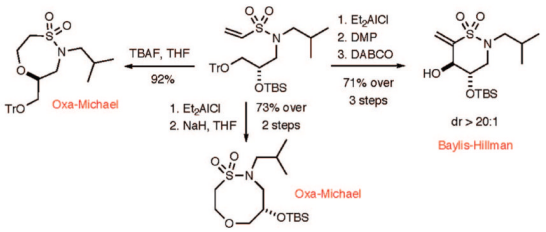
Published in final edited form as:
*Org Lett*. 2008 July 17; 10(14): 2951–2954. doi:10.1021/ol8009072.

# Synthesis of Sultam Scaffolds via Intramolecular Oxa-Michael and Diastereoselective Baylis—Hillman Reactions

**Aihua Zhou** and **Paul R. Hanson***
Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045-7582, and the Center for Chemical Methodologies and Library Development (CMLD) at the University of Kansas

## Abstract




A divergent synthetic approach to new sultams utilizing intramolecular oxa-Michael and Baylis—Hillman reactions of readily prepared vinyl sulfonamides and suitably protected amino alcohols, is reported. A variety of seven- and eight-membered ring sultam scaffolds were synthesized using oxa-Michael pathways, whereas both five- and six-membered rings were synthesized using Baylis—Hillman methods. Baylis—Hillman reactions proceed with good to excellent levels of diastereoselectivity, and oxa-Michael reactions leading to eight-membered ring sultams provide empirical evidence validating 8-*endo-trig* cyclization pathways.

Sulfonamides and their analogs have a rich chemical and biological history and have emerged as a promising class of compounds in drug discovery.[1] Sultams (cyclic sulfonamides), although not found in nature, have also shown potent biological activity, including several displaying a wide spectrum of activities.[2] The more prominent include the antiepileptic agent Sulthiame[3] (Figure 1), Brinzolamide[4] for the treatment of glaucoma, the COX-2 inhibitors Ampiroxicam[5] and S-2474,[6] and selective inhibitors of cysteine proteases involved in the progression of malaria.[7] In addition, a number of benzodithiazine dioxides and benzoxathiazepine 1,1-dioxides displaying anti-HIV-1 activity[8] and the ability to activate glucokinase[9] (type II diabetes), respectively, have been uncovered.

Traditionally, sultam syntheses have relied on classical cyclization protocols and a number of transition-metal-catalyzed processes that have recently been reported.[10] Interest in the generation of new sultams for biological screening has provided impetus for exploring the Michael-accepting ability of vinyl sulfonamides. In particular, we aimed to study the titled



*phanson@ku.edu.

**Supporting Information Available**: Experimental details and spectral characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

intramolecular oxa-Michael and Baylis—Hillman approaches for the synthesis of chiral, nonracemic sultams.

The oxa-Michael[11] and Baylis—Hillman[12,13] reactions have emerged as simple yet powerful methods for C—O and C—C bond formation. Both processes necessitate the presence of a competent electron-deficient Michael accepting moiety. The intermolecular oxa-Michael reaction has a long history dating back to its original discovery in 1878, roughly 5 years before the well-known Michael reaction was revealed.[11] The intramolecular version of the oxa-Michael reaction has seen a renaissance and has been extensively utilized in natural product synthesis for over 2 decades.[14]

In contrast, the Baylis—Hillman reaction was discovered in 1972.[12] Intramolecular versions of the Baylis—Hillman reaction have only recently gained favor,[13] where elegant work in this area has elevated the status of the intramolecular variant.[15] Although the Michael accepting ability of vinyl sulfones is well-documented,[16] their vinyl sulfonamide counterparts have assumed a far less prominent role as viable Michael acceptors.[10,17] We herein report the first examples of intramolecular oxa-Michael and Baylis—Hillman reactions of vinyl sulfonamides to afford an array of novel five-, six-, seven-, and eight-membered ring sultam scaffolds in good to excellent yields. The Baylis—Hillman reactions proceed with good to excellent levels of diastereoselectivity, ultimately yielding interesting sultam scaffolds. Overall, this divergent route can be used to produce skeletally diverse scaffolds from a single percursor in excellent yields.

