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Metathesis cascade strategies (ROM–RCM–CM): a DOS approach to skeletally diverse sultams

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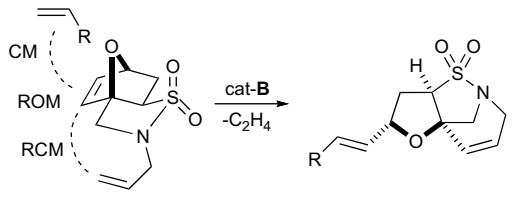
ABSTRACT

The development of a ring-opening metathesis/ring-closing metathesis/cross-metathesis (ROM–RCM–CM) cascade strategy to the synthesis of a diverse collection of bi- and tricyclic sultams is reported. In this study, functionalized sultam scaffolds derived from intramolecular Diels–Alder (IMDA) reactions undergo metathesis cascades to yield a collection of tricyclic sultams. Additional appendage-based diversity was achieved by utilizing a variety of CM partners.

1. Introduction

Diversity-oriented synthesis (DOS) has emerged as a powerful strategy in the generation of structurally complex and skeletally diverse small molecules.[1] Collections of such small molecules can possess a wide range of physical and biological properties and as such are ideal for probing chemical space to identify novel lead compounds.[2] The development of simple methodology, which allows for the generation of skeletal diversity, is one of the most challenging facets of DOS. A number of efficient strategies have emerged employing skeletal rearrangement utilizing both functional-group-pairing (FGP)[1d,3] strategies and tandem metathesis (TM) strategies.[4] In this regard, we envisioned an approach whereby skeletally diverse sultam scaffolds could be generated using a domino ring-opening metathesis (ROM)/ring-closing metathesis (RCM)/cross-metathesis (CM) cascade sequence on a readily derived oxa-norbornenyl sultam. Recently a number of strategies employing ROM–CM strategies of norbornenes, oxa-norbornenes, and aza-norbornenes derivatives have appeared.[5] In particular, a number of key metathesis cascades and strategies have emerged, some in the context of DOS.[6] Herein is reported the application of an ROM–RCM–CM strategy for the generation of a collection of skeletally diverse sultams starting from a central norbornenyl sultam core derived from a diastereoselective intramolecular Diels–Alder (IMDA) reaction (Scheme 1).



Scheme 1.

Sultams (cyclic sulfonamide analogs) have emerged as important targets in drug discovery due to their potent biological activities. A number of reports have highlighted an assortment of sultams that display potent activity including inhibition of COX-2 (Ampiroxicam),[7,8] HIV integrase,[9] and cysteine protease involved in the progression of maleria.[10] Recently, a number of transition metal-catalyzed approaches to sultams have come to light, including ring-closing metathesis (RCM).[11] Our continued interest in the development of new synthetic routes toward structurally diverse sulfur-containing small molecules[11,12] for library production has prompted the following investigation on the application of metathesis cascade processes for their construction.

2. Results and discussion

The intramolecular Diels–Alder (IMDA) reaction of both vinyl sulfonates[13] and vinyl sulfonamides[14] with substituted furans, pioneered by Metz and co-workers, has provided an efficient route

