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An RCM Strategy to Stereodiverse δ-Sultam Scaffolds

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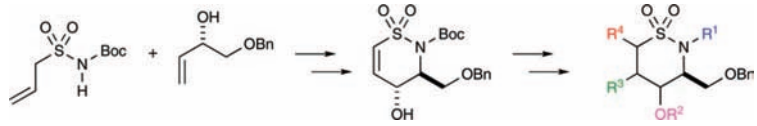
ABSTRACT



An asymmetric approach for the synthesis of substituted δ-sultams with multiple synthetic handles is described. This study demonstrates the facile construction of a stereochemically diverse array of substituted δ-sultams, more specifically substituted 3,4,5,6-dihydro 1,2-thiazine 1,1-dioxides. A pivotal Mitsunobu alkylation/RCM sequence is used to assemble key allyl sultam building blocks possessing a C3 stereogenic handle. All subsequent reactions are achieved with high levels of diastereoselectivity to afford enantiopure δ-sultams in good yields.

Compounds containing the sulfonamide moiety have gained wide popularity due to their extensive chemical and biological profiles, making them promising candidates in drug discovery.[1] Sultams (cyclic sulfonamides), although not found in nature,[2] have also shown potent biological activity, including several with medicinal value. A brief survey of the literature reveals that there are more than 60 sultams with impressive biological activity. The more prominent include the antiepileptic agent sulthiame (**1**) (Figure 1),[3] brinzolamide (**2**)[4] for the treatment of glaucoma, the COX-2 inhibitors ampiroxicam (**3**)[5] and S-2474 (**4**),[6] novel benzodithiazine dioxides with both antiviral and anticancer activities (**5**),[7a] selective inhibitors of calpain I (**6**),[7b] and most recently pyrrolo[1,2-*b*][1,2,5]benzothiadiazepines,[8] a new class of

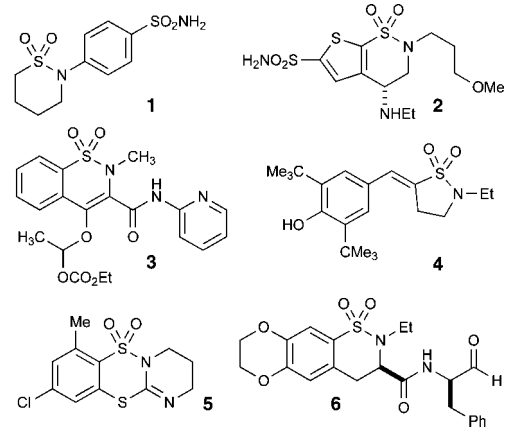


Figure 1. Biologically active sultams.

potential agents for treatment against chronic myelogenous leukemia. In addition, this impressive biological profile is augmented by a number of chemical properties including facile coupling pathways for their formation, stability to

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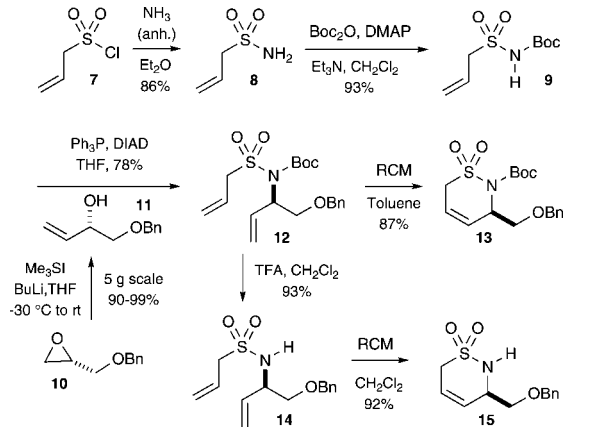
hydrolysis, polarity, and their crystalline nature. Taken collectively, these attributes have allowed sultams to emerge as privileged structures in drug discovery.