The titled route began with the assembly of TBS-protected amino alcohols, which represent cheap and versatile building blocks for sultam scaffold synthesis. These TBS-protected alcohols were reacted with 2-chloroethanesulfonyl chloride to produce vinyl sulfonamides **2** in good yields (Scheme 1). Subsequent benzylation/allylation reactions of vinyl sulfonamides **2** yielded vinyl sulfonamides **3** in good yields over three steps. The intramolecular oxa-Michael reaction was initiated by TBS-deprotection with TBAF in THF to afford the unique seven- and eight-membered ring sultams, respectively, in excellent yield under mild condition.

Several examples of this straighforward procedure were examined as outlined in Table 1. In all cases the cyclization proceeded without incident. In several cases, the entire linear sequence could be run without the need for chromatography, ultimately resulting in the production of oxathiazepine- and oxathiazocine-dioxides, seven- and eight-membered ring systems, in excellent yields, respectively. To the best of our knowledge, this work represents the first report of using intramolecular oxa-Michael reactions to generate an eight-membered ring and enriches Baldwin's rules for ring closure.[18]

An orthogonal pathway leading to an intramolecular Baylis—Hillman reaction was next investigated. We observed that the intramolecular oxa-Michael reaction pathway was not operative under acidic conditions, and thus, a 10 mol % aqueous solution of HCl was implemented for TBS-deprotection of vinylsulfonamide **3**. Subsequent Dess—Martin oxidation yielded the aldehyde vinyl sulfonamide, which underwent smooth Baylis—Hillman reaction upon the addition of DABCO (10 mol %). Overall, the intramolecular Baylis—Hillman reaction was completed within 2–4 h, affording the vinyl sultam **5** in excellent yields and with moderate to good levels of diastereoselectivity (Table 2). Several other organocatalysts such as DMAP, DBU, quinine, quinidine, and brucine were also screened in this process. Overall, DABCO proved to be the most efficient for both yield and competitive diastereoselectivity.[19,20]

The TBS-protected prolinol-derived vinyl sulfonamide **7** was next studied where treatment with TBAF resulted in the production of the bicyclic sultam **8** in excellent yields via an oxa-Michael pathway (Scheme 2). In contrast, treatment of **7** with the aforementioned orthogonal

conditions involving acidic deprotection, oxidation, and addition of DABCO yielded the bicyclic sultam **10** with good yield and excellent diastereoselective ratio.

The method was extended to the readily prepared secondary alcohol, TBS-protected *trans*-2-amino-cyclohexanol (Scheme 3). Vinylsulfonylation and benzylation yielded the vinyl sulfonamide **12** in excellent yields. Treatment with TBAF yielded the bicyclic sultam **13** in excellent yield via an oxa-Michael pathway, and treatment with the orthogonal Baylis—Hillman conditions yielded the unique bicyclic vinyl sultam **15** in modest yield and extended reaction time (53%, 72 h) yet with excellent diastereoselectivity (dr > 95:5).

We next investigated the feasibility of extending the method to the generation of $\delta$-sultams (Scheme 4). To address this question, chiral, nonracemic amino TBS-protected alcohol **16** was synthesized starting from (*S*)-glycidyl trityl ether.[21] Subsequent TBS-protection and vinylsulfonylation with 2-chloroethanesulfonyl chloride afforded vinyl sulfonamide **18**. TBS-deprotection with TBAF afforded the $\delta$-sultam **19** in excellent yield via an intramolecular oxa-Michael pathway. The Baylis—Hillman pathway was initiated by use of a selective, orthogonal deprotection of the trityl ether in **18** at -10 °C using $Me_2AlCl$ ($CH_2Cl_2$ solution) to yield vinylsulfonamide **20** in good yield. The resulting alcohol was oxidized to aldehyde **21** using the Dess—Martin agent as previously described. Treatment with DABCO afforded the $\delta$-sultam scaffold **22** in excellent yield and diastereoselectivity (dr > 95:5).[22] The intramolecular oxa-Michael reaction of **20** was also pursued to afford the eight-membered-ring sultam by using NaH in THF. This reaction proceeded quickly and gave a high yield of the eight-membered-ring sultam **23**.