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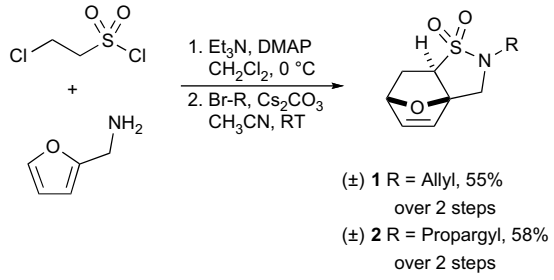
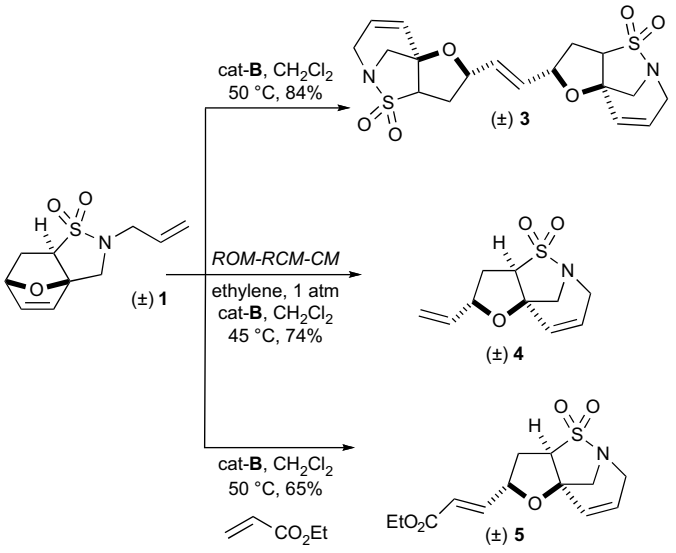
to highly versatile intermediates rich in stereochemistry and functionality. Norbornene systems of this type possess a strained internal double bond, and thus are attractive scaffolds for application of the aforementioned metathesis cascades. To this effect, we set about the synthesis of IMDA-derived sultams **1** and **2** from commercially available starting materials.[14c] 2-Chloroethanesulfonyl chloride was coupled with furfurylamine to afford the corresponding sulfonamide in 86% yield. Alkylation of the resulting sulfonamide followed by in situ IMDA afforded the corresponding tricyclic sultams **1** and **2** in 55% and 58% yield, respectively (Scheme 2), as single diastereomers.



Scheme 2.

With scaffold **1** in hand, the application of the proposed ROM–RCM–CM cascade protocol was explored. Thus, sultam **1** was subjected to 5 mol% of $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ [cat-**B**],[15] at 0.005 M in CH_2Cl_2 at 45 °C under argon for 3 h, to afford homodimer **3** in 84% yield. In order to circumvent this homodimerization pathway, a cross-metathesis partner was used to yield the desired product. Utilization of ethylene has been well reported in the application of ROM–RCM–CM, whereby a terminal olefin is ultimately produced.[6] With this in mind, sultam **1** was subjected to standard cascade conditions under an atmosphere of ethylene, in ethylene degassed solvent. As anticipated, the corresponding sultam **4** bearing a terminal olefin was afforded in 74% yield with ethylene acting as the final cross-metathesis partner. Building on this result, studies were directed toward the addition of a cross-metathesis partner to prevent dimerization and incorporate an additional point of diversity.[5] When **1** was resubjected in the presence of 10 equiv of ethyl acrylate, 10 mol% of cat-**B** in 0.005 M CH_2Cl_2 at 50 °C, the desired bridged tricyclic sultam **5** derived from ROM–RCM–CM was isolated in 65% yield (Scheme 3).

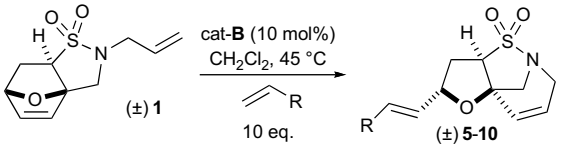


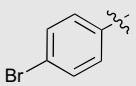
Scheme 3.

With the successful application of an ROM–RCM–CM protocol, the scope of possible cross-metathesis partners was investigated. These included a variety of acrylates such as methyl acrylate and *tert*-butyl acrylate affording the desired products in good yield (Table 1, entries 1–3). Surprisingly, the application of methyl vinyl ketone (MVK) did not afford the desired product. In addition to acrylates, styrene and acrylonitrile were utilized as the cross-metathesis partner. It was found that under standard reaction conditions the desired products were isolated as the sole product in good yields (Table 1, entries 4–6).