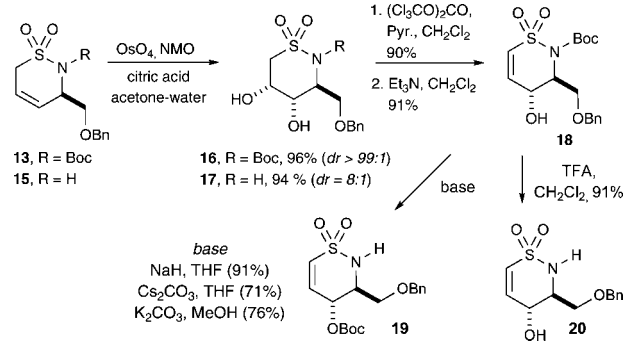
Traditionally, sultam synthesis has relied on classical cyclization protocols such as Pictet−Spengler,[8] Friedel−Crafts,[9] dianion,[10] cyclization of aminosulfonyl chlorides,[11] [3 + 2] cycloadditions,[12] and Diels−Alder reactions.[13] Recently, however, a number of transition-metal-catalyzed approaches to sultams have come to light, including the use of Pd-,[14] Au-,[15] Cu-,[16] and Rh-catalyzed cyclizations.[17] Moreover, RCM has been reported to generate several interesting sulfur-containing heterocycles with biological potential.[2,18] Our continuous interest in the development of transition-metal-catalyzed approaches to sulfur and phosphorus heterocycles (*S*- and *P*-heterocycles)[18] has prompt us to investigate an RCM approach for the synthesis of chiral, nonracemic sultams. The method is designed to afford sultams containing multiple handles as attractive scaffolds for potential library production with the ultimate goal of uncovering interesting biological leads. The method we herein report utilizes a key Mitsunobu alkylation reaction to install a stereogenic center at C3 (Scheme 1). Ensuing metathesis is used as the cyclization event to yield key allyl sultam building blocks **13** and **15**. All subsequent reactions leading to more complex building blocks are achieved with high levels of diastereoselectivity to afford enantiopure δ-sultams in good yields (Schemes 2–5).

Scheme 1. RCM Strategy to Sultams **13** and **15**



Our approach began with the multigram production of allylsulfonyl chloride (**7**).[19] Subsequent amination with anhydrous NH_3, following the procedure reported by Belous and co-workers, afforded sulfonamide **8** in good yields.[19] Monoprotection with Boc_2O[20] afforded sulfonamide **9** (93%), possessing an acidic proton (N−H) suitable for Mitsunobu alkylation (Scheme 1). Mitsunobu reaction with chiral, nonracemic alcohol **11**, derived from epoxide **10** using the Christie protocol,[21] afforded the RCM precursor **12** in good yield (78%). Initial attempts to obtain **13** via RCM using the second-generation Grubbs catalyst[22] in refluxing CH_2Cl_2 or DCE were unsuccessful. Subsequent RCM studies revealed that **13** could be obtained in good yield when toluene was used as the solvent under refluxing conditions. Alternatively, Boc-removal in diene **12** using TFA, followed by RCM in refluxing CH_2Cl_2, afforded the δ-sultam **15** in excellent yield.[23]

Scheme 2. Facile Route to γ-Hydroxy Sultam **18**



The diastereoselective route to the desired δ-sultam **18** continued with dihydroxylation of cyclized products **13** and **15** (Scheme 2). When sultam **15** (R = H) was first subjected

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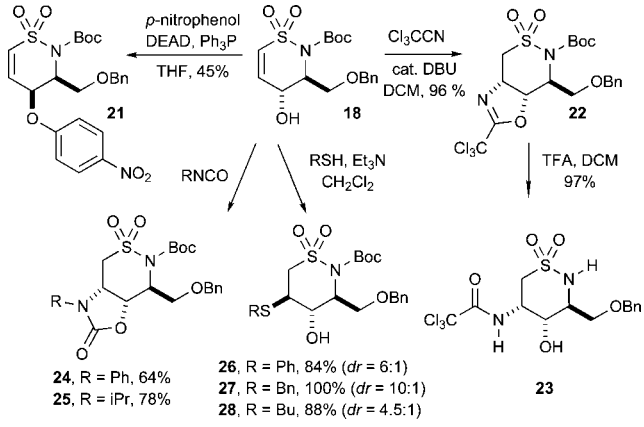
to dihydroxylation, an inseparable mixture of diastereomers (dr ~8:1) was obtained. However, dihydroxylation of the Boc-protected sultam **13** resulted in the formation of *cis*-diol **16** as a single diastereomer in excellent yield (96%). This result further substantiates the aforementioned $A^{1,2}$ effects,[23] which presumably force the CH_2OBn group at C3 into an axial orientation, thus accentuating dihydroxylation from the opposite face. The relative stereochemistry of **16** was confirmed by X-ray crystallography (see the Supporting Information). Conversion of this diol to the respective carbonate was achieved using triphosgene,[24,25] followed by base-promoted elimination with Et_3N[25] under refluxing DCM to afford the γ-hydroxy vinyl δ-sultam **18** in 91% yield. This protocol was previously shown in our laboratory to be applicable to the synthesis of phosphono sugars.[25] Attempted functionalization of the C4 hydroxyl group in sultam **18** using various inorganic bases such as NaH, Cs_2CO_3, or K_2CO_3 resulted in an unexpected intramolecular Boc-migration onto the γ-hydroxy group, providing δ-sultam **19** in good to excellent yields (Scheme 2). Schreiber and co-workers have previously reported an analogous Boc group migration event.[26] Treatment of sultam **18** with TFA in CH_2Cl_2 resulted in Boc removal to afford the γ-hydroxy vinyl δ-sultam **20** as a crystalline solid in 91% yield.