In summary, the first examples of intramolecular oxa-Michael and Baylis—Hillman reactions to synthesize five-, six-, seven-, and eight-membered ring sultams have been attained. Moreover, empirical evidence validating 8-*endo*-*trig* cyclization pathways in oxa-Michael reactions has been presented that enriches Baldwin's rules for ring closure. The titled oxa-Michael and Baylis—Hillman reactions are completed within short order and occur with excellent yields. In addition, good to excellent levels of diastereoselectivity were achieved throughout the Baylis—Hillman study. Overall, these two reactions can be conveniently combined into one synthetic route to produce skeletally diverse scaffolds from a single percursor in excellent yields. In addition, the method is highly amenable to library generation and current efforts are currently engaged in this endeavor.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgment

This investigation was generously supported by funds provided by the National Institutes of General Medical Sciences Center for Chemical Methodologies and Library Development at the University of Kansas (P50 GM069663) and NIGMS Pilot-Scale Libraries Program (NIH P41 GM076302). The authors thank Dr. David VanderVelde (Director of the NMR Laboratory at The University of Kansas) for helpful discussions regarding NMR structure assignments. The authors also thank Daiso Co., Ltd., Fine Chemical Department for donation of trityl-protected glycidol. (email: akkimura@daiso.co.jp).

## References

(1) (a). Drews J. Science 2000;287:1960–1964. [PubMed: 10720314] (b) Scozzafava A, Owa T, Mastrolorenzo A, Supuran CT. Curr. Med. Chem 2003;10:925–953. [PubMed: 12678681]

(2) (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 MR, Russo MA, Amadori S, Cirilli R, La Torre F, Salimei PS. J. Med. Chem 2006;49:5840–5844. [PubMed: 16970408] (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. [PubMed: 16279796]

(3). Tanimukai H, Inui M, Hariguchi S, Kaneko Z. Biochem. Pharmacol 1965;14:961–970. [PubMed: 5835875]

(4). Wroblewski T, Graul A, Castaner J. Drugs Future 1998;23:365–369.

(5). Rabasseda X, Hopkins SJ. Drugs Today 1994;30:557–563.

(6). Inagaki M, Tsuri T, Jyoyama H, Ono T, Yamada K, Kobayashi M, Hori Y, Arimura A, Yasui K, Ohno K, Kakudo S, Koizumi K, Suzuki R, Kato M, Kawai S, Matsumoto S. J. Med. Chem 2000;43:2040–2048. [PubMed: 10821716]

(7). Valente C, Guedes RC, Moreira R, Iley J, Gut J, Rosental PJ. Biorg. Med. Chem. Lett 2006;16:4115–4119.

(8). Brzozowski F, Saczewski F, Neamati N. Bioorg. Med. Chem. Lett 2006;16:5298–5302. [PubMed: 16908143]

(9). McKerrecher D, Pike KG, Waring MJ. PCT Int. Appl. 20062006125972

(10). For an extensive list of both classical and transition-metal-catalyzed cyclization reactions, see: Jiménez-Hopkins M, Hanson PR. Org. Lett 2008;10:2223–2226.2226 [PubMed: 18447383]

(11) (a). Loydl F. Justus Liebigs Ann. C 1878;192:80–89.Berkessel, A. Methods of Organic Chemistry (Hueben-Weyl). Vol. 4th ed. Vol. Vol. E21e. G. Thieme; Stuttgart: 1952. p. 4818-4856.and references therein (c) Enders D, Haertwig A, Raabe G, Runsink J. Angew Chem., Int. Ed 1996;35:2388–2390.and references therein (d) Shi Y-L, Shi M. Org. Biomol. Chem 2007;5:1499–1504. [PubMed: 17571176]

(12). Baylis, AB.; Hillman, MED. German Patent. 2155113. 1972. Chem. Abstr 1972;77:34174q.

