst, D. A.; Poon, K. W. C.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R. *Tetrahedron Lett*. **2002**, *43*, 917-921.

(8)   (a) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev*. **2004**, *104*, 2239-2258. (b) Moriggi, J.-M.; Brown, L. J.; Castro, J. L.; Brown, R. C. D. *Org. Biomol. Chem*. **2004**, *2*, 835-844. (c) Freitag, D.; Schwab, P.; Metz, P. *Tetrahedron*

*Lett.* **2004**, *45*, 3589-3592. (d) Karsch, S.; Freitag, D.; Schwab, P.; Metz, P. *Synthesis* **2004**, *10*, 1696-1712.

(9)    Enders, D.; Moll, A.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, 1271-1274.

(10)   (a) Merten, S.; Fröhlich, R.; Kataeva, O. *Adv. Synth. Catal.* **2005**, *347*, 754-758. (b) Vasudevan, A.; Tseng, P-S.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 8591-8593.

(11)   (a) Liu, X.-Y.; Li, C.-H.; Che, C.-M. *Org. Lett.* **2006**, *8,* 2707-2710. (b) Dauban, P.; Dodd, R. H. *Org. Lett.* **2000**, *2,* 2327-2329. (c) Dauban, P.; Sanière, L.; Aurélie, T.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123,* 7707-7708. (d) Sherman, E. S.; Chemler, S. R.; Tan, T. B.; Gerlits, O. *Org. Lett*. **2004**, *6*, 1573-1575. (e) Zeng, W.; Chemler, S. R.; *J. Am. Chem. Soc.* **2007**, *129*, 12948-12949.

(12)   Amino alcohols found through SciFinder commercially available search of aminoethanol substructure.

(13)   Schreiber, S. L. *Science* **2000**, *287*, 1964–1969.

(14)   Information obtained from Gerry Lushington, KU CMLD

# Chapter 3

## Sultam Library Information

## 3.1 Synthesis of an Oxa-Michael Library of Sultams

The 95-member oxa-Michael library was planned as an extension of previously reported syntheses in a library format. Previous results had shown that the reaction conditions were well tolerated by all substrates and intermediates and yielded products with a minimal amount of purification, leading to the development of a one-pot methodology. Due to the ease and speed of production in this one-pot method, the library was to be carried out in a one-pot fashion in parallel reaction vessels. Two points of diversity were incorporated into the basic framework, rising from the amino alcohol starting materials (R1) as well as a variety of alkylating and benzylating agents (R2). Commercially available, enantiopure amino alcohols were also used to set both ring size and chirality of the resulting thiooxaazepines (Scheme 1).

**Scheme 1:** *Intramolecular oxa-Michael Reaction to Generate Sultams*
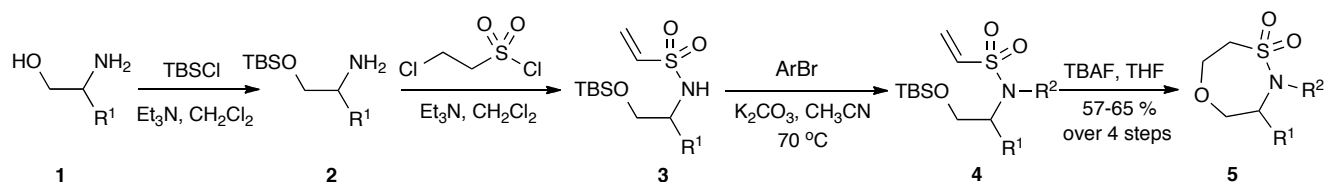


The syntheses of the sultam library was carried out in parallel synthetic tubes. TBSCl (1.05 equiv.) dissolved in CH$_2$Cl$_2$ was added respectively to parallel tubes containing a solution of an amino alcohol (1.0 equiv.), triethylamine (3.0 equiv.) and small amount of DMAP (0.05 equiv.) in CH$_2$Cl$_2$. After addition, the reactions were stirred overnight and checked by TLC for completion. The reactions were cooled to 0 ºC and additional triethylamine (3.0 equiv.) was added along with 2-chloroethanesulfonyl chloride (1.05 equiv.). After 2 h, the crude reation mixtures were washed with brine and evaporated under a sample concentrator to yield crude vinyl sulfonamides. The resultant crude vinyl sulfonamides were re-dissolved in calculated amount of acetonitrile and distributed into parallel tubes for diversification. To each tube, two equivalents of potassium carbonate were added, followed by the addition of alkylating or benzylating agents (1.05 equiv.). All reaction tubes were simultaneously heated at 80 ºC for 5 h, then cooled down to rt. Solid potassium carbonate was removed by filtration. Acetonitrile solvent in filtrate was evaporated from the reaction vessels, and the resulting crude vinyl sulfonamide was directly submitted to oxa-Michael reaction conditions. 1 M TBAF in

THF solution was added into alkylated vinyl sulfonamide solution in THF in parallel tubes to initiated the intramolecular oxa-Michael cyclization, after 2 h, saturated ammonium chloride solution was added, followed by the addition of $CH_2Cl_2$ to extract organic layer. The combined organic layers were dried over $MgSO_4$, and evaporated via a sample concentrator. The final products (seven and eight-membered sultams) were finally purified by Mass-Directed Fractionation (MDF).

Diversification components were chosen from commercially available amino acids and alkylating agents. The goal of building block selection was to take advantage of the wide variety of available materials in producing a diverse array of sultams. The amino acids had both cyclic and acyclic structures in a variety of conformations. This aims to produce sultams with a multitude of 3-dimensional shapes in order to maximize the number of possibly biologically relevant interactions explored in the screening process. In a similar line of thinking, the alkylating agents chosen made use of the variety of substituted benzyl bromides, which not only were excellent alkylating agents, but had both electron-withdrawing and electron-donating substituents in differing positions. The building blocks of amino alcohols and alkylating agents for library production are shown in Scheme 2.

**Scheme 2.** Building Blocks for Sultam Synthesis

**Amino Alcohols (R$^1$)**



**Alkylating Agents (R$^2$)**
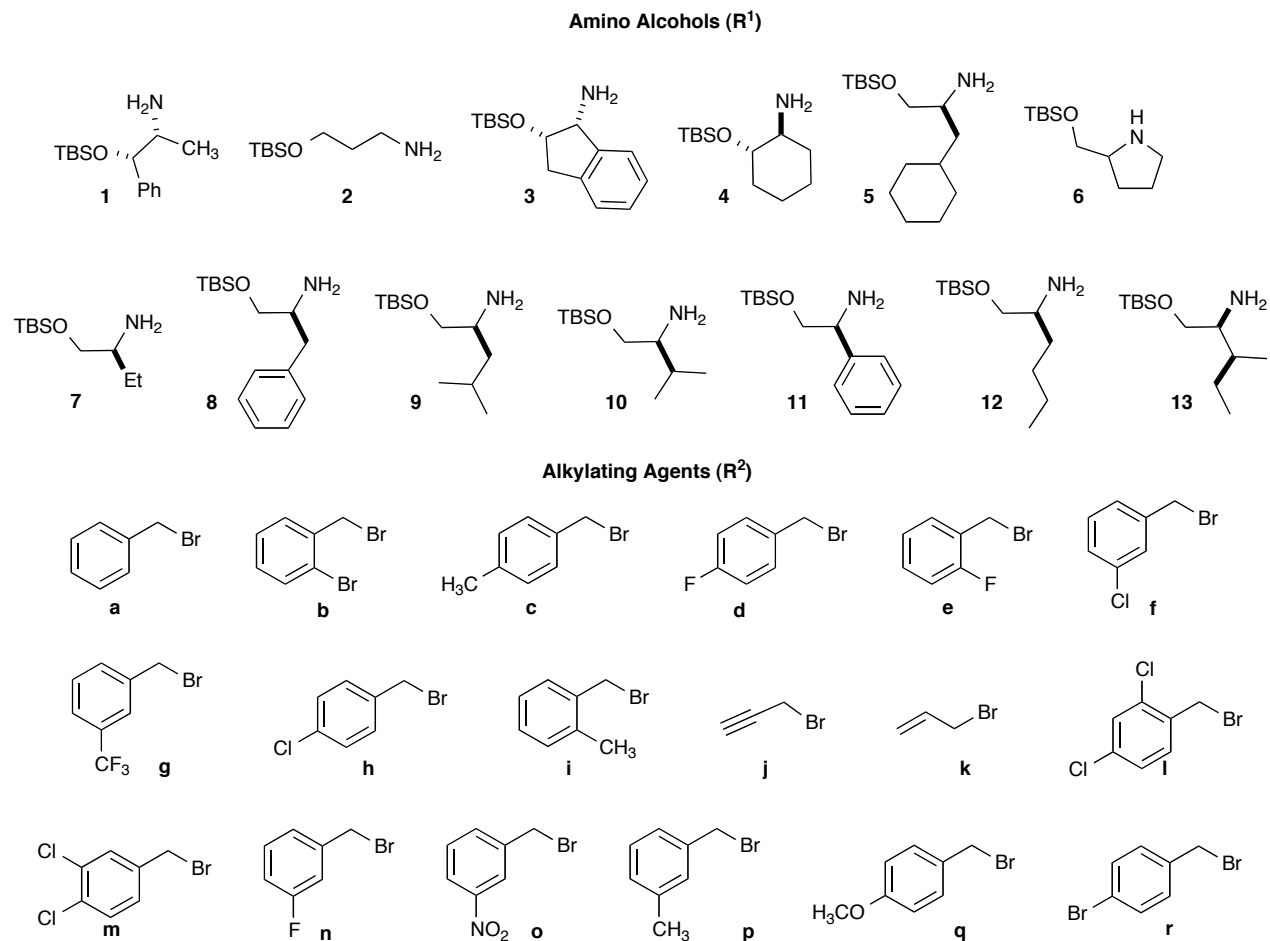


The purities of crude products and final products were analyzed by HPLC. Most crude products were isolated with purities ranging from 80~90%, with final purities ranging from 95-100% after MDF (Scheme 4), all these compounds have been submitted for high throuput screening for biological testing. This method afforded not only 7 and 8-membered sultams, but also generated monocyclic, bi-cyclic and tri-cyclic sultams with different stereogenic centers.

**Table 1: A 95-Member Sultam Library**
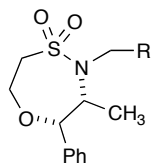


| Entry | R$^2$ | Sultam | Yield % | Purity % |
|---|---|---|---|---|
| 1 | -C$_6$H$_5$ | **1a** | 37.4 | 100 |
| 2 | 2-Br-C$_6$H$_4$ | **1b** | 18.5 | 100 |
| 3 | 4-CH$_3$-C$_6$H$_4$ | **1c** | 18.7 | 100 |
| 4 | 4-F-C$_6$H$_4$ | **1d** | 27 | 100 |
| 5 | 2-F-C$_6$H$_4$ | **1e** | 11.5 | 100 |
| 6 | 3-Cl-C$_6$H$_4$ | **1f** | 31.4 | 100 |
| 7 | 3-F$_3$C-C$_6$H$_4$ | **1g** | 29.9 | 96.2 |
| 8 | 2-CH$_3$-C$_6$H$_4$ | **1i** | 17.4 | 100 |



| Entry | R2 | Sultam | Yield % | Purity % |
|---|---|---|---|---|
| 9 | -C$_6$H$_5$ | **2a** | 39 | 100 |
| 10 | 2-Br-C$_6$H$_4$ | **2b** | 46 | 100 |
| 11 | 4-CH$_3$-C$_6$H$_4$ | **2c** | 37 | 100 |
| 12 | 4-F-C$_6$H$_4$ | **2d** | 36.6 | 100 |
| 13 | 2-F-C$_6$H$_4$ | **2e** | 47.2 | 100 |
| 14 | 3-Cl-C$_6$H$_4$ | **2f** | 50.9 | 100 |

| 15 | 3-F$_3$C-C$_6$H$_4$ | **2g** | 36.3 | 100 |
|---|---|---|---|---|
| 16 | 2-CH$_3$-C$_6$H$_4$ | **2i** | 46.5 | 100 |

| 23 | 3-F$_3$C-C$_6$H$_4$ | **3g** | 75.9 | 100 |
|---|---|---|---|---|
| 24 | 4-Cl-C$_6$H$_4$ | **3h** | 57 | 100 |
| 25 | 2-CH$_3$-C$_6$H$_4$ | **3i** | 68.6 | 100 |



| Entry | R$^2$ | Sultam | Yield % | Purity % |
|---|---|---|---|---|
| 17 | -C$_6$H$_5$ | **3a** | 71.4 | 99.9 |
| 18 | 2-Br-C$_6$H$_4$ | **3b** | 52.7 | 99.9 |
| 19 | 4-CH$_3$-C$_6$H$_4$ | **3c** | 58.5 | 100 |
| 20 | 4-F-C$_6$H$_4$ | **3d** | 57.9 | 100 |
| 21 | 2-F-C$_6$H$_4$ | **3e** | 74.1 | 100 |
| 22 | 3-Cl-C$_6$H$_4$ | **3f** | 78.8 | 100 |



| Entry | R$^1$ | Sultam | Yield % | Purity % |
|---|---|---|---|---|
| 30 | -C$_6$H$_5$ | **4a** | 49 | 99.6 |
| 31 | 2-Br-C$_6$H$_4$ | **4b** | 60.5 | 100 |
| 32 | 4-CH$_3$-C$_6$H$_4$ | **4c** | 54.5 | 100 |
| 33 | 4-F-C$_6$H$_4$ | **4d** | 60.0 | 99 |
| 34 | 2-F-C$_6$H$_4$ | **4e** | 51.7 | 100 |
| 35 | 3-Cl-C$_6$H$_4$ | **4f** | 69.4 | 99 |