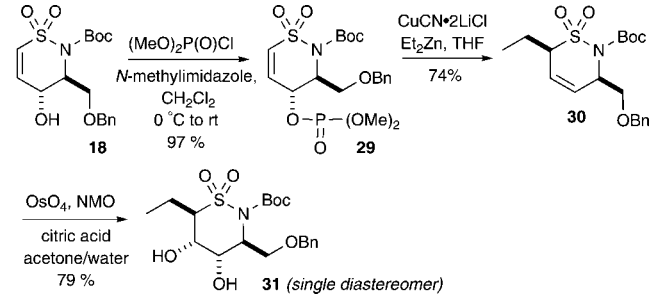
Scheme 3. Diversification of Sultam **18**



With the desired scaffold **18** in hand, we turned our attention to an array of diversification reactions highlighted in Scheme 3. Mitsunobu reaction with *p*-nitrophenol afforded allylic ether **21** in moderate yields. Attempts to perform the Mitsunobu reaction with phenol or substituted phenols containing electron-donating groups were unsuccessful. We next focused on the addition of nucleophiles into **18**. Consequently, **18** was treated with Cl_3CCN in the presence of catalytic amounts of DBU in CH_2Cl_2 to afford trichloroacetimidate **22** in excellent yield (96%) via an intramolecular Michael addition. Further treatment of **22** with TFA (CH_2Cl_2 at rt) afforded amino alcohol **23** in 97% yield (Scheme 3). This concept was expanded to isocyanates in attempts to form bicyclic sultams. Treatment of **18** with phenyl isocyanate (PhNCO) and Et_3N in CH_2Cl_2 at reflux afforded sultam **24** in good yield (64%) via conjugate addition (Scheme 3). When isopropyl isocyanate (^{i}PrNCO) was utilized under identical conditions, prolonged reaction times were necessary to obtain the cyclized product **25** in good yield (78%).

Intermolecular nucleophilic additions of thiols were next explored. Previous work reported by Roush[27] revealed that vinyl sulfonamides are good Michael acceptors of sulfur nucleophiles. Addition of PhSH to sultam **18** in the presence of catalytic amounts of Et_3N (CH_2Cl_2 at rt)[28] afforded sultam **26** in good yield (84%) as a mixture of inseparable diastereomers (dr ~6:1) as determined by ^{1}H NMR. Addition of $PhCH_2SH$ under identical reaction conditions afforded sultam **27** in quantitative yield as a separable mixture of diastereomers with improved diastereoselectivity (dr ~10:1). Addition of butanethiol resulted in the formation of sultam **28** in 88% yield as a mixture of inseparable diastereomers (dr ~4.5:1). The addition of 2-methyl-propane-2-thiol [$(CH_3)_3CSH$] under the same reaction conditions failed to produce the Michael adduct, presumably due to steric factors.

Scheme 4. Diastereoselective Phosphate Displacement



Interest in potential diversification at the α-position of sultam **18** led us to explore installation of alkyl groups with the ultimate goal of incorporating different functional groups throughout the periphery of the ring. In order to accomplish this, we explored the use of an S_N2' cuprate displacement of the corresponding phosphate.[29] Thus, treatment of **18** with $(MeO)_2P(O)Cl$ in the presence of *N*-methylimidazole in

(23) These results indicated that $A^{1,2}$-strain between the vicinally substituted Boc-group at N2 and the CH_2OBn group at C3 presumably force the two terminal olefins to orient in opposite directions, thus requiring higher temperatures for cyclization.