(13). Basavaiah D, Rao AJ, Satyanarayana T. Chem. Rev 2003;103:811–891. [PubMed: 12630854]

(14) (a). See ref 11c and references therein.(b) Nicolaou KC, Hwang C-K, Duggan ME. J. Am. Chem. Soc 1989;111:6682–6690. (c) Evans DA, Gauchet-Prunet JA. J. Org. Chem 1993;58:2446–2453. (d) Li M, O'Doherty GA. Org. Lett 2006;8:6087–6090. [PubMed: 17165936] (e) Ahmed MM, Mortensen MS, O'Doherty GA. J. Org. Chem 2006;71:7741–7746. [PubMed: 16995681] (f) Chandrasekhar S, Rambabu C, Shyamsunder T. Tetrahedron Lett 2007;48:4683–4685.

(15) (a). Roth F, Gygax P, Frater G. Tetrahedron Lett 1992;33:1045–1048. (b) Wang L-C, Luis AL, Agapiou K, Jang H-Y, Krische MJ. J. Am. Chem. Soc 2002;124:2402–2403. [PubMed: 11890765] (c) Frank SA, Mergott DJ, Roush WR. J. Am. Chem. Soc 2002;124:2404–2405. [PubMed: 11890766] (d) Keck GE, Welch DS. Org. Lett 2002;4:3687–3690. [PubMed: 12375919] (e) Huddleston RR, Krische MJ. Synlett 2003;12:21. (f) Reddy LR, Saravanan P, Corey EJ. J. Am. Chem. Soc 2004;126:6230–6231. [PubMed: 15149210] (g) Yeo JE, Yang X, Kim HJ, Koo S. Chem. Commun 2004:236–237. (h) Aroyan CE, Vasbinder MM, Miller SJ. Org. Lett 2005;7:3849–3851. [PubMed: 16119914] (i) Shi M, Chen LH, Li CQ. J. Am. Chem. Soc 2005;127:3790–3800. [PubMed: 15771513] (j) Krafft ME, Haxell TFN, Seibert KA, Abboud KA. J. Am. Chem. Soc 2006;128:4174–4175. [PubMed: 16568961] (k) Teng W-D, Huang R, Kwong CK-W, Shi M, Toy PH. J. Org. Chem 2006;71:368–371. [PubMed: 16388661] (l) Nakano A, Takahashi K, Ishihara J, Hatakeyama S. Org. Lett 2006;8:5357–5360. [PubMed: 17078717]

(16) (a). Truce WE, Wellisch E. J. Am. Chem. Soc 1952;74:2881–2884. (b) Luis A-L, Krische MJ. Synthesis 2004:2579–2585. (c) Meadows DC, Gervay-Hague J. Med. Res. Rev 2006;26:793–814. [PubMed: 16788979] (d) Oh K. Org. Lett 2007;9:2973–2975. [PubMed: 17602641] (e) Esteves AP, Silva ME, Rodrigues LM, Oliveira-Campos AMF, Hrdina R. Tetrahedron Lett 2007;48:9040–9043. (f) Das I, Pal TK, Pathak T. J. Org. Chem 2007;72:9181–9189. [PubMed: 17956119]

(17). Reddick JJ, Cheng J, Roush WR. Org. Lett 2003;5:1967–1970. [PubMed: 12762698]

(18). Although Baldwin defined 7-*endo-trig* as favorable, 8-*endo-trig* pathways were not defined; see: Baldwin JE. J. Chem. Soc., Chem. Commun 1976;73:4–736.736

(19). The stereochemistry of major product 5 was determined by 1D-NOE and NOESY experiments; see Supporting Information.

(20). To the best of our knowledge, this work represents the first report of using an intramolecular Baylis—Hillman reaction to generate a sultam.

(21). Regioselective ring-opening of glycidyl trityl ether with isobutylamine gave the amino alcohol 16 in excellent yield.

(22). Confirmed by $^{1}H$ measurements in different NMR solvents; see Supporting Information.