| 36 | 3-F$_3$C-C$_6$H$_4$ | **4g** | 61.2 | 100 |
|---|---|---|---|---|
| 37 | 4-Cl-C$_6$H$_4$ | **4h** | 52.4 | 95.9 |

| 38 | 2-CH$_3$-C$_6$H$_4$ | **4i** | 59.5 | 100 |
|---|---|---|---|---|



| Entry | R$^1$ | R$^2$ | Sultam | Yield % | Purity % |
|---|---|---|---|---|---|
| 39 | | Bn | **5a** | 62.4 | 99.8 |
| 40 | | 2-BrBn | **5b** | 69.9 | 99.9 |
| 41 | | 4-CH$_3$Bn | **5c** | 51.5 | 100 |
| 42 | | 4-FBn | **5d** | 63.5 | 100 |
| 43 | | 2-FBn | **5e** | 66.3 | 100 |
| 44 | | 3-ClBn | **5f** | 62.9 | 100 |
| 45 | | 3-F$_3$CBn | **5g** | 83.6 | 100 |
| 46 | | 4-ClBn | **5h** | 62.4 | 99.6 |
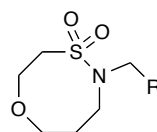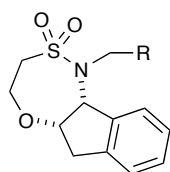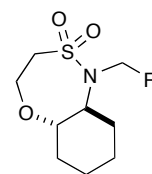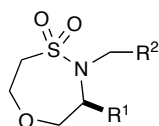
48

| 47 | Pro | **NA** | **6** | 55.3 | 97.8 |
|----|-----|--------|-------|------|------|
| 48 | Et | Bn | **7a** | 71.6 | 100 |
| 49 | Et | 2-BrBn | **7b** | 71.6 | 100 |
| 50 | Et | 4-CH$_3$Bn | **7c** | 35.1 | 99.6 |
| 51 | Et | 4-FBn | **7d** | 66.1 | 100 |
| 52 | Et | 2-FBn | **7e** | 75 | 100 |
| 53 | Et | 3-ClBn | **7f** | 78.6 | 100 |
| 54 | Et | 3-F$_3$CBn | **7g** | 81.8 | 100 |
| 55 | Et | 4-ClBn | **7h** | 57.9 | 100 |
| 56 | Et | 2-MeBn | **7i** | 75 | 99.7 |
| 57 | Bn | Bn | **8a** | 80.4 | 100 |
| 58 | Bn | 2-BrBn | **8b** | 88.1 | 100 |
| 59 | Bn | 4-CH$_3$Bn | **8c** | 76.8 | 99.8 |
| 60 | Bn | 4-FBn | **8d** | 87.5 | 100 |

| 61 | Bn | 2-FBn | **8e** | 96.1 | 99.2 |
|----|------|-------------------|--------|------|------|
| 62 | Bn | 3-ClBn | **8f** | 100 | 100 |
| 63 | Bn | 3-F$_3$CBn | **8g** | 100 | 100 |
| 64 | Bn | 4-ClBn | **8h** | 87.6 | 100 |
| 65 | Bn | 2-MeBn | **8i** | 88.3 | 100 |
| 66 | Bn | propargyl | **8j** | 92.9 | 100 |
| 67 | Bn | vinyl | **8k** | 95.5 | 99.2 |
| 68 | Bn | 2,4-ClBn | **8l** | 100 | 98.2 |
| 69 | Bn | 3,4-ClBn | **8m** | 100 | 100 |
| 70 | Bn | 3-FBn | **8n** | 94.5 | 100 |
| 71 | Bn | 3-NO$_2$Bn | **8o** | 100 | 99.5 |
| 72 | $t$-Bu | Bn | **9a** | 100 | 100 |
| 73 | $t$-Bu | 2-BrBn | **9b** | 96.4 | 100 |
| 74 | $t$-Bu | 4-CH$_3$Bn | **9c** | 95.2 | 100 |

| 75 | *t*-Bu | 4-FBn | **9d** | 96.5 | 100 |
| 76 | *t*-Bu | 2-FBn | **9e** | 89.7 | 100 |
| 77 | *t*-Bu | 3-ClBn | **9f** | 100 | 100 |
| 78 | *t*-Bu | 3-F$_3$CBn | **9g** | 100 | 100 |
| 79 | *t*-Bu | 4-ClBn | **9h** | 96.5 | 100 |
| 80 | *t*-Bu | 2-MeBn | **9i** | 92.5 | 99.8 |
| 81 | *t*-Bu | propargyl | **9j** | 91.3 | 100 |
| 82 | *t*-Bu | vinyl | **9k** | 100 | 100 |
| 83 | *t*-Bu | 2,4-ClBn | **9l** | 100 | 99.3 |
| 84 | *t*-Bu | 3,4-ClBn | **9m** | 100 | 97.5 |
| 85 | *t*-Bu | 3-FBn | **9n** | 95.3 | 100 |
| 86 | *t*-Bu | 3-NO$_2$Bn | **9o** | 99.5 | 100 |
| 87 | *t*-Bu | 3-MeBn | **9p** | 95.6 | 100 |
| 88 | *t*-Bu | 4-OMeBn | **9q** | 100 | 79.8 |

| 89 | Ph | Bn | **11a** | 84.0 | 99.3 |
|----|------|----------|---------|------|------|
| 90 | Ph | 4-FBn | **11d** | 81.0 | 100 |
| 91 | Ph | 2-FBn | **11e** | 78.0 | 100 |
| 92 | Ph | 3,4-ClBn | **11m** | 91.0 | 92.0 |
| 93 | Ph | 3-FBn | **11n** | 77.0 | 92.0 |
| 94 | Bu | 4-BrBn | **12r** | 88.0 | 95.6 |
| 95 | *i*-Bu | 4-BrBn | **13r** | 78.1 | 87.0 |

# Figure 1: Bioactivity of Selected Submitted Compounds



**Proteasome Inhibitors** 72.655 *μM*

Inhibitor of **Pseudomonas aeruginosa PvdQ acylase** 12.687 *μM*

Inhibitors of **A1 Apoptosis** (HMC 1-8 low) 240.4 *μM*

Inhibitors of the **SUMOylation** Pathway 291.5 *μM*

Sensitize **Mycobacterium Tuberculosis** to Beta-lactam Antibiotics 100 *μM*
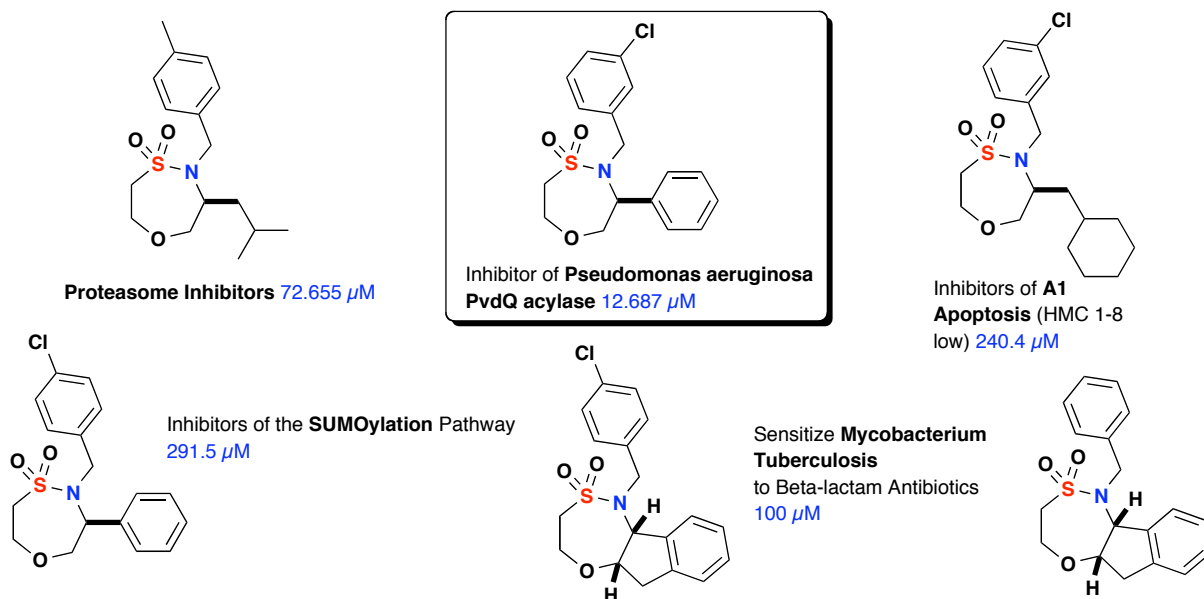
## 3.2 Baylis-Hillman Products

A small sample library of substituted Baylis-Hillman products was also produced. Less of these compounds were produced than the Oxa-Michael sultams due to the relative ease of the Oxa-Michael methodology. Also, due to the highly substituted nature of the 5-member sultams, they are better suited as scaffolds for functionalization than endproducts in themselves. With this in mind a small library was submitted for biological testing to determine if the core structures had bioactive potential. Thus far no positive results have been found.

**Scheme 3:** *Synthesis of Baylis-Hillman Dervied Sultams*
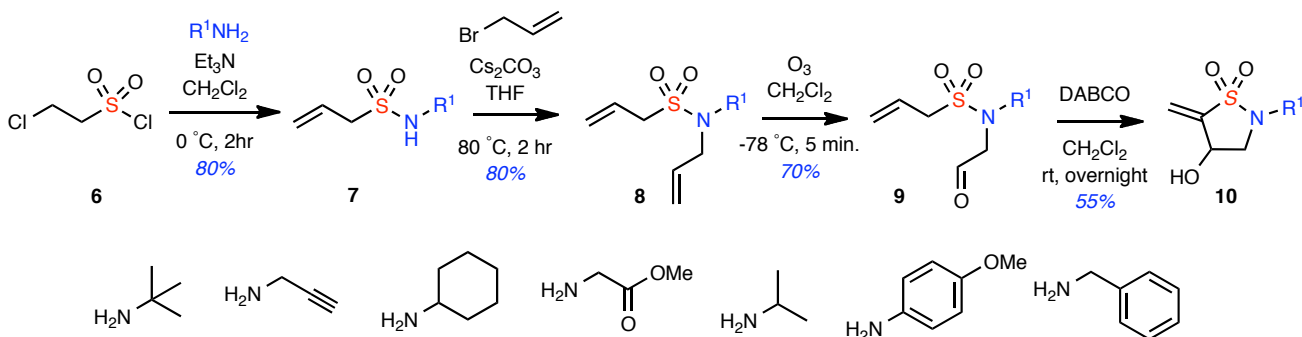
**Table 2: A Sample Library of Baylis-Hillman Products**
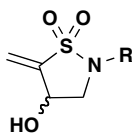


| Entry | R | Yield % | Purity % |
|-------|---|---------|----------|
| **10a** | *i*Pr | 37.4 | 100 |
| **10b** | 4-OMe-Ph | 18.5 | 100 |
| **10c** | Bn | 27 | 100 |
| **10d** | CycHex | 11.5 | 100 |
| **10e** | *t*Bu | 31.4 | 100 |
| **10f** | propargyl | 29.9 | 96.2 |
| **10g** | CH$_2$COOMe | 17.4 | 100 |

**Conclusion:**

A 95-sultam library of sultams using intramolecular oxa-Michael reaction of vinyl sulfonamides was accomplished. All reactions involved were "click-type" reactions. The 4-step reaction sequence proceeded without flash chromatography of reaction intermediates; easy work-up and preparative HPLC/MS purification provided high yield and purity library products. Of the compounds submitted for screening, several have

54

displayed bioactivity, including a 12 µM inhibitor of Pseudomonas Aeruginosa PvdQ acylase. A small library of Baylis-Hillman products were synthesized and submitted, but have not yet demonstrated activity in the assays. All the sultams reported herein have been submitted to NIH biological outreach partners for biological screening through the NIH Molecular Library Screening Network (NIH-MLSCN).

# Chapter 4

# Experimental Procedures and Data

### 3.1 General Methods

All air and moisture sensitive reactions were carried out in flame-dried glassware under argon atmosphere with necessary gas-tight syringes, cannulaes, and septa. Stirring was achieved with oven-dried magnetic stir bars. $Et_2O$, toluene, THF and $CH_2Cl_2$ were purified by passage through the Solv-Tek purification system employing activated $Al_2O_3$. $Et_3N$ was purified by passage over basic alumina and stored over KOH. Butyl lithium was purchased from Aldrich and titrated prior to use. Glycidol ether was acquired from Daiso Co. Ltd., Fine Chemical Department and used without further purification. Flash column chromatography was performed with Sorbent Technologies (30930M-25, Silica Gel 60A, 40-63 um). Thin layer chromatography was performed on silica gel $60F_{254}$ plates (EM-5717, Merck). Visualization of TLC spots was achieved through the use of a UV lamp (254nm) and $KMnO_4$ stain. Deuterated solvents were purchased from Cambridge Isotope laboratories. $^1H$, $^{13}C$ NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-400 MHz spectrometer operating at 400 MHz and 100 MHz respectively or a Bruker Avance-500 MHz spectrometer operating at 500 MHz and 125 MHz respectively. Observed rotations at 589 nm were measured using AUTOPOL IV Model automatic polarimeter. High-resolution mass spectrometry (HRMS) was recorded on a LCT Premier Spectrometer (Micromass UK Limited) operating on ESI (MeOH).