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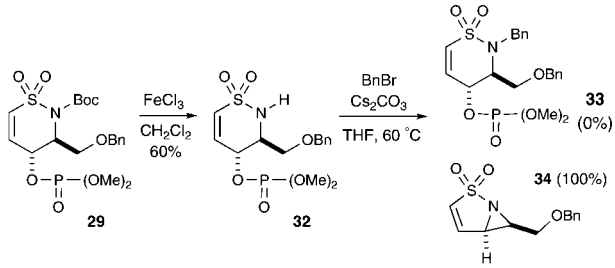
CH_2Cl_2 at 0 °C afforded allylic phosphate **29** in excellent yield (97%) (Scheme 4).[30] Subjection of allylic phosphate **29** to conjugate addition via ethyl cuprate formation under Knochel's conditions[31] was performed by adding an excess of diethylzinc cuprate to provide sultam **30** in good yield (74%) and excellent regio- and diastereoselectivity. The 3,6-disubstituted *δ*-sultam **30** was tentatively assigned as the diastereomer arising from anti addition in accordance with the Corey mechanism.[29b,c] This product was further dihydroxylated under Os-mediated conditions to afford *cis*-diol **31** as a single diastereomer in good yield (79%).

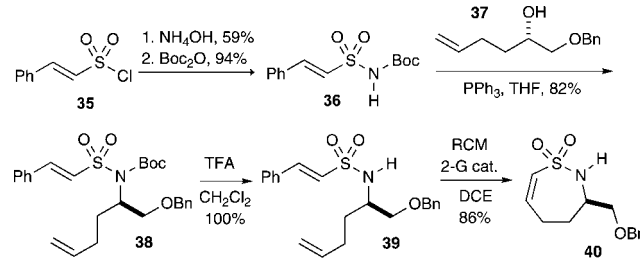
Scheme 5. Unexpected Internal S_N2 Displacement Pathway



A diversification/cuprate addition strategy was next explored. This approach involved deprotection via removal of the *N*-Boc group, followed by benzylation at the free N−H site to generate sultam **33** (Scheme 5). Initial attempts to remove the Boc group in sultam **29** using TFA in CH_2Cl_2 resulted in hydrolysis of the phosphate moiety. Milder reaction conditions were then studied and revealed that treatment of sultam **29** with 1.0−1.5 equiv of $FeCl_3$[32] (CH_2Cl_2, rt, 30 min) afforded, after aqueous workup, sultam **32** in 60% yield. Introduction of an alkyl group at the nitrogen was sought via benzylation under basic conditions (BnBr, Cs_2CO_3, THF, 65 °C) to obtain benzyl sultam **33**. However, a product lacking both phosphate and benzyl moieties was isolated and later confirmed as aziridine **34**. This unexpected product is presumably the result of direct internal nucleophilic displacement of the C(4)-substituted phosphate. Additional studies concerning this internal S_N2 displacement pathway are underway.

The RCM strategy utilized for the facile assembly of *δ*-sultam scaffolds prompted our efforts into extending this methodology for the construction of 7-membered vinylic sultams as outlined in Scheme 6. Thus, treatment of styrylsulfonyl chloride[33] **35** with NH_4OH, followed by slow addition of Boc_2O,[20] afforded Boc-protected styrylsulfonamide **36** in high yield (94%). Mitsunobu alkylation with chiral, nonracemic alcohol **37**[34] afforded diene **38** in 82% yield. Removal of the Boc-group utilizing TFA in CH_2Cl_2 at rt provided sulfonamide **39** in quantitative yield. RCM in refluxing DCE afforded the seven-membered ring vinylic sultam **40** in 86% yield.

Scheme 6. RCM Strategy to Seven-Membered Sultam **40**



In conclusion, we have demonstrated a new method to synthesize a stereochemically diverse array of substituted 1,2-thiazine 1,1-dioxides. These scaffolds represent novel sultams, which can be utilized in the production of versatile and novel libraries. These studies are underway and will be reported in due course.

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Supporting Information Available: Experimental details and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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