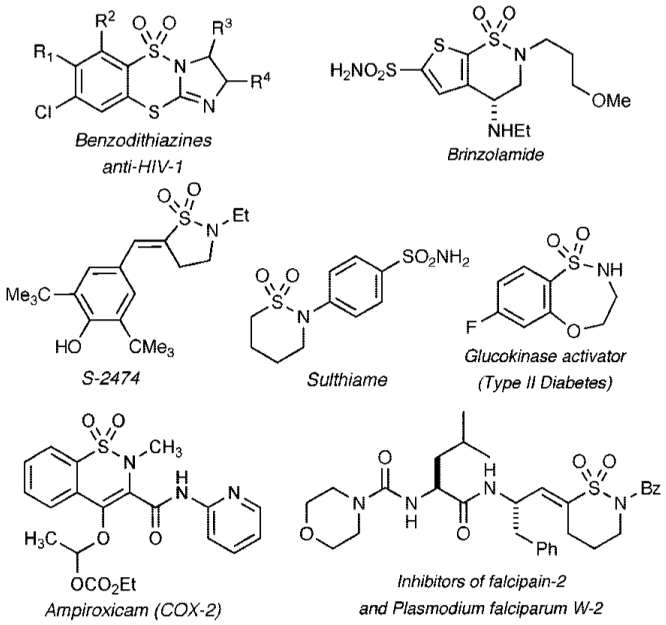
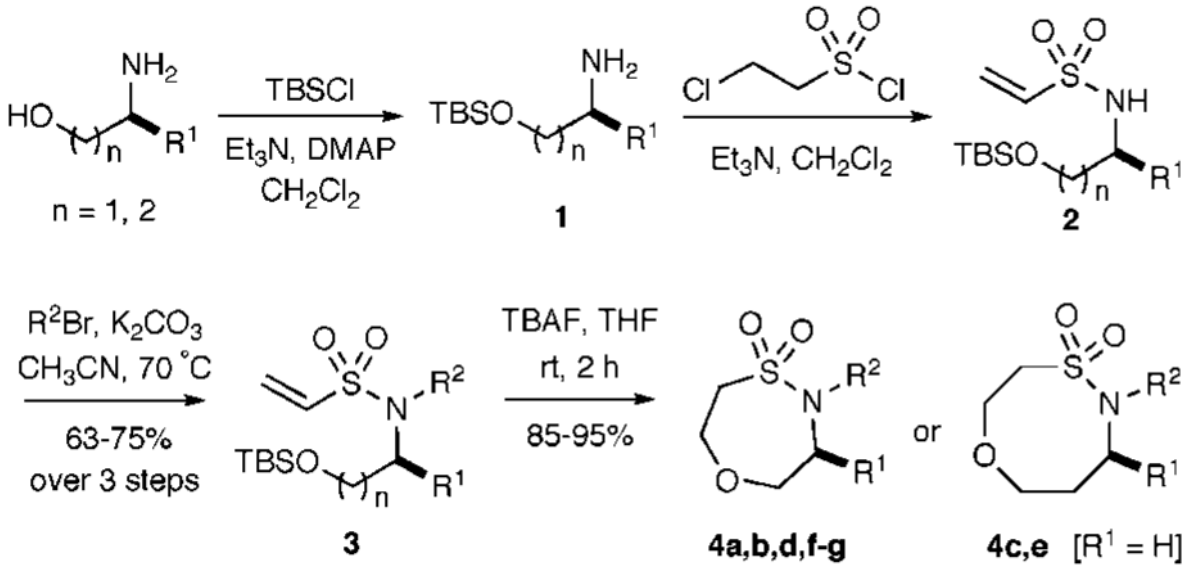