**General Procedure for the TBS protection of amino alcohols:** To a RB flask with stirbar valanol was added (2.0 g, 17 mmol) in CH2Cl2 (34 mL, 0.5M). To the solution, triethylamine (4.7mL, 34 mmol), a catalytic amount of DMAP (159 mg, 1.7 mmol), and TMSCl (2.55 g, 17 mmol) was added and the reaction was stirred overnight. The reaction was extracted in water and EtOAc x3 and washed with brine to yield a pale yellow oil.

**General procedure for the one-pot synthesis of thiaoxaazepines:** To a RB flask with stirbar (*S*)-1-(*tert*-butyldimethylsilyloxy)-3-methylbutan-2-amine was added (0.5425 g, 2.5 mmol) in DCM (25 mL, 0.1M). The solution was cooled to 0 ºC and $Et_3N$ (1.045 mL, 7.5 mmol) followed by 2-chloro-ethane sulfonyl chloride (0.263 mL, 2.5 mmol) was added. The reaction was allowed to stir at 0 ºC for 2 hours monitoring by TLC. Following completion of the reaction, a 5 mL portion of the solution was placed in a screw-cap

Pyrex© tube with stirbar. CsCO$_3$ (488.8 mg, 1.5 mmol) and 4-methoxybenzyl bromide (138.5 mg, 0.75 mmol) was added. The reaction was heated to 80 ºC and allowed to stir overnight. Following completion of the reaction, the tube was removed from the bath and allowed to cool to room temperature. TBAF (0.5 mL, 1M in THF) was added and the reaction was allowed to stir for 20 min at rt. The reaction was evaporated under reduced pressure and columned in 5:1 hexanes: ethyl acetate to give to product as a colorless oil.

**General Procedure for the Intramolecular Baylis-Hillman Reaction:** (The sulfonamide linchpin was prepared according to the previous procedure for the oxa-Michael reaction) To a stirring solution of a TBS protected sulfonamide (1 equiv.) in trace amount of THF, 10 mol% HCl was added. The deprotected vinyl sulfonamide alcohol was extracted with CH$_2$Cl$_2$ dried, and filtered. The resulting alcohol was dissolved in CH$_2$Cl$_2$, Dess-Martin periodinate (2 equiv.) was added, and stirred for 2 hours. The reaction was washed with NaHCO$_3$ to remove the resultant solid acid, filtered, and extracted. DABCO (0.10 equiv) was added to the crude vinyl sulfonamide aldehyde in CH$_2$Cl$_2$. Stirring continues for 2-4 hours until the reaction was complete.

## 3.2 Selected Library Data

**(S)-*N*-2-benzyl-3-phenyl-5,1,2-oxathiazepane-1,1-dioxide (11a)**
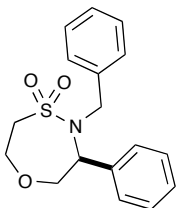


$[\alpha]_D^{20}$ -6.1 (c 0.50, CH$_2$Cl$_2$), colorless oil; **FTIR** (CH$_2$Cl$_2$): 3053, 2985, 1421, 1271, 894, 761 cm$^{-1}$; **$^1$H-NMR** (CDCl$_3$, 400Hz): δ (ppm) 7.41 (aromatic CH, 4H), 7.33-7.25 (aromatic CH, 4H), 4.85 (d, $J$ = 15.3 Hz, 1H), 4.36 (dd, $J$ = 5.5, 10.9 Hz, 1H), 4.21 (t, $J$ = 12.2, 1H), 4.13 (ddd, 1H), 4.13 (d, $J$ = 5.5 1H), 4.06 (d, $J$ = 15.4, 1H), 3.94 (td, $J$ = 2.2, 9.4 Hz, 1H), 3.42 (dt, $J$ = 2.1, 10.2 Hz, 1H), 2.93 (ddd, $J$ = 4.5, 10.9, 14.8 Hz, 1H) **$^{13}$C-NMR** (CDCl$_3$, 100MHz): δ 138.07, 136.05, 129.70 (4), 128.43 (4), 127.08 (2), 76.17,

60.19, 59.42, 58.77, 51.24 **HRMS** (ESI) m/z expected: 335.0992 m/z found: 353.1334 (M+NH₄)

**(S)-*N*-2-(4-fluorobenzyl)-3-phenyl-5,1,2-oxathiazepane-1,1-dioxide (11d)**
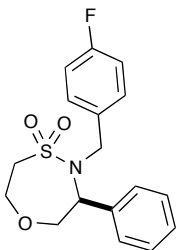


$[\alpha]_D^{20}$ -21.4 (c 0.50, CH₂Cl₂), colorless oil; **FTIR** (CH₂Cl₂): 3053, 2985, 1421, 1253, 894, 777 cm⁻¹; **¹H-NMR** (CDCl₃, 400Hz): δ (ppm) 7.42-7.28 (aromatic CH, 5H) 7.13 (d, *J* = 8.3 Hz, 1H), 4.73 (d, *J* = 15.4, 1H), 4.28 (dd, *J* = 5.4, 10.7 Hz, 1H), 4.19 (t, *J* = 12.1, 1H), 4.13 (ddd, 1H), 4.13 (d, *J* = 5.5 1H), 4.06 (**d**, *J* = 15.4, 1H), 3.96 (td, *J* = 2.2, 12.2 Hz, 1H), 3.42 (dt, *J* = 2.3, 14.2 Hz, 1H), 3.28 (ddd, *J* = 4.5, 11.5 15.2 Hz, 1H); **¹³C-NMR** (CDCl₃, 100MHz): δ 137.07, 136.05, 132.42 (2),130.78 (2), 129.43 (2), 129.29, 128.75 (2), 122.08, 76.77, 66.49, 63.74, 57.77, 52.84; **HRMS** (ESI) m/z expected: 351.0696 m/z found: 410.1297 (M+NH₄+CH₃CN)

**(S)-*N*-2-(2-fluorobenzyl)-3-phenyl-5,1,2-oxathiazepane-1,1-dioxide (11e)**
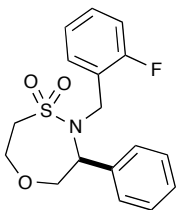


$[\alpha]_D^{20}$ -13.4 (c 0.50, CH₂Cl₂), colorless oil; **FTIR** (CH₂Cl₂): 3060, 2985, 2304, 1421, 1288, 1245, 896, 783 cm⁻¹; **¹H-NMR** (CDCl₃, 400Hz): δ (ppm) 7.45-7.25 (aromatic CH, 5H) 7.08 (d, *J* = 7.6, 1H), 7.00 (m, 2H) 4.82 (d, *J* = 15.5, 1H), 4.40 (dd, *J* = 5.5, 11.6, 1H) 4.26 (t, *J* = 12.1 Hz, 1H), 4.23-4.14 (m, 3H), 4.01 (td, *J* = 2.3, 12.3 Hz, 1H), 3.49 (dt, *J* = 2.3, 14.2 Hz, 1H), 3.36 (ddd, 4.5, 11.3, 14.2 Hz, 1H); **¹³C-NMR** (CDCl₃, 100MHz): δ 161.86, 138.64, 135.88, 130.86, 128.64 (2), 128.26, 127.75 (2), 124.29, 115.20, 114.32,

75.62, 66.37, 62.94, 57.75, 52.91; **HRMS** (ESI) m/z expected: 317.1086 m/z found: 335.1459 (M+NH$_4$)

## (6S)-5-[(3,4-dichlorophenyl)methyl]-6-phenyl-1,4,5-oxathiazepane 4,4-dioxide (11m)
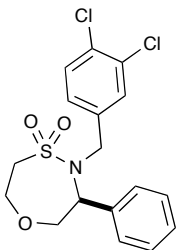


$[\alpha]_D^{20}$ -37 (c 0.50, CH$_2$Cl$_2$), colorless oil; **FTIR** (CH$_2$Cl$_2$): 3053, 2985, 2684, 2304, 1421, 1265, 894, 777, 703 cm$^{-1}$; $^1$**H-NMR** (CDCl$_3$, 400Hz): δ (ppm) 7.33-7.20 (aromatic CH, 6H) 7.04 (dd, J= 2.0, 8.2 Hz, 1H), 4.59 (d, J= 15.6 Hz, 1H) 7.10 (m, 1H) 4.82 (d, J = 15.5, 1H), 4.40 (dd, J = 5.6, 10.9 Hz, 1H), 4.26 (t, J = 12.9, 1H), 4.17 (m, 2H), 4.00 (td, J = 2.2, 11.2, 1H), 3.49 (dt, J = 2.4, 14.17, 1H), 3.36 (ddd, J = 4.5, 11.4, 30.1 Hz, 1H); $^{13}$**C-NMR** (CDCl$_3$, 100MHz): δ 138.51, 130.14 128.73 (2), 127.93 (2), 127.72 (2), 124.26 115.50, 114.80, 76.76, 66.51, 63.72, 57.75, 52.86; **HRMS** (ESI) m/z expected: 385.0306 m/z found: 444.0906

## *N*-2-(3-Fluorobenzyl)-3(*S*)-phenyl-5,1,2-oxathiazepine-1,1-dioxide (11n)
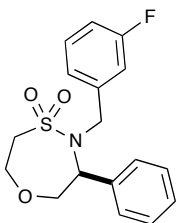


$[\alpha]_D^{20}$ -17.0 (c 0.50, CH$_2$Cl$_2$), colorless oil; **FTIR**: 2956, 1454, 1335, 1140, 733 cm$^{-1}$; $^1$**H-NMR** (CDCl$_3$, 400 MHz): δ (ppm) 7.44-6.98 (m, 9H), 4.82 (d, J = 15.5 Hz, 1H), 4.23 (dd, J = 10.8, 5.4 Hz, 1H), 4.19 (overlap, 3H), 4.00 (ddd, J = 13.5, 11.5, 2.3 Hz, 1H), 3.49 (ddd, J =13.2, 2.4, 2.3 Hz, 1H), 3.37 (ddd, J = 11.4, 4.5, 2.7 Hz, 1H); $^{13}$**C-NMR** (CDCl$_3$, 100 MHz): δ (ppm) 163.8, 161.8, 138.6, 136.0, 130.2, 128.7, 128.2, 127.4, 124.2, 115.6, 75.7, 66.5, 63.7, 57.8, 52.9; **HRMS** (ESI) m/z calculated for C$_{17}$H$_{22}$N$_2$FO$_3$S 353.1335 (M+NH$_4$)$^+$, found 353.1134.

## (6S)-5-[(4-bromophenyl)methyl]-6-butyl-1,4,5-oxathiazepane-4,4-dioxide (12r)
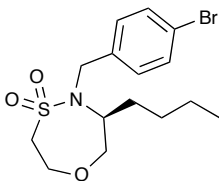


$[\alpha]_D^{20}$ -47.4 (c 0.50, $CH_2Cl_2$), colorless oil; **FTIR** ($CH_2Cl_2$): 3053, 2985, 1421, 1336, 1269, 1141, 1120, 703 cm$^{-1}$; **¹H-NMR** (CDCl$_3$, 400Hz): δ (ppm) 7.29 (m, 1H) 7.19 (m, 2H), 4.73 (d, $J$ = 15.4, 1H), 6.98 (td, $J$ = 2.2, 6.9, 1H)  4.35 (q, $J$ = 5.6, 12.7 Hz, 2H), 4.19 (dt,  $J$ = 1.8, 6.3, 1H), 4.06 (m, 1H), 3.92 (m, 1H), 3.83 (t, $J$ = 11.3, 1H), 3.71 (m, 1H), 3.34 (m, 1H), 1.35 (m, 2H), 1.00 (m, 4H), 0.67 (t, $J$ = 6.6, 3H); **¹³C-NMR** (CDCl$_3$, 100MHz): δ  161.83,140.14, 129.98,  124.02, 115.55,  114.77, 74.53 65.09, 55.87, 54.50, 30.74, 28.47,  23.37, 13.78; **HRMS** (ESI) m/z expected: 361.0347 m/z found: 420.0900 (M+NH$_4$+CH$_3$CN)

## *N*-2-(4-Bromobenzyl)-3(*S*)-isobutyl-5,1,2-oxathiazepine-1,1-dioxide (13r)
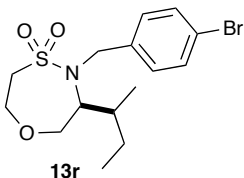


$[\alpha]_D^{20}$ -35.0 (c 0.5, $CH_2Cl_2$), colorless oil; **FTIR**: 3053, 2985, 1421, 1261, 1155, 894, 734 cm$^{-1}$; **¹H-NMR** (CDCl$_3$, 400 MHz): δ (ppm) 7.46-7.31 (m, 4H), 4.46 (d, $J$ = 15.8 Hz, 1H), 4.12 (d, $J$ = 15.8 Hz, 1H), 4.07 (dd, $J$ = 12.6, 6.4 Hz, 1H), 3.93 (overlap, 2H), 3.63 (m, 1H), 3.38 (ddd, $J$ = 14.4, 7.0, 4.7 Hz, 1H), 3.28 (ddd, $J$ = 14.3, 6.3, 4.5 Hz, 1H), 1.45 (m, 1H), 1.33 (m, 1H), 078 (m, 1H), 0.69 (d, $J$ = 6.7 Hz, 3H), 0.47 (t, $J$ = 7.4 Hz, 3H); **¹³C-NMR** (CDCl$_3$, 100 MHz): δ (ppm) 136.5, 31.8, 130.5, 121.7, 73.8, 68.2, 61.8, 54.3, 50.8, 36.4, 27.5, 15.4, 10.1; **HRMS** (ESI) m/z calculated for $C_{15}H_{26}N_2BrO_3S$ 393.0848 (M+NH$_4$)$^+$, found 393.0844.