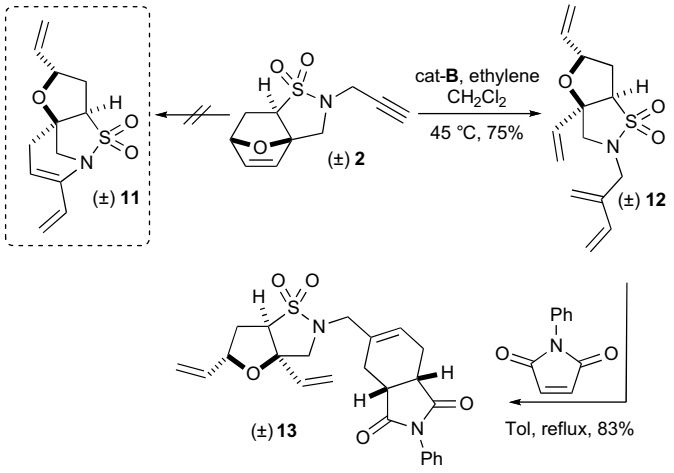
With this result in hand, application of the metathesis cascade was applied to the propargyl-substituted sultam **2**. In this case, a ring-opening metathesis/ring-closing enyne metathesis/cross-metathesis (ROM–RCEM–CM) sequence was envisioned as a means of generating skeletal diversity. Moreover, reaction of sultam **2** in the presence of ethylene would afford the desired product **11** bearing a diene motif, allowing for additional incorporation of diversity via a [4+2] cycloaddition with activated dienophiles.

Table 1



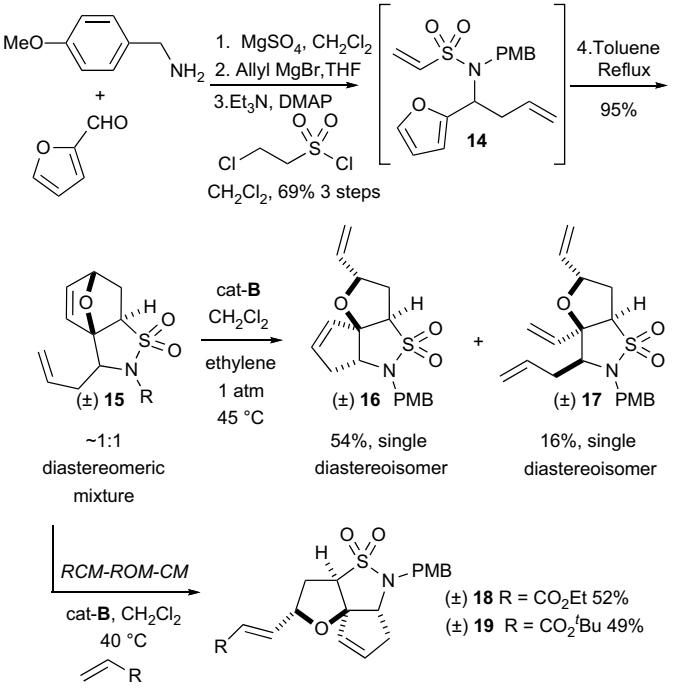
Entry	R	Product	Yield
1	CO_2Et	(±) **5**	65%
2	CO_2Me	(±) **6**	56%
3	$CO_2{}^tBu$	(±) **7**	78%
4		(±) **8**	81%
5		(±) **9**	80%
6	CN	(±) **10**	67%

However, when sultam **2** was subjected to the ROM–RCEM–CM conditions none of the desired product was obtained, instead the corresponding bicyclic tetraene **12** was isolated in good yield (75%). This result indicates that sultam **2** undergoes an intermolecular enyne metathesis with ethylene instead of the corresponding intramolecular process. Subsequent heating of **12** with maleimide afforded the corresponding [4+2] *cis*-cycloadduct **13** in 83% yield as an inseparable, 1:1 mixture of diastereomers (Scheme 4).[16]



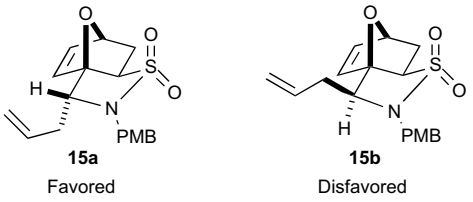
Scheme 4.

Building on these results, we investigated the synthesis of a modified sultam scaffold whereby the simple relocation of the allyl group in **1** by one carbon would allow for the generation of new tricyclic sultams **15**–**17** (Scheme 5). Relocation of the tethered allyl group also enhances structural diversity by yielding a new fused-ring system. Thus, 2-furaldehyde was condensed with *p*-methoxy benzyl amine generating the corresponding imine, which was subsequently converted to the requisite furfuryl-substituted allyl amine by the addition of allyl magnesium bromide. Sulfonylation with 2-chloroethanesulfonyl chloride produced the corresponding vinyl sulfonamide **14**, which when heated at 100 °C for 12 h afforded the desired IMDA-derived scaffold **15** in 95% as a mixture of diastereomers (~1:1).[17] Addition of cat-**B** to sultam **15** in the presence of ethylene afforded the desired tricyclic sultam **16** as a single diastereoisomer via an ROM–RCM–CM cascade. Spectroscopic analysis including key ^{1}H NMR NOE studies determined that diastereomer **15a** selectively underwent cyclization to give the cis-fused tricyclic sultam **16**.