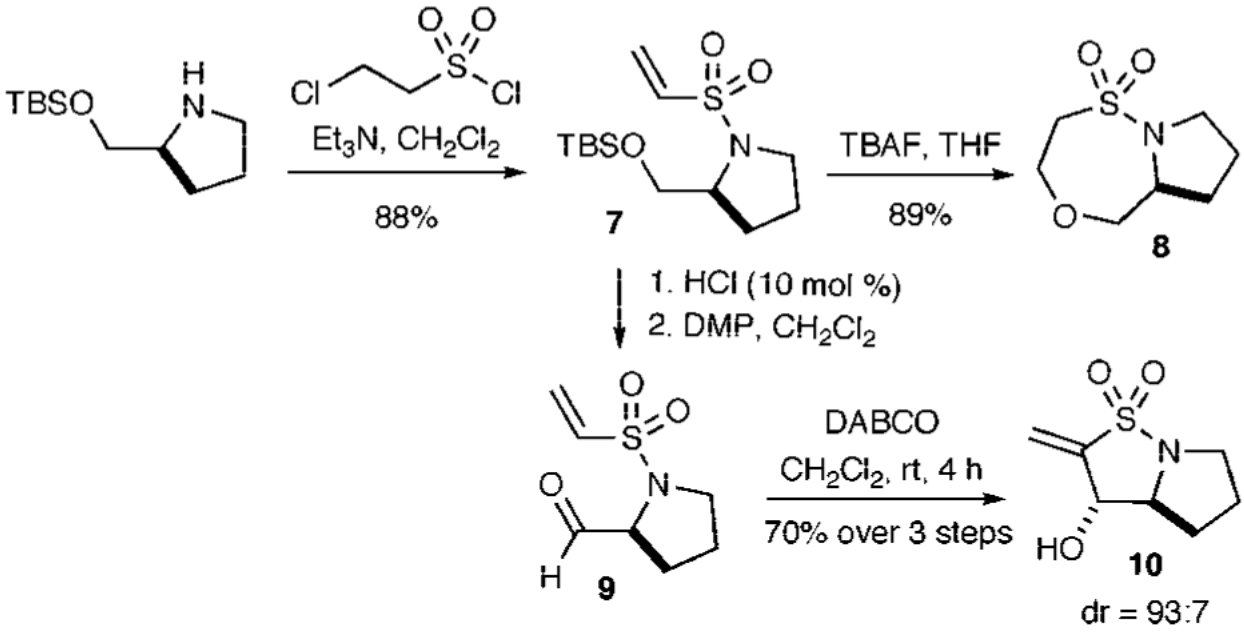