**Intermediates for and Final Compounds Baylis-Hillman-derived Sultams.**

**N-benzyl-vinylsulfonamide 7c**
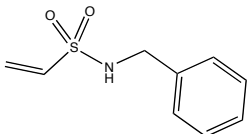


$^1$**H-NMR** (CDCl$_3$, 400Hz): δ (ppm) 7.30 (s, 5H), 6.51 (dd, J= 6.8, 10.4, 1H), 6.27 (d, J= 10.4, 1H), 5.90 (d, J= 10.0, 1H), 4.64 (s, 1H), 4.30 (d, J = 6.4, 2H)

**N-(tert-butyl)-vinylsulfonamide 7e**
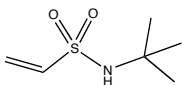


$^1$**H-NMR** (CDCl$_3$, 400Hz): δ (ppm) 6.58 (dd, J = 10.0, 16.8, 1H), 6.21 (d, J = 16.4, 1H), 5.89 (d, J = 9.6, 1H), 4.23 (s, 1H), 1.39 (s, 9H)

**N-Allyl-N-isopropyl-vinylsulfonamide 8a**
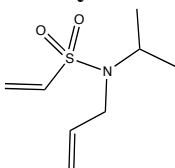


$^1$**H-NMR** (CDCl$_3$, 400Hz): δ (ppm) 6.42 (dd, J = 10.0, 16.1, 1H), 6.18 (d, J = 16.4, 1H), 5.86 (d, J = 9.6, 1H), 5.27 (dd, J = 17.4, 1H), 5.20 (dd, J = 10.4, 1H), 4.02 (m, 1H), 3.81 (dd, J=0.80, 6.0, 2H), 1.18 (d, J=6.8, 6H)

**N-Allyl-N-benzyl-vinylsulfonamide 8c**
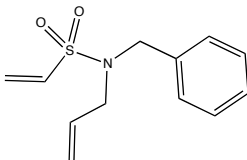


$^1$**H-NMR** (CDCl$_3$, 400Hz): δ (ppm) 7.32 (s, 5H), 6.42 (dd, J= 6.8, 10.4, 1H), 6.24 (d, J= 10.4, 1H), 5.90 (d, J= 10.0, 1H), 5.74 (m, 1H), 5.20 (dd, J=17.4, 17.4, 2H) 4.73 (s, 2H), 3.72 (d, J = 6.8, 2H),

**N-isobutyl-N-(2-oxoethyl)ethenesulfonamide 9a**
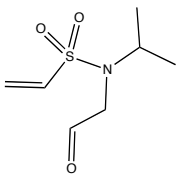


$^1$**H-NMR** (CDCl$_3$, 400Hz): δ (ppm) 9.60 (s, 1H), 6.58 (dd, $J$ = 9.6, 16.4, 1H), 6.25 (dd, $J$ = 0.80, 10.0, 1H), 5.95 (dd, $J$ = 0.40, 10.8, 1H), 4.10 (m, $J$ = 7.2, 7.2, 7.2, 1H), 3.18 (s, 1H), 1.41 (d, $J$ = 6.8, 6H)

**N-(*tert*-butyl)-N-(2-oxoethyl)ethenesulfonamide 9e**
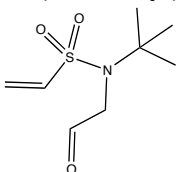


$^1$**H-NMR** (CDCl$_3$, 400Hz): δ (ppm) 9.57 (s, 1H), 6.63 (dd, $J$ = 10.0, 16.8, 1H), 6.27 (dd, $J$ = 0.80, 16.4, 1H), 5.86 (dd, $J$ = 0.40, 9.6, 1H), 4.02 (s, 1H), 1.36 (s, 9H)

**Methyl-2-(N-(2-oxoethyl)vinylsulfonamido)acetate 9g**
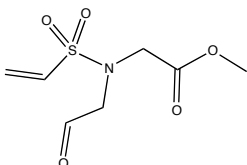


$^1$**H-NMR** (CDCl$_3$, 400Hz): δ (ppm) 9.64 (s, 1H), 6.55 (dd, $J$ = 6.4, 16.4, 1H), 6.26 (d, $J$ = 16.4, 1H), 6.00 (d, $J$ = 9.6, 1H), 4.11 (s, 2H), 4.09 (s, 2H), 3.74 (s, 3H)

**2-Isopropyl-4-hydroxy-5-methyleneisothiazolidine 1,1-dioxide 10a**
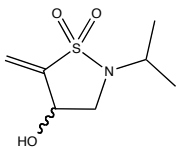


$^1$**H-NMR** (CDCl$_3$, 400Hz): δ (ppm) 6.20 (s, 1H), 5.95 (s, 1H), 4.94 (s, 1H), 3.50 (dd), 3.10 (ddd, 1H), 2.85 (s, 1H), 1.25 (m, 6H) $^{13}$**C-NMR** (CDCl$_3$, 100 MHz): δ (ppm) 148.1, 118.1, 65.2, 50.0, 45.2, 21.3

## 4-Hydroxy-2-(4-methoxyphenyl)-5-methyleneisothiazolidine 1,1-dioxide 10b
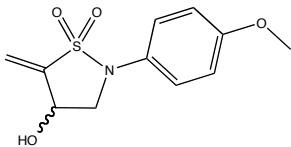


**$^1$H-NMR** (CDCl$_3$, 400Hz): δ (ppm) 7.21 (d, $J$ = 8.6, 2H), 6.89 (d, $J$ = 8.6, 2H), 6.20 (s, 1H), 5.95 (s, 1H), 4.75 (s, 1H), 3.78 (s, 3H), 3.31 (dd, 6.8, 10.2, 1H), 3.22 (s, 1H), 2.51 (dd, $J$ = 5.0, 10.2, 1H) **$^{13}$C-NMR** (CDCl$_3$, 100 MHz): δ (ppm) 159.7, 148.4, 130.0, 119.4, 113.1, 64.9, 55.3, 52.9

## 2-Benzyl-4-hydroxy-5-methyleneisothiazolidine 1,1-dioxide 10c
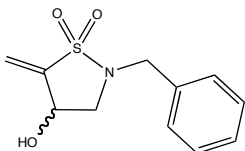


**$^1$H-NMR** (CDCl$_3$, 400Hz): δ (ppm) 7.30 (s, 5H), 6.22 (s, 1H), 5.97 (s, 1H), 4.78 (s, 1H), 4.16 (s, 2H), 3.34 (dd, $J$ = 6.7, 10.1, 1H), 2.96 (dd, $J$ = 4.9, 10.2, 1H) **$^{13}$C-NMR** (CDCl$_3$, 100 MHz): δ (ppm) 148.1, 134.6, 128.9, 119.2, 65.1, 52.0, 47.4

## 2-Cyclohexyl-4-hydroxy-5-methyleneisothiazolidine 1,1-dioxide 10d
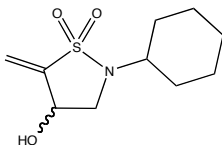


**$^1$H-NMR** (CDCl$_3$, 400Hz): δ (ppm) 6.16 (s, 1H), 5.89 (s, 1H), 4.81 (s, 1H), 4.78 (s, 1H), 3.84(q, 2H), 3.12 (dd, $J$ = 6.7, 10.1, 1H), 2.77 (dd, $J$ = 4.9, 10.2, 1H) **$^{13}$C-NMR** (CDCl$_3$, 100 MHz): δ (ppm) 148.8, 118.0, 77.3, 65.5, 53.0, 48.4, 31.1, 25.4

### 2-(*tert*-Butyl)-4-hydroxy-5-methyleneisothiazolidine 1,1-dioxide 10e
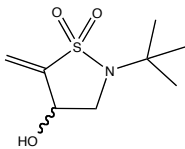


$^1$**H-NMR** (CDCl$_3$, 400Hz): δ (ppm) 6.11 (s, 1H), 5.85 (s, 1H), 4.80 (s, 1H), 3.59 (dd, *J* = 6.4, 10.0, 1H),  3.18 (dd, *J* = 5.2, 5.2, 1H), 1.41 (s, 9H) $^{13}$**C-NMR** (CDCl$_3$, 100 MHz): δ (ppm) 149.9, 117.6, 77.2, 64.5, 49.9, 28.0

### 4-Hydroxy-5-methylene-2-(prop-2-yn-1-yl)isothiazolidine 1,1-dioxide 10f
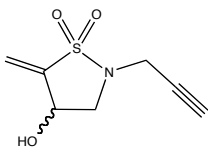


$^1$**H-NMR** (CDCl$_3$, 400Hz): δ (ppm) 6.22 (s, 1H), 6.01 (s, 1H), 4.91 (s, 1H), 3.93 (s, 1H), 3.66 (q, 2H), 3.46 (dd, *J* = 6.7, 10.1, 1H), 3.26 (dd,  *J* = 4.9, 10.2, 1H) 2.99 2.37 2.16 $^{13}$**C-NMR** (CDCl$_3$, 100 MHz): δ (ppm) 146.8, 118.4, 77.5, 75.4, 73.1, 54.3, 33.0

### Methyl 2-(4-hydroxy-5-methylene-1,1-dioxidoisothiazolidin-2-yl)acetate 10g
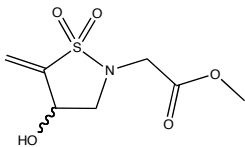


$^1$**H-NMR** (CDCl$_3$, 400Hz): δ (ppm) 6.12 (s, 1H), 5.96 (s, 1H), 4.78 (s, 1H), 3.55 (s, 1H), 3.27 (dd, 1H), 3.05 (dd, *J* = 6.7, 10.1, 1H) $^{13}$**C-NMR** (CDCl$_3$, 100 MHz): δ (ppm) 169.5, 147.9, 119.2, 69.6, 54.1, 52.5, 43.8

**Appendix:**

**NMR Spectra**

## (S)-*N*-2-benzyl-3-phenyl-5,1,2-oxathiazepane-1,1-dioxide (11a)
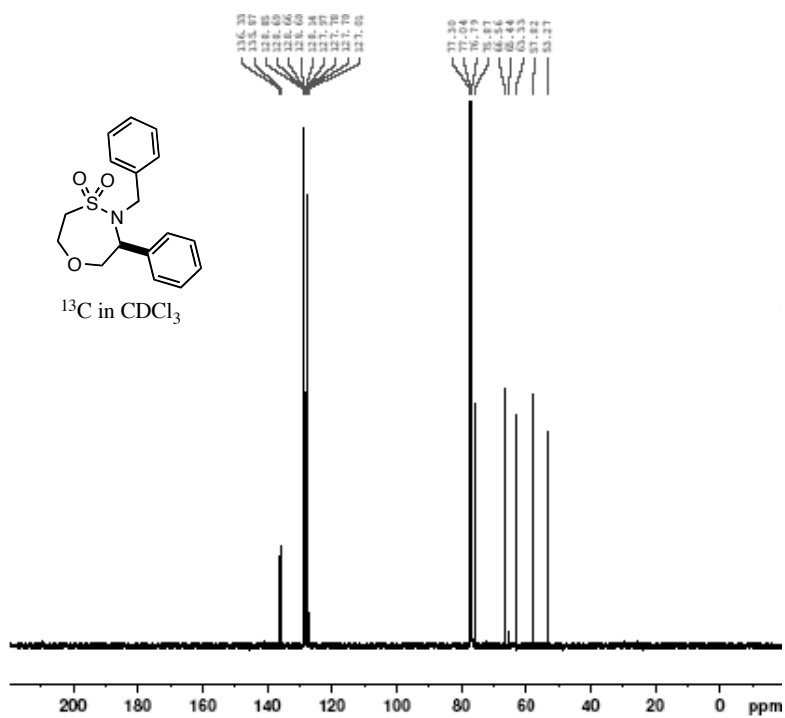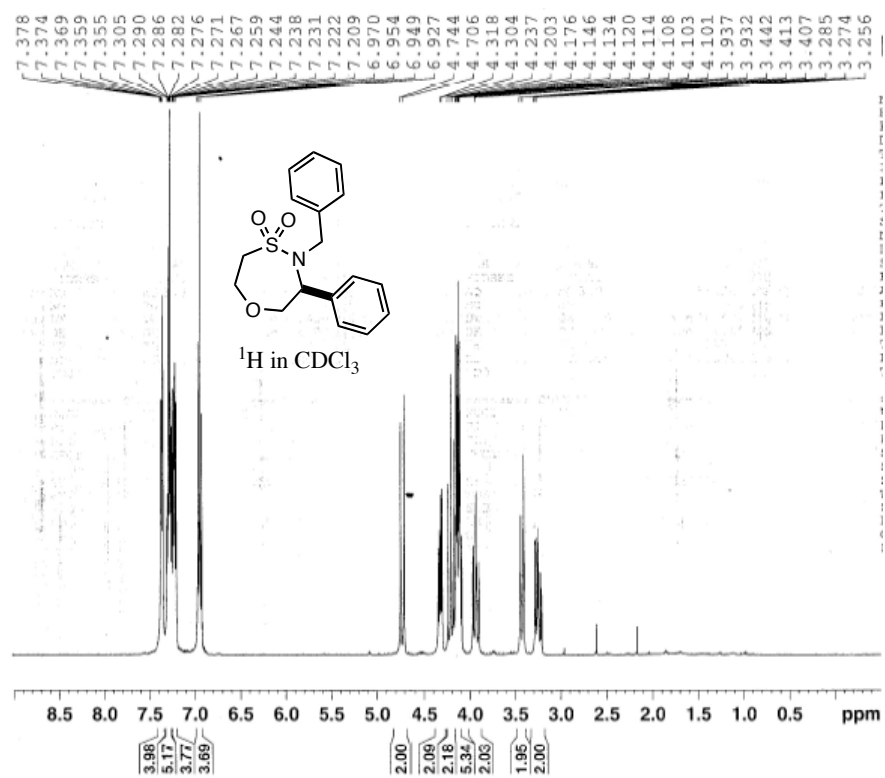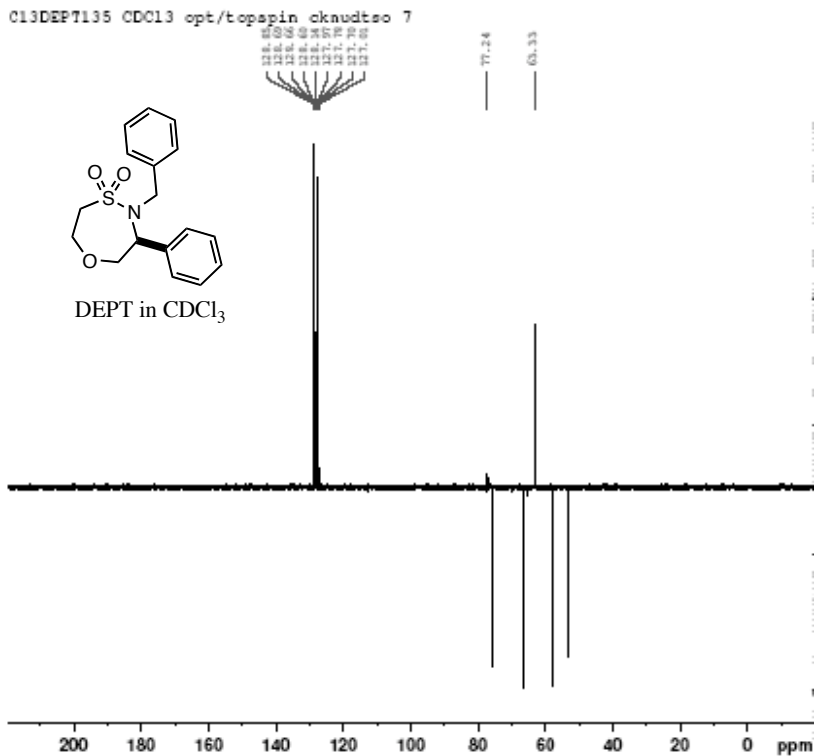