Scheme 5.

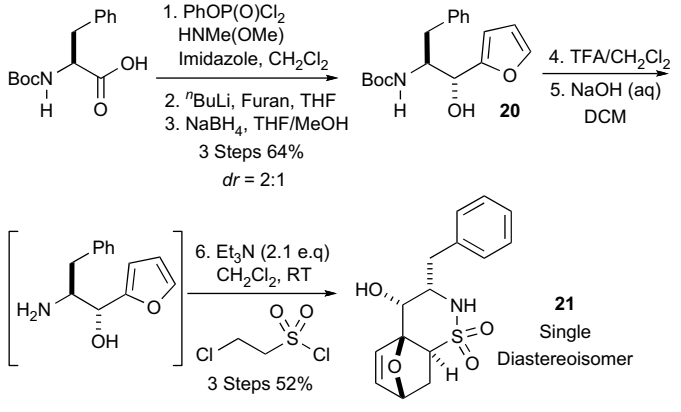
In addition to the formation of **16**, a small amount of sultam **17** resulting from ROM–CM of diastereomer **15b** with ethylene was isolated. It is proposed that in the case of diastereomer **15b**, an unfavorable steric interaction between the homoallyl substituent and the oxo-bridge prevents proper alignment between the ruthenium alkylidene and the norbornenyl olefin, thus hindering metathesis. However, this interaction is alleviated in the case of the diastereomer **15a**, where the allyl group is oriented away from the oxygen bridge under the bicyclic ring in direct proximity of the strained norbornenyl olefin (Scheme 6). In addition to steric effects, the corresponding cyclized RCM product of **17** would have a trans ring junction in a bicyclo[3.3.0] ring system, which under the reversible conditions of the reaction would most likely be disfavored.



Scheme 6.

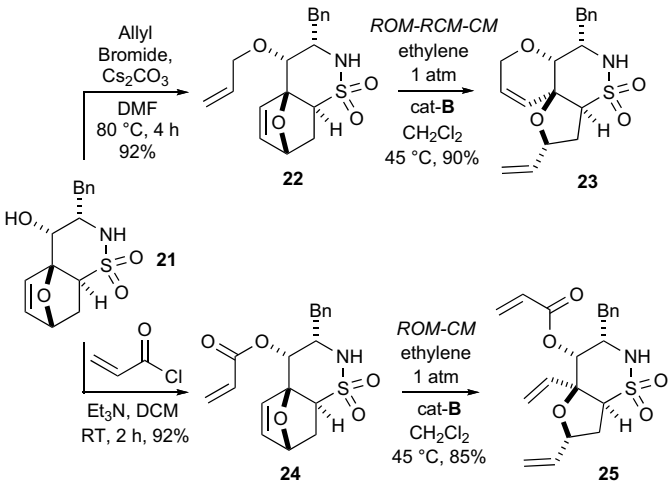
During this investigation we were concurrently developing the synthesis of an IMDA-derived sultam **21** bearing additional handles and therefore probed its utility in the metathesis cascade protocol. In this regard, *N*-Boc-phenylalanine was converted to the corresponding Weinreb amide and treated with lithiated furan. Subsequent reduction of the furyl ketone yielded the corresponding *N*-Boc amino alcohol **20** as a mixture of diastereoisomers (~2:1) in 64% yield over three steps.[18] Removal of the Boc group furnished the corresponding amino alcohol, which was taken on crude to a one-pot, sulfonylation/diastereoselective IMDA sequence to afford the desired tricyclic sultam **21**, as a single diastereoisomer in 52% yield over three steps (Scheme 7).[14]

From a DOS perspective, sultam **21** represents an attractive scaffold due to a number of features, including (i) the presence of both free hydroxy (OH) and free sulfonamide (NH) groups, (ii) structural rigidity, (iii) stereochemistry, and (iv) peripheral functionality. These features allow for the generation of focused



Scheme 7.

libraries to probe chemical space via two approaches. One is via simple peripheral diversification and the second is via skeletal diversity utilizing the aforementioned ROM–RCM–CM cascade protocol. To this effect, chemoselective O-allylation of **21** yielded the desired intermediate **22**,[19] which when subjected to the standard ROM–RCM–CM sequence yielded the desired tricyclic sultam **23** in 90% yield (Scheme 8).

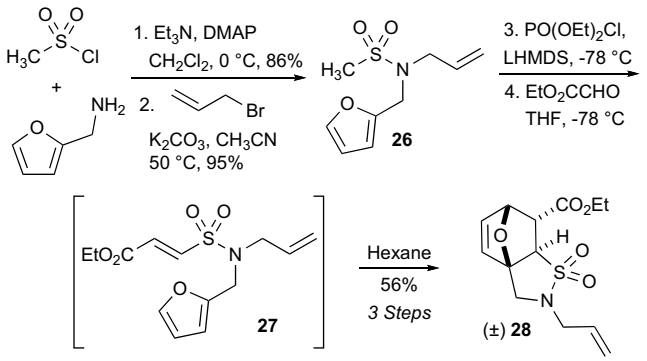


Scheme 8.

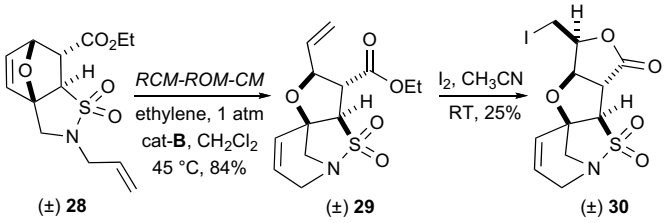
Building on this result, selective acylation of **21** yielded the corresponding sultam intermediate **24** in 92% yield. Submission to the standard metathesis cascade conditions in the presence of ethylene yielded the triene sultam **25** as the sole product via an ROM–CM process. Taken collectively, sultams **1**, **15**, and **21** are tricyclic, IMDA-derived scaffolds that upon submission to the metathesis cascade protocol generate skeletally diverse [6.6.5] or [6.5.5] fused-ring sultam systems. In addition, both pathways retain a functional handle (SO_2NH) for late stage peripheral diversification. Ultimately, selective choice of the olefin appendage in **21** allows additional skeletal diversity in the formation of either tricyclic sultam **23** or bicyclic sultam **25**, presumably due to variable olefin reactivity types (I, II, II or IV) as defined by Grubbs affecting the site of the initial metathesis event.[20]

The synthesis of a sultam scaffold bearing an ester functional handle was envisioned as an alternative strategy toward the synthesis of functionalized derivatives of **1**. This goal could be achieved via incorporation of the ester moiety in the dienophile component of the IMDA protocol, as reported by Overman and co-workers.[21] To this effect, furfurylamine was mesylated then subsequently allylated to yield sulfonamide **26** in 82% over two steps. Generation of the phosphonate, followed by Horner–Wadsworth–Emmons reaction, yielded a mixture of uncyclized sulfonamide **27** and IMDA-derived sultam **28** after purification to remove any remaining starting material. Addition of hexane to the crude mixture resulted in the sole precipitation of **28**, yielding X-ray quality crystals (Scheme 9).

It is noteworthy to mention that it was observed that in both $CDCl_3$ and MeOD-d_4, sultam **28** undergoes retro-IMDA to the corresponding sultam **27** over time.[22] It is believed that the nature of the solvent catalyzes the retro-IMDA reaction indicating the increased reactivity of the bridged tricyclic system in comparison to sultams **1** and **15**. Despite this observation, the corresponding sultam **28** underwent the metathesis cascade transformation in the presence of ethylene in CH_2Cl_2 to yield the desired tricyclic sultam **29** (Scheme 10). Formation of an additional lactone ring was achieved using iodolactonization between the ethyl ester and the terminal olefin in the presence of I_2 to afford polycyclic product **30** as a single isomer, albeit in low yield.



Scheme 9.



Scheme 10.

3. Conclusion

In conclusion, the synthesis of a collection of diverse bi- and tricyclic sultams has been achieved in an overall DOS approach utilizing an ROM–RCM–CM cascade strategy. A variety of functionalized, tricyclic sultams were generated as precursors for the metathesis cascade strategy. These precursors were derived from a diastereoselective IMDA reaction in good yields and selectivity. The ROM–RCM–CM proceeded in good to excellent yields generating sultams possessing both skeletal and appendage-based diversity that was controlled by elements incorporated into the sultam precursors or via the cross-metathesis partner selected.

4. Experimental section

4.1. General

All air and moisture sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere using standard gas tight syringes, cannulas, and septa. Stirring was achieved with oven-dried, magnetic stir bars. CH_3CN was purified by passage through the Solv-Tek purification system employing activated Al_2O_3.[24] Et_3N was purified by passage over basic alumina and stored over KOH. Flash column chromatography was performed with SiO_2 obtained from Sorbent Technologies (30930M-25, Silica Gel 60A, 40–63 μm). Metathesis catalysts were provided by Materia and used without further purification. Thin layer chromatography was performed on silica gel 60F254 plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz, respectively; or a Bruker Avance operating at 500 MHz and 125 MHz, respectively. High-resolution mass spectrometry (HRMS) and FAB spectra were obtained on a VG Instrument ZAB double-focusing mass spectrometer. Melting points were obtained on a Thomas Hoover capillary melting point apparatus. Optical rotations were carried out on a Rudolph Automatic Polarimeter (AUTOPOL IV).

*4.1.1. 6H-3a,6-Epoxy-1,2-benzisothiazole, 2,3,7,7a-tetrahydro-2-allyl, 1,1-dioxide [(±) **1**]*

Into a flame dried flask under argon were added furfurylamine (1.05 mL, 11.9 mmol), Et_3N (1.66 mL, 11.9 mmol), and dry CH_2Cl_2 (20 mL). After stirring at 0 °C for 10 min, 2-chloroethanesulfonyl chloride (0.96 mL, 9.2 mmol) was added and the reaction flask stirred at rt for 2 h. The crude reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude material was dissolved in dry CH_3CN (50 mL, 0.2 M) to which K_2CO_3 (3.9 g, 32.0 mmol) was added. After stirring for 5 min, allyl bromide (2.8 mL, 32.0 mmol) was added and the reaction mixture was stirred at 60 °C, until SM disappeared as monitored by TLC analysis. After such time, the crude reaction mixture was filtered through a pad of Celite, concentrated under reduced pressure, and purified by flash chromatography (1:1 hexane:EtOAc) to yield **1** (1.15 g, 5.0 mmol, 55%) as a white solid. Mp 98 °C; FTIR (neat): 1442, 1301, 1068, 1137 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.53 (dd, *J*=5.7, 1.7 Hz, 1H), 6.37 (d, *J*=5.7 Hz, 1H), 5.88 (ddt, *J*=16.6, 10.1, 6.4 Hz, 1H), 5.30 (ddq, *J*=24.7, 10.1, 1.3 Hz, 2H), 5.23 (dd, *J*=4.5, 1.7 Hz, 1H), 3.84 (d, *J*=11.3 Hz, 1H), 3.80–3.75 (m, 2H), 3.62 (d, *J*=11.3 Hz, 1H), 3.18 (dd, *J*=7.9, 3.6 Hz, 1H), 2.61–2.55 (m, 1H), 1.81 (dd, *J*=12.3, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 139.5, 134.1, 132.4, 119.7, 90.5, 79.7, 60.5, 48.9, 47.6, 29.2; HRMS calculated for $C_{10}H_{13}NNaO_3S$ $(M+Na)^+$ 250.0514; found 250.0518.

*4.1.2. 6H-3a,6-Epoxy-1,2-benzisothiazole, 2,3,7,7a-tetrahydro-2-propargyl, 1,1-dioxide [(±) **2**]*

Using a similar procedure as that used to produce sultam **1**, *N*-(2-furanylmethyl)ethanesulfonamide (1.0 g, 5.28 mmol) and propargyl bromide (2.8 mL, 32.0 mmol) yielded **2** (68.9 mg, 3.0 mmol, 58%) as a white solid. Mp 150 °C; FTIR (neat): 3226, 1304, 1282, 1140 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.55 (dd, *J*=1.7, 5.7 Hz, 1H), 6.42 (d, *J*=5.7 Hz, 1H), 5.26 (dd, *J*=4.5, 1.6 Hz, 1H), 4.10–4.02 (m, 2H), 3.93 (dd, *J*=17.7, 2.5 Hz, 1H), 3.81 (d, *J*=11.4 Hz, 1H), 3.18 (dd, *J*=7.9, 3.6 Hz, 1H), 2.61–2.55 (m, 1H), 2.37 (t, *J*=2.5 Hz, 1H), 1.81 (dd, *J*=12.4, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 139.5, 134.1, 90.7, 79.8, 76.8, 74.1, 60.5, 48.8, 34.7, 29.1; HRMS calculated for $C_{10}H_{11}NNaO_3S$ $(M+Na)^+$ 248.0357, found 248.0347.

*4.1.3. Sultam (**3**)*

To a flame dried flask was added dry CH_2Cl_2 (95 mL, 0.005 M), which was degassed for 30 min with argon. After such time, sultam **1** (0.1 g, 0.44 mmol) and cat-**B** (0.04 g, 0.044 mmol) were added and the reaction mixture was refluxed at 45 °C for 3 h. The crude reaction mixture concentrated under reduced pressure and purified by flash chromatography (1:1 hexane/EtOAc) to provide **3** (15.7 mg, 0.36 mmol, 84% yield) as a white solid. Mp 227 °C; FTIR (neat): 1336, 1164, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.28 (ddd, *J*=10.1, 5.1, 2.1 Hz, 1H), 5.76 (ddd, *J*=6.7, 3.4, 1.7 Hz, 1H), 5.55 (dt, *J*=10.1, 2.5 Hz, 1H), 4.84 (d, *J*=6.0 Hz, 1H), 4.19 (dt, *J*=19.5, 2.5 Hz, 1H), 3.79 (dt, *J*=19.6, 2.2 Hz, 1H), 3.71 (dd, *J*=11.0, 5.7 Hz, 1H), 3.59 (dd, *J*=12.2, 1.9 Hz, 1H), 3.24 (dd, *J*=12.2, 1.8 Hz, 1H), 2.71 (dddd, *J*=14.0, 8.1, 5.8, 2.1 Hz, 1H), 2.14–2.06 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 134.2, 134.2, 131.2, 130.9, 124.1, 124.1, 87.6, 80.9, 80.7, 71.0, 71.0, 51.9, 50.9, 34.1, 34.1; HRMS calculated for $C_{18}H_{22}N_2NaO_6S_2$ $(M+Na)^+$ 449.0817, found 449.0816.

4.2. General procedure A for ROM–RCM–CM metathesis cascade

To a flame dried flask was added dry CH_2Cl_2 (0.005 M), which was degassed for 30 min with argon. To this were added sultam (1 equiv), cat-**B** (10 mol %), and CM partner (10 equiv). The reaction mixture was refluxed at 45 °C for 3 h. The crude reaction mixture was concentrated under reduced pressure and purified by flash chromatography (1:1 hexane/EtOAc) to afford the desired compound.

*4.2.1. Sultam [(±) **4**]*

According to general procedure **A**, **1** (80 mg, 0.3 mmol) and cat-**B** (30 mg, 0.03 mmol) were added to ethylene degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **(±) 4** [50 mg, 0.22 mmol, 74%] as a yellow solid. Mp 91 °C; FTIR (neat): 2925, 1350, 1338, 1166 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.28 (dq, *J*=10.1, 2.1 Hz, 1H), 5.80 (ddd, *J*=17.0, 10.4, 6.4 Hz, 1H), 5.57–5.48 (m, 1H), 5.33–5.25 (m, 1H), 5.19 (dt, *J*=10.4, 1.1 Hz, 1H), 4.82 (dd, *J*=14.6, 6.9 Hz, 1H), 4.18 (dt, *J*=19.5, 2.4 Hz, 1H), 3.76 (dt, *J*=19.5, 2.2 Hz, 1H), 3.70 (ddd, *J*=10.9, 6.0, 1.9 Hz, 1H), 3.59 (dd, *J*