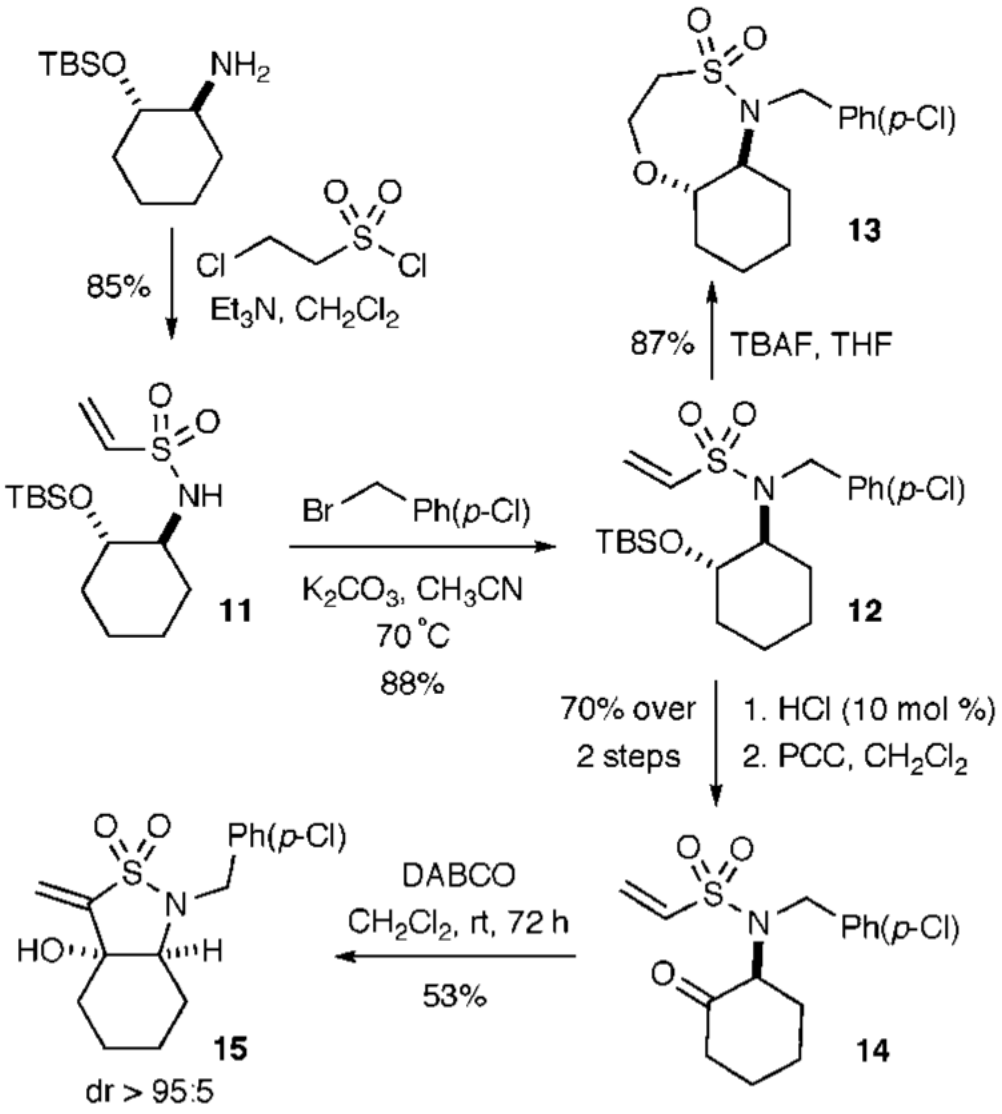

**Figure 1.**
Biologically active sultams.



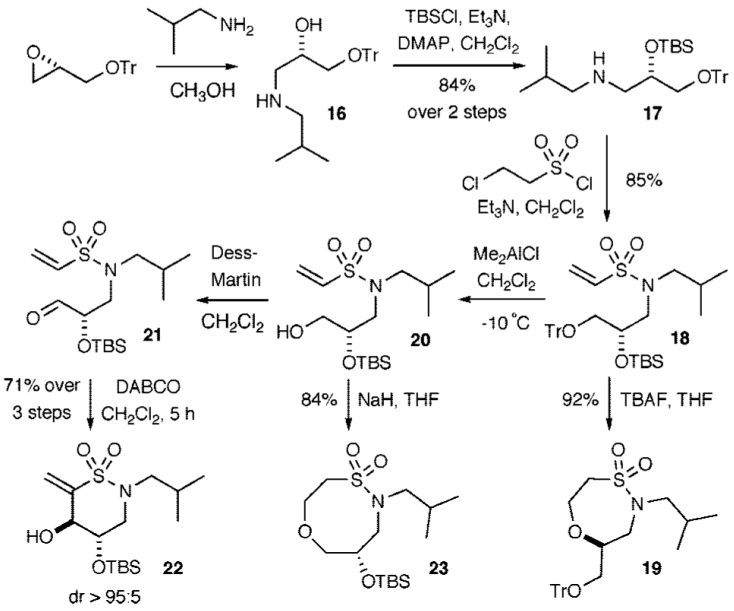

**Scheme 1.**
Synthesis of Seven- and Eight-Membered Ring Sultams via Intramolecular Oxa-Michael Reactions




**Scheme 2.**
Synthesis of Bicyclic Sultam Scaffold




**Scheme 3.**
Baylis—Hillman Reaction via Keto Vinyl Sulfonamide

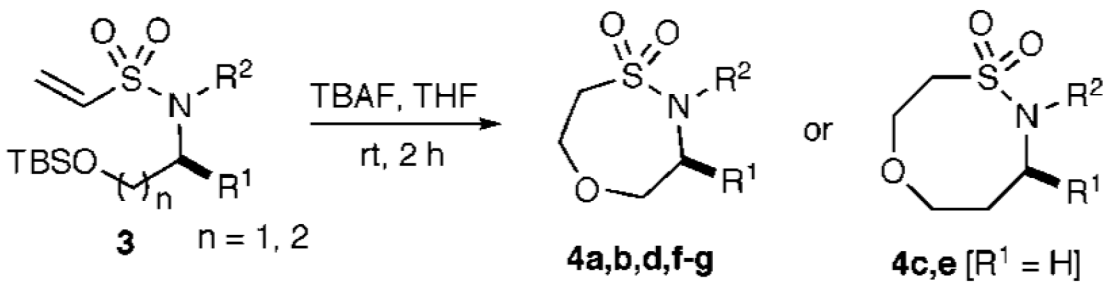



**Scheme 4.**

Highly Diastereoselective Intramolecular Baylis—Hillman Reaction to Generate $\delta$-Sultam

**Table 1**

Synthesis of Seven- and Eight-Membered Ring Sultams via Intramolecular Oxa-Michael Reactions



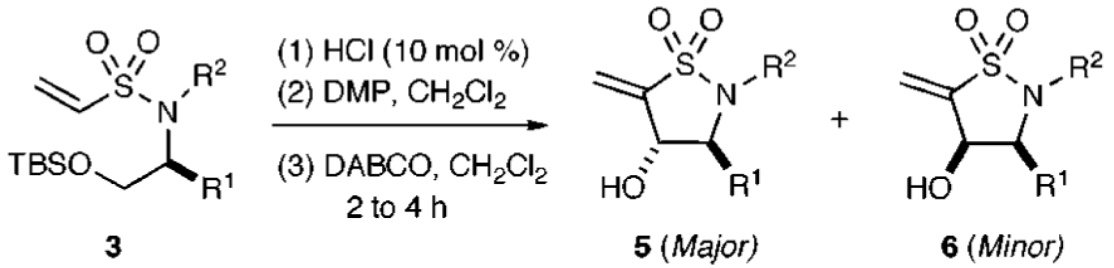

| entry | product | n | $R^1$ | $R^2$ | total yield[a] (%) |
|---|---|---|---|---|---|
| 1 | **4a** | 1 | *i*-Pr | $CH_2CH{=}CH_2$ | 61 |
| 2 | **4b** | 1 | $CH_2Ph$ | $CH_2Ph$(*o*-Br) | 60 |
| 3 | **4c** | 2 | H | $CH_2CH{=}CH_2$ | 54 |