$^1$H in CDCl$_3$



$^{13}$C in CDCl$_3$

DEPT in CDCl$_3$

**(S)-*N*-2-(4-fluorobenzyl)-3-phenyl-5,1,2-oxathiazepane-1,1-dioxide (11d)**

$^1$H in CDCl$_3$

¹³C in CDCl₃

DEPT in CDCl₃

## (S)-*N*-2-(2-fluorobenzyl)-3-phenyl-5,1,2-oxathiazepane-1,1-dioxide (11e)



$^1$H in CDCl$_3$

C13CPD CDC13 opt/topspin cknudtso 19



$^{13}$C in CDCl$_3$

# (6S)-5-[(3,4-dichlorophenyl)methyl]-6-phenyl-1,4,5-oxathiazepane 4,4-dioxide (11m)



$^1$H in CDCl$_3$



$^{13}$C in CDCl$_3$

C13DEPT135 CDC13 opt/topspin cknudtso 1

DEPT in CDCl$_3$

200  180  160  140  120  100  80  60  40  20  0  ppm

**_N_-2-(3-Fluorobenzyl)-3(_S_)-phenyl-5,1,2-oxathiazepine-1,1-dioxide (11n)**



PROTON CDC13 /opt/topspin cknudtso 40

$^1$H in CDCl$_3$

8.5  8.0  7.5  7.0  6.5  6.0  5.5  5.0  4.5  4.0  3.5  3.0  2.5  2.0  1.5  1.0  0.5  ppm

1.97  4.20  1.00  1.98    1.01  1.02  1.00  2.57  1.03  1.01  1.01

$^{13}$C in CDCl$_3$

DEPT in CDCl$_3$

# (6S)-5-[(4-bromophenyl)methyl]-6-butyl-1,4,5-oxathiazepane-4,4-dioxide (12r)
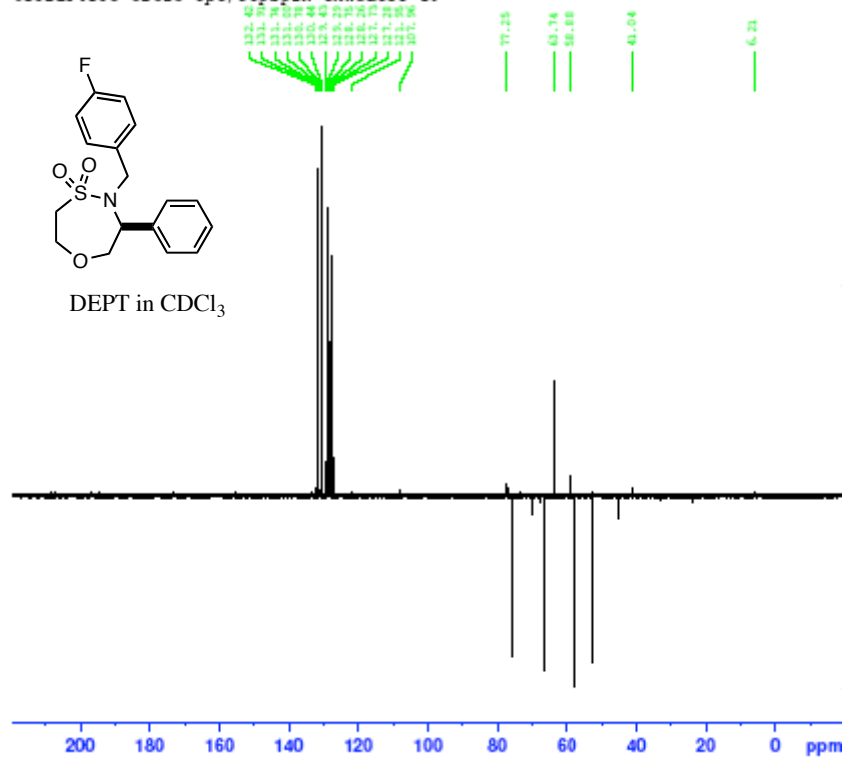


$^1$H in CDCl$_3$

C13CPD CDC13 opt/topspin cknudtso 20
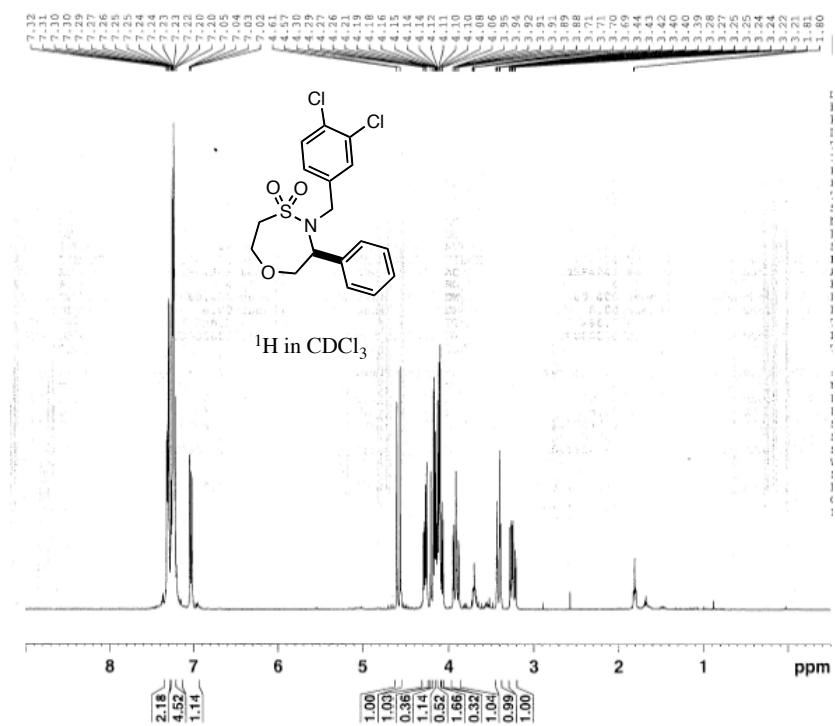
$^{13}$C in CDCl$_3$

C13DEPT135 CDC13 opt/topspin cknudtso 20
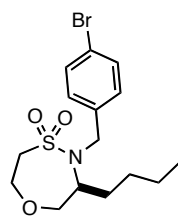
DEPT in CDCl₃

**N-2-(4-Bromobenzyl)-3(S)-isobutyl-5,1,2-oxathiazepine-1,1-dioxide (13r)**
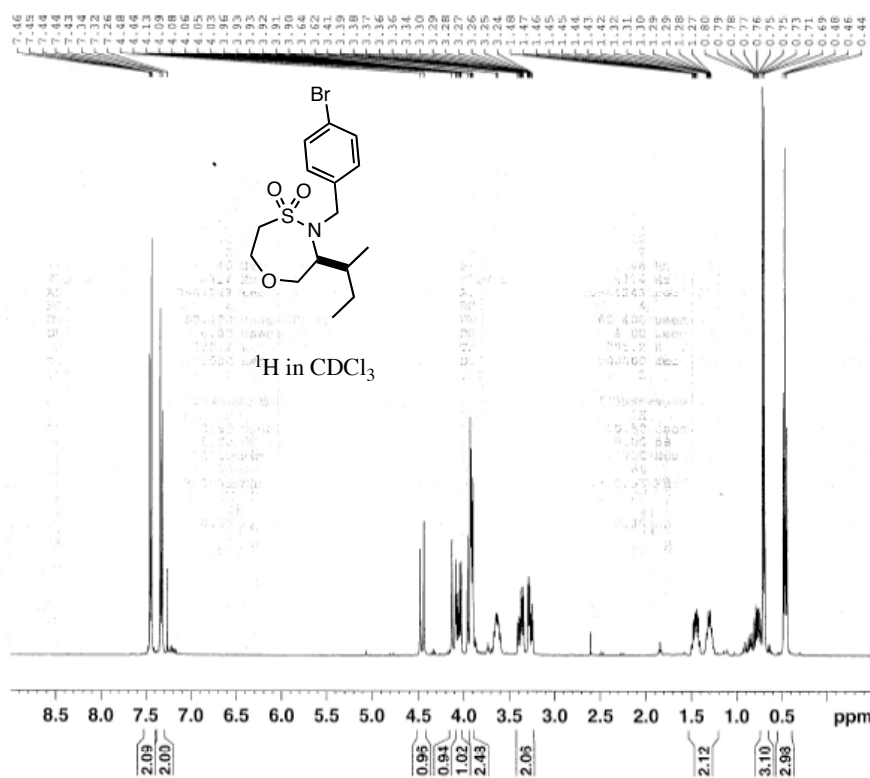
¹H in CDCl₃

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

$^{13}$C in CDCl$_3$

DEPT in CDCl$_3$

## Selected Intermediates for Baylis-Hillman-derived Sultams.
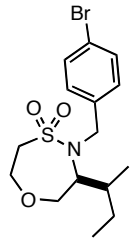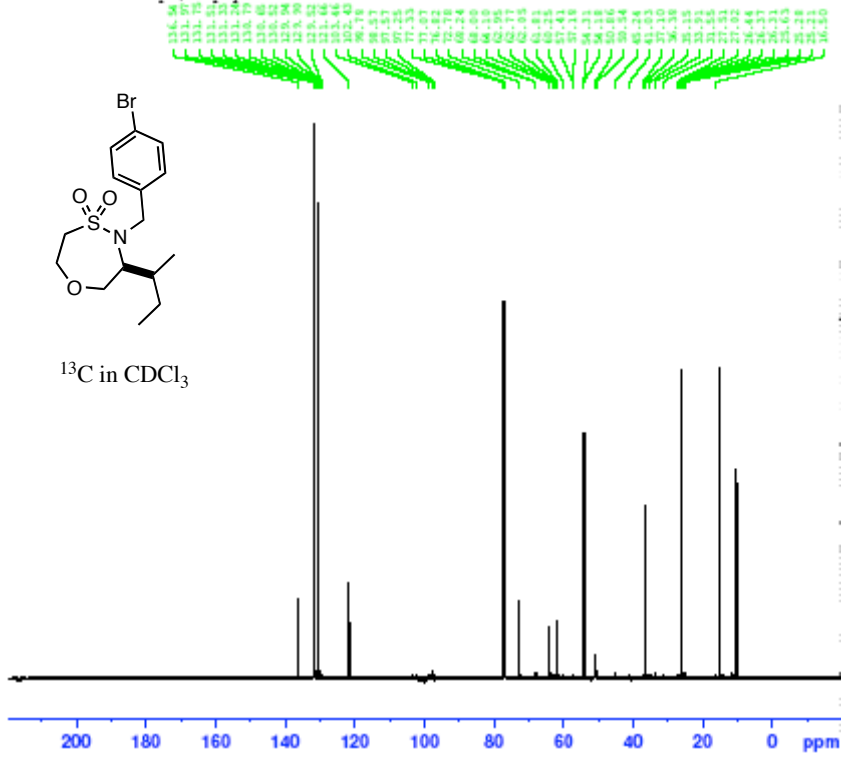
### *N*-benzyl-vinylsulfonamide 7c
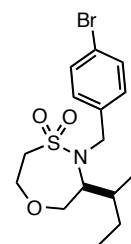


$^1$H in CDCl$_3$



DEPT in CDCl$_3$

### *N*-(*tert*-butyl)-vinylsulfonamide 7e
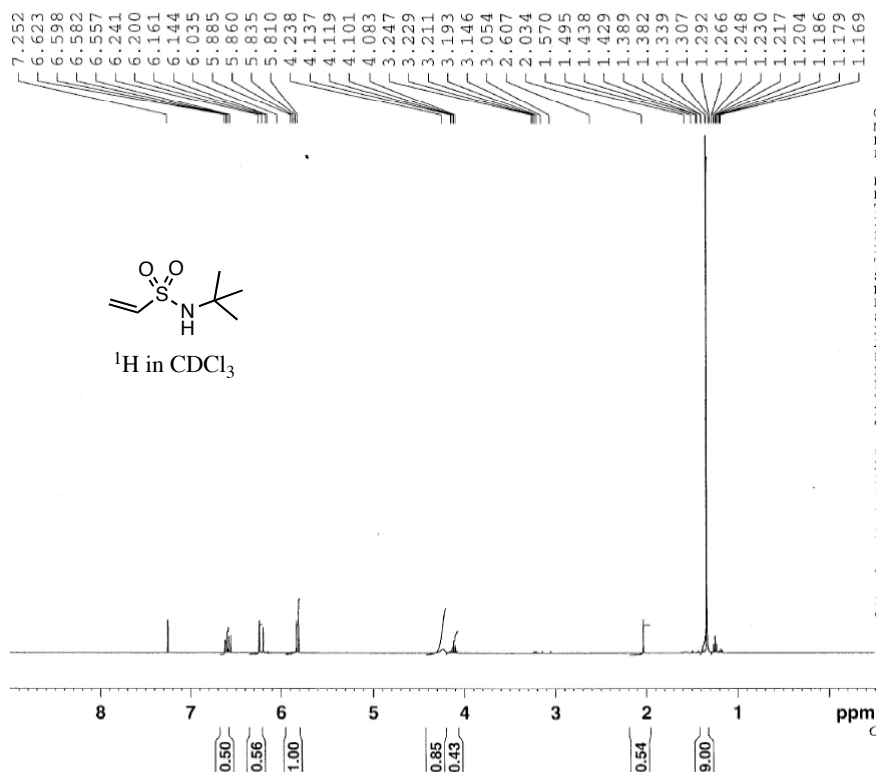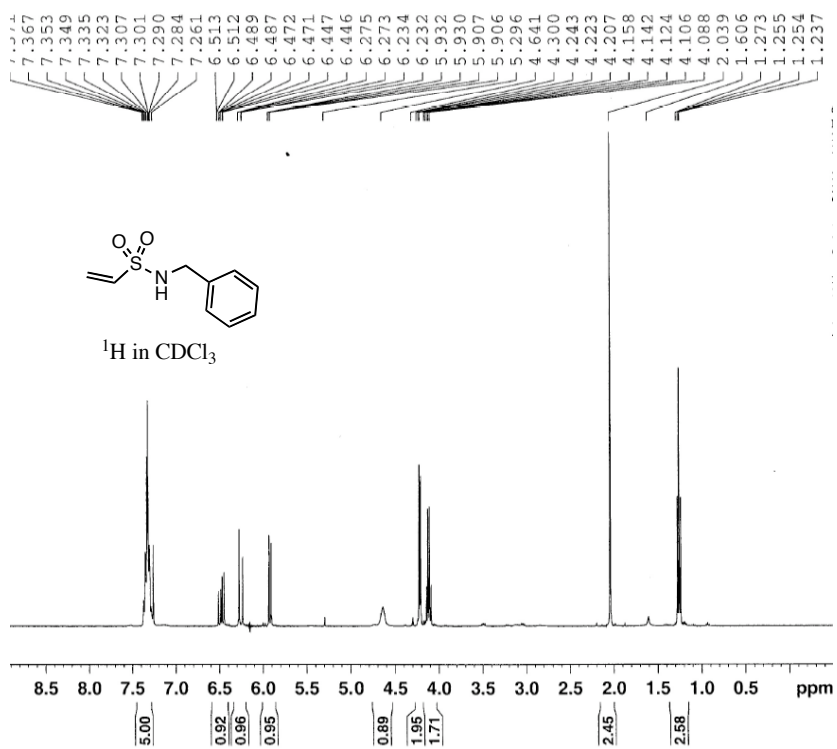


$^1$H in CDCl$_3$

### *N*-benzyl-vinylsulfonamide 7c



$^1$H in CDCl$_3$

## *N*-Allyl-*N*-isopropyl-vinylsulfonamide 8a



¹H in CDCl₃

## *N*-Allyl-*N*-benzyl-vinylsulfonamide 8c



¹H in CDCl₃
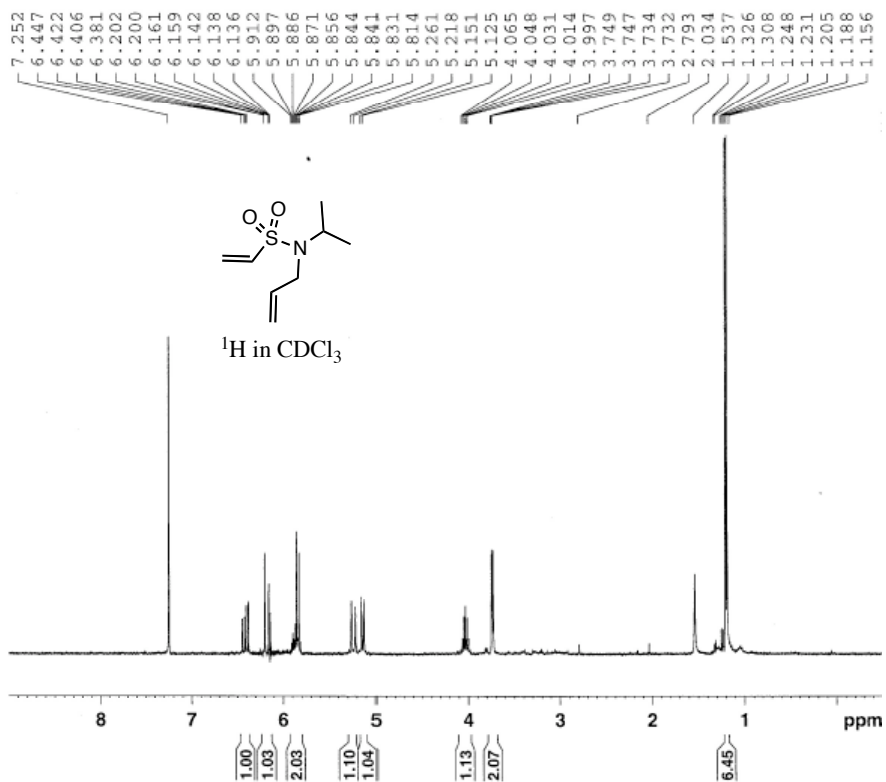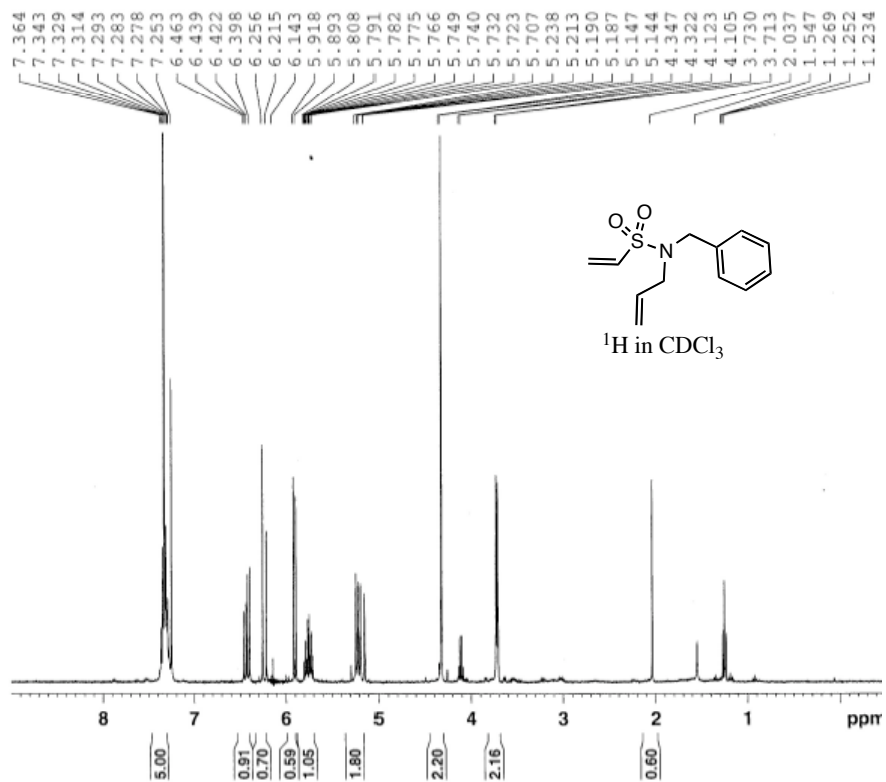
### *N*-isopropyl-*N*-(2-oxoethyl)ethenesulfonamide 9a



<sup>1</sup>H in CDCl<sub>3</sub>
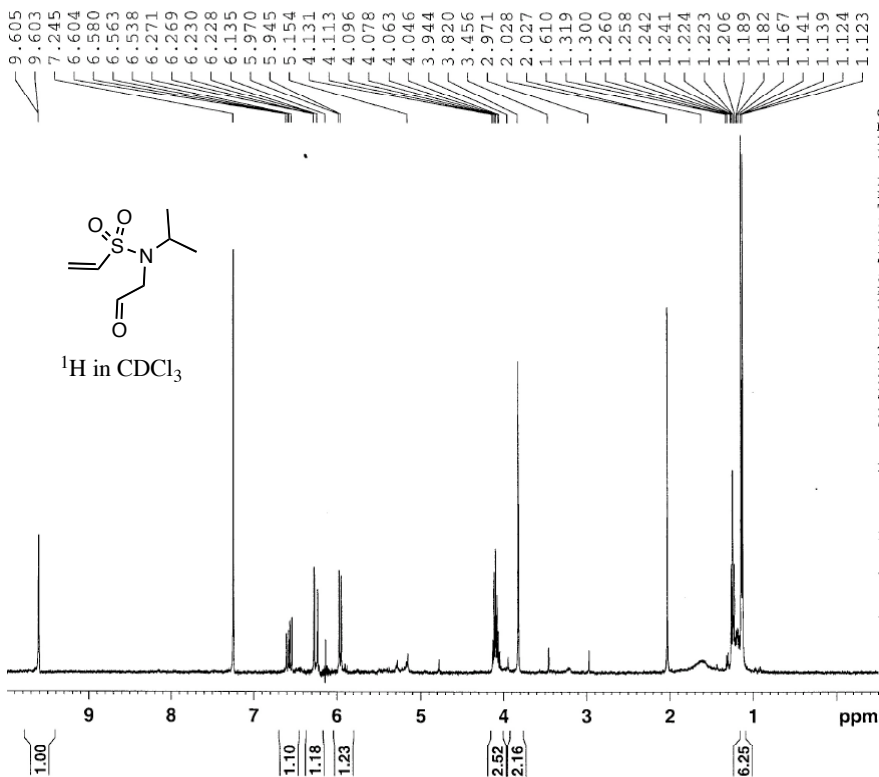
### *N*-isopropyl-*N*-(*tert*-butyl)ethenesulfonamide 9e
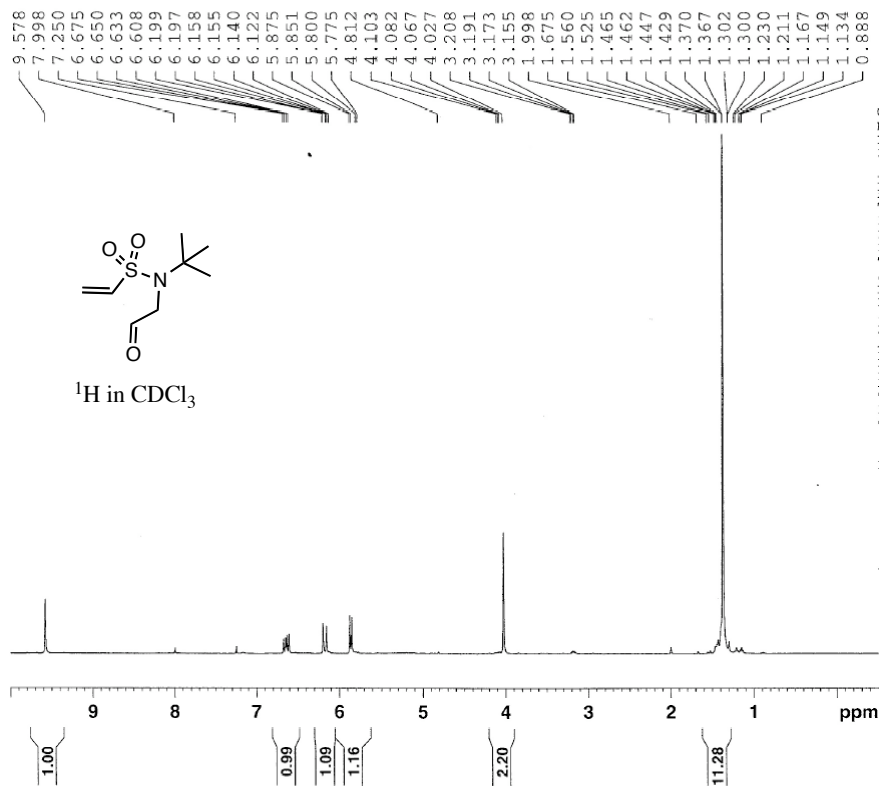


<sup>1</sup>H in CDCl<sub>3</sub>

**Methyl-2-(*N*-(2-oxoethyl)vinylsulfonamido)acetate 9g**



$^1$H in CDCl$_3$
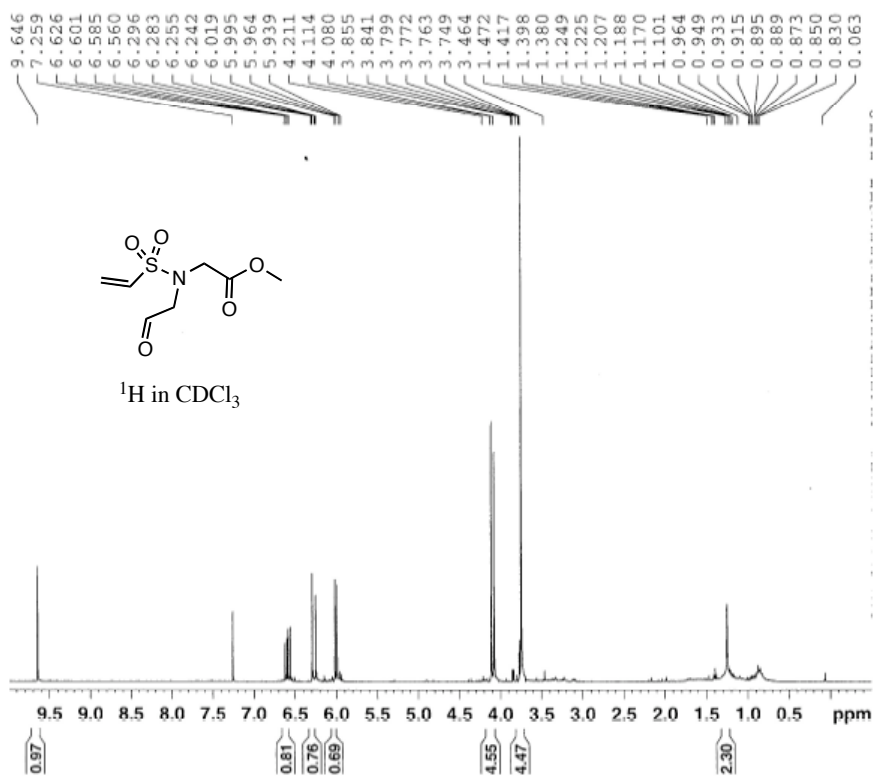
**Final Compounds Baylis-Hillman-derived Sultams.**

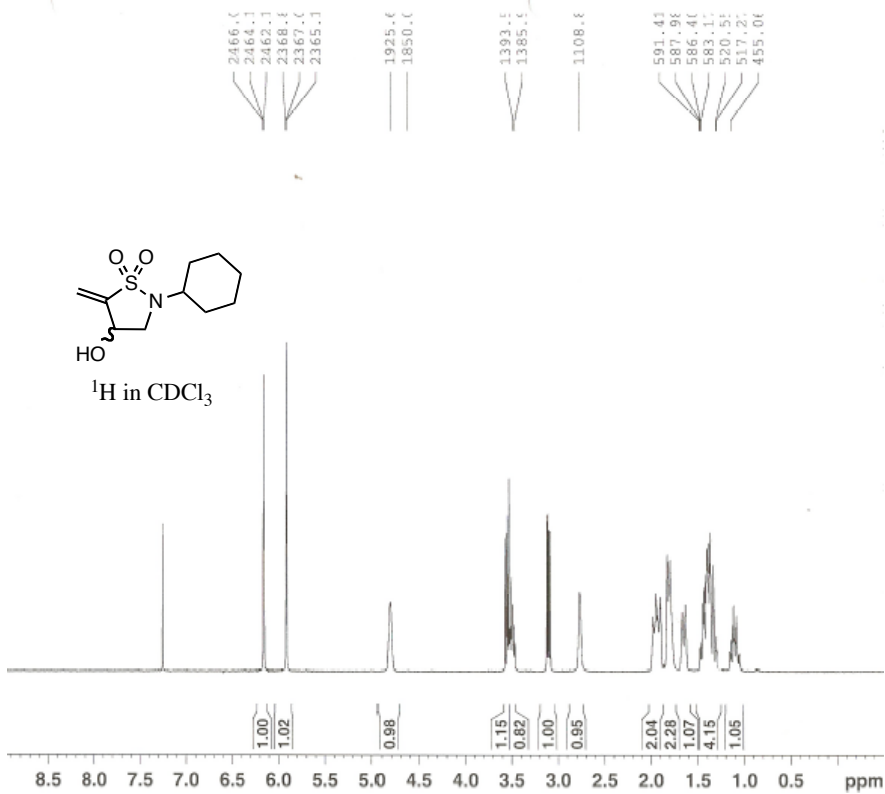**2-isopropyl-4-hydroxy-5-methyleneisothiazolidine 1,1-dioxide 10a**
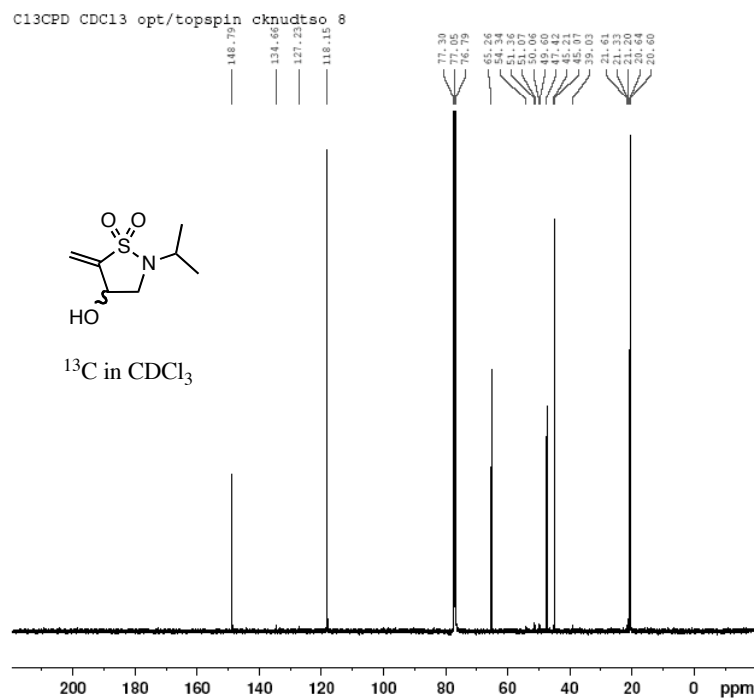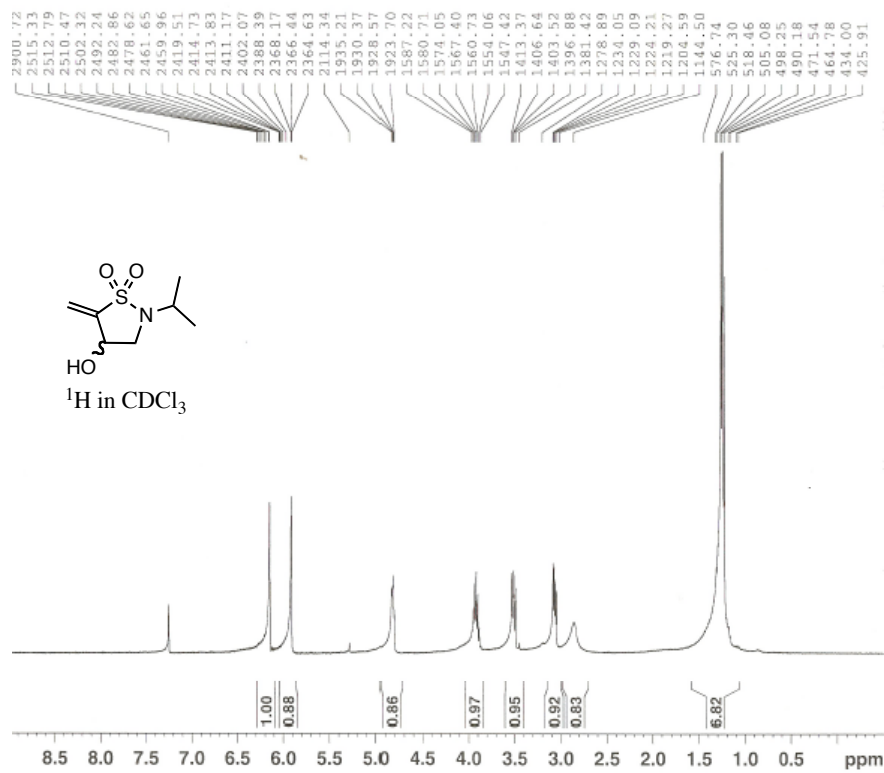


¹H in CDCl₃



¹³C in CDCl₃

# 4-hydroxy-2-(4-methoxyphenyl)-5-methyleneisothiazolidine 1,1-dioxide 10b
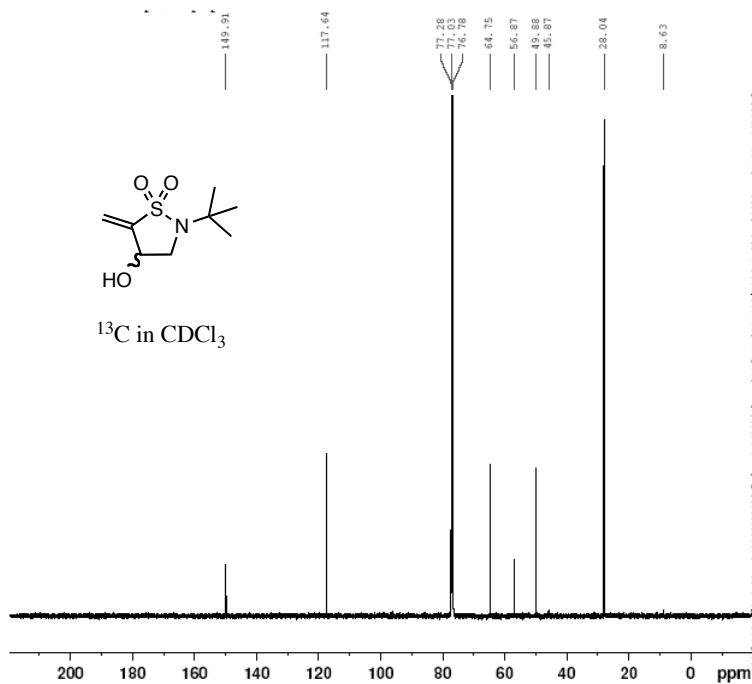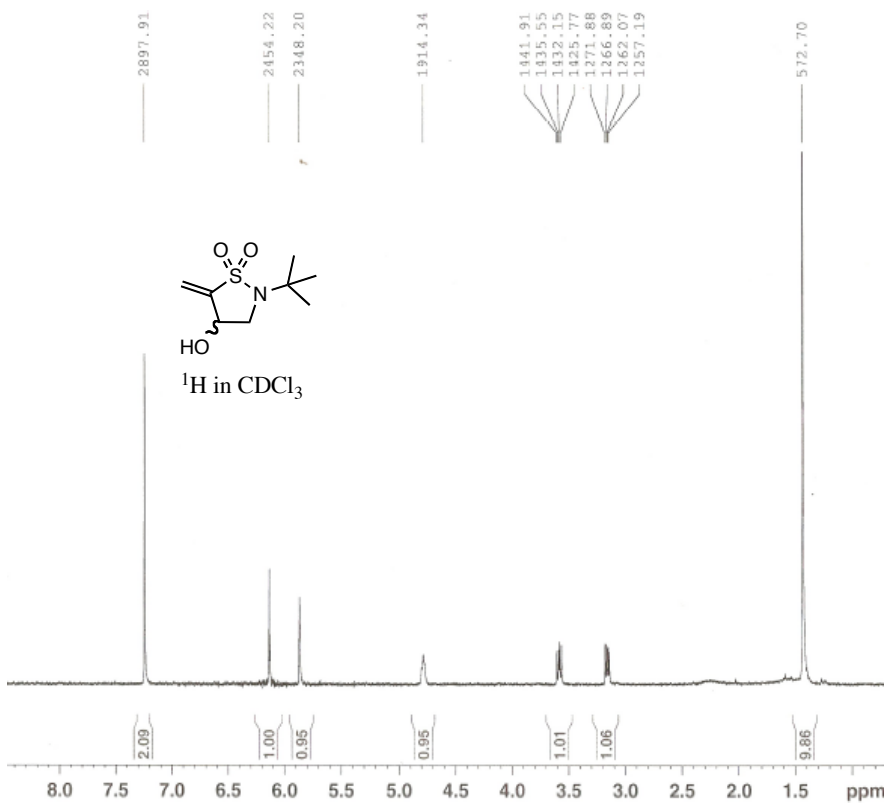


$^1$H in CDCl$_3$



$^{13}$C in CDCl$_3$

## 2-benzyl-4-hydroxy-5-methyleneisothiazolidine 1,1-dioxide 10c



$^1$H in CDCl$_3$
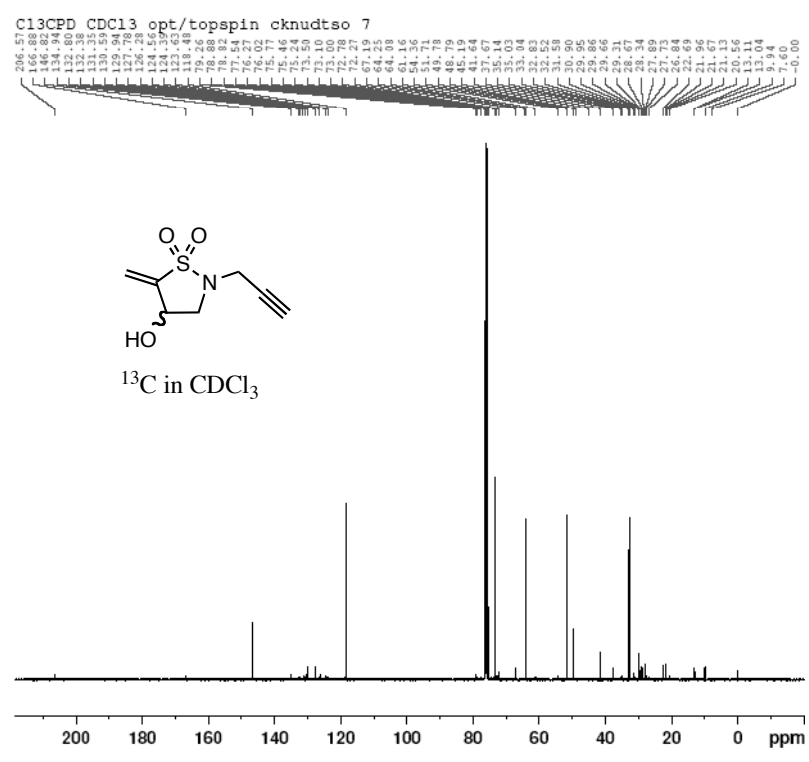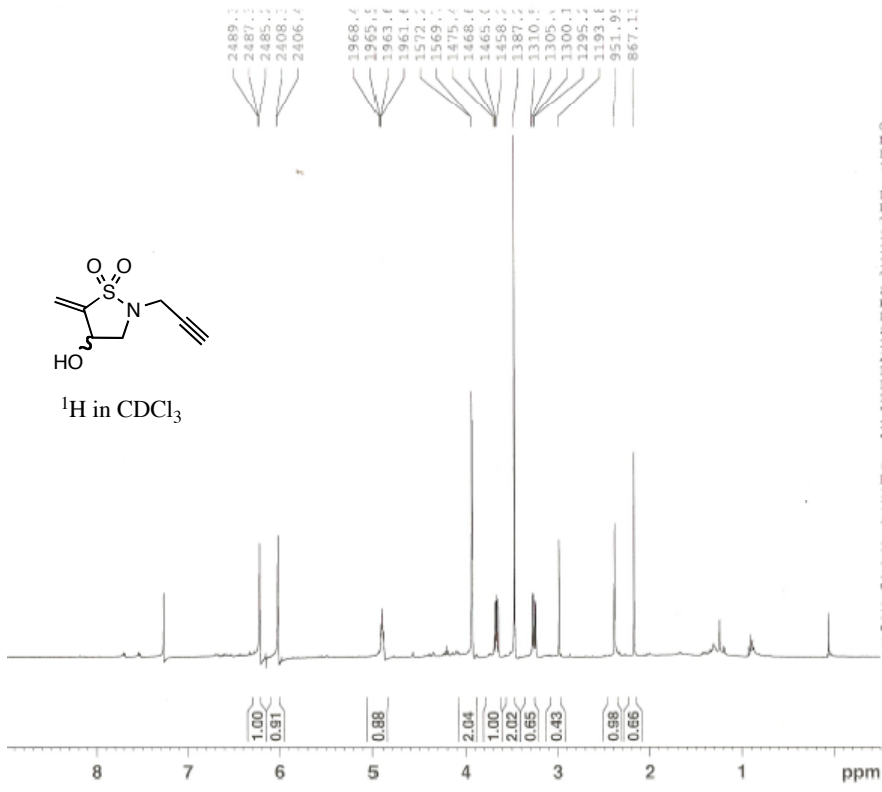


$^{13}$C in CDCl$_3$

C13CPD CDC13 opt/topspin cknudtso 4
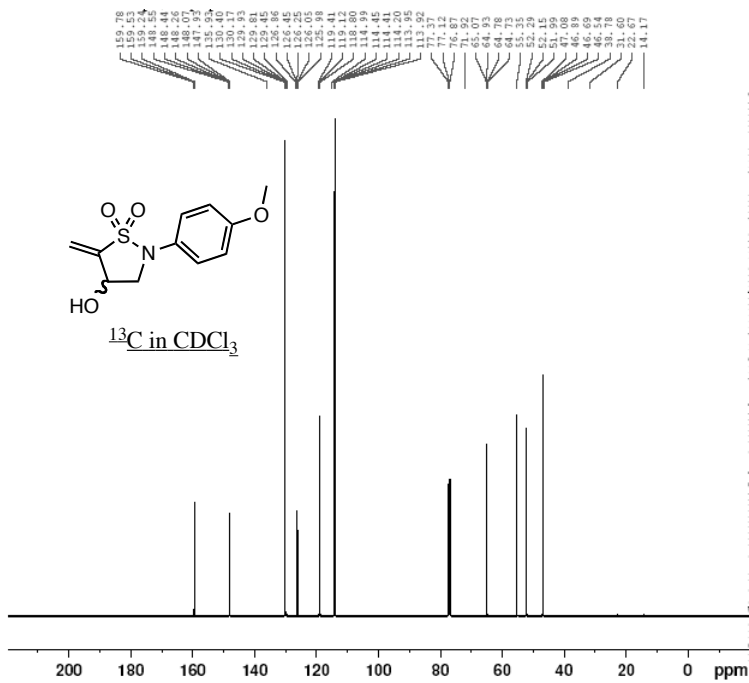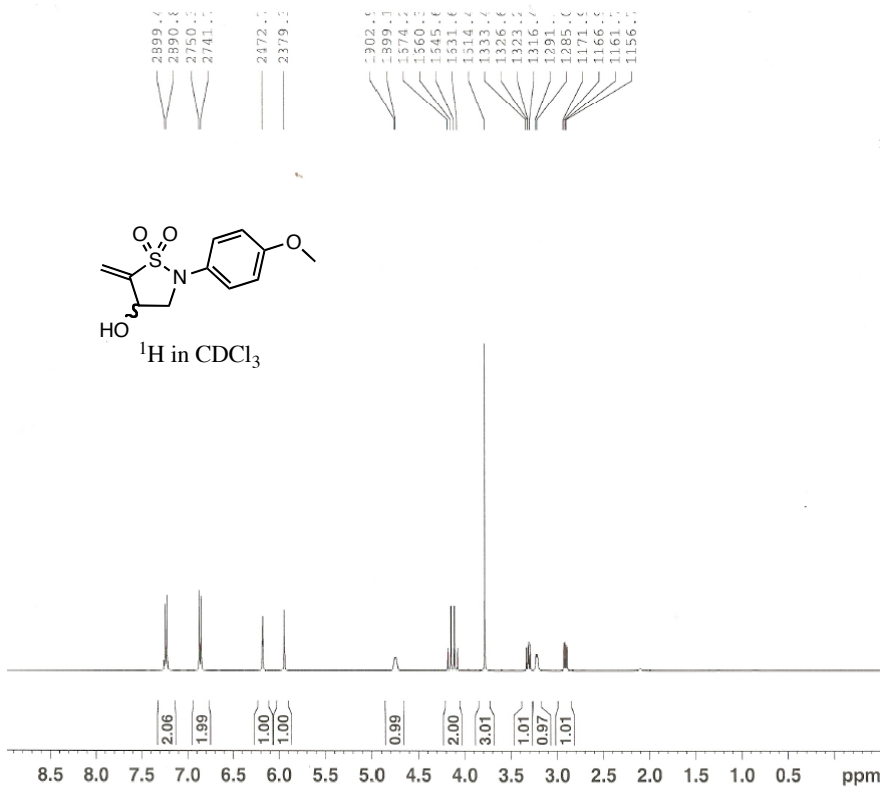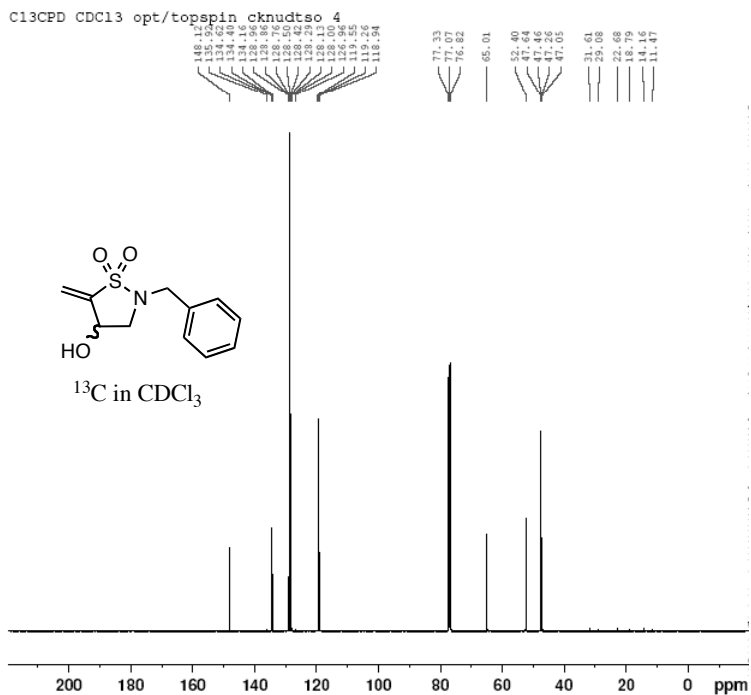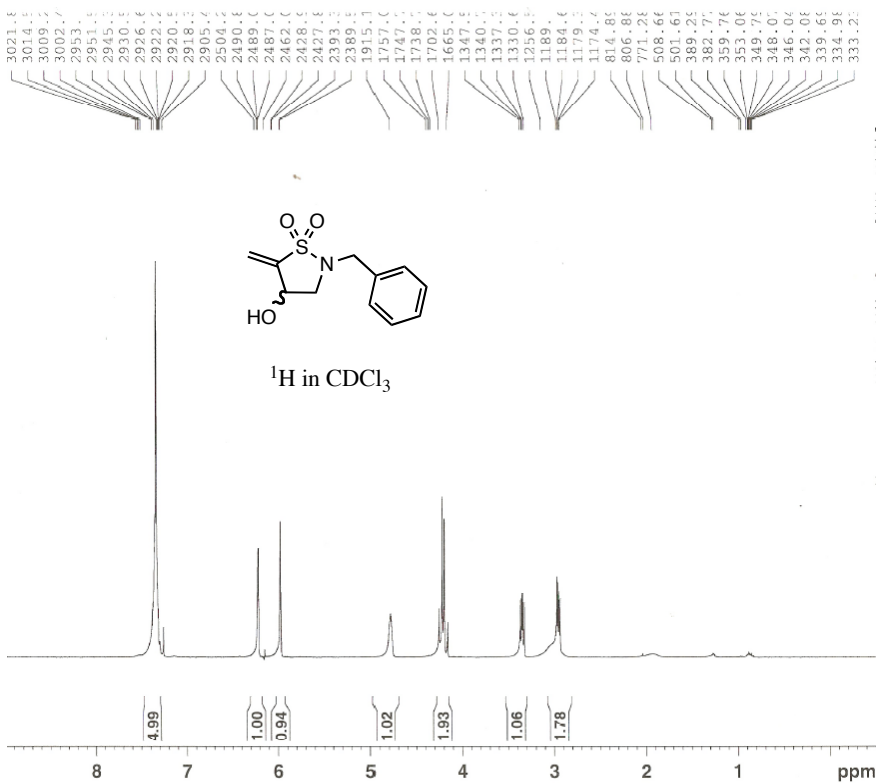
## 2-Cyclohexyl-4-hydroxy-5-methyleneisothiazolidine 1,1-dioxide 10d

**2-(*tert*-butyl)-4-hydroxy-5-methyleneisothiazolidine 1,1-dioxide 10e**

¹H in CDCl₃



¹³C in CDCl₃

**4-Hydroxy-5-methylene-2-(prop-2-yn-1-yl)isothiazolidine 1,1-dioxide 10f**

$^1$H in CDCl$_3$



C13CPD CDC13 opt/topspin cknudtso 7

$^{13}$C in CDCl$_3$

**Methyl 2-(4-hydroxy-5-methylene-1,1-dioxidoisothiazolidin-2-yl)acetate 10g**

¹H in CDCl₃



C13CPD CDC13 opt/topspin cknudtso 5

¹³C in CDCl₃