| 4 | **4d** | 1 | $CH_2Ph$ | $CH_2Ph$(*o*-Me) | 59[b] |
| 5 | **4e** | 2 | H | $CH_2Ph$(*o*-F) | 53[b] |
| 6 | **4f** | 1 | *i*-Bu | $CH_2Ph$(*m*-Cl) | 58[b] |
| 7 | **4g** | 1 | *i*-Bu | $CH_2Ph$ | 61[b] |

[a] Total yield of all four steps.

[b] Sultams **4d—g** were synthesized through chromatography-free linear synthesis; see Supporting Information for reaction procedure.

**Table 2**

Intramolecular Baylis—Hillman Reactions




| entry | product | $R^1$ | $R^2$ | yield[a] (%) | dr (5/6) |
|---|---|---|---|---|---|
| 1 | **5a/6a** | *i*-Pr | $CH_2CH{=}CH_2$ | 69 | 63:37 |
| 2 | **5b/6b** | *i*-Bu | $CH_2Ph$(*o*-Br) | 71 | 62:38 |
| 3 | **5c/6c** | *i*-Bu | $CH_2CH{=}CH_2$ | 67 | 76:24 |
| 4 | **5d/6d** | $CH_2Ph$ | $CH_2CCH$ | 69 | 77:23 |
| 5 | **5e/6e** | $CH_2Ph$ | $CH_2Ph$(*o*-Br) | 72 | 88:12 |
| 6 | **5f/6f** | $CH_2Ph$ | $CH_2Ph$ | 71 | 90:10 |

[a]Yield of three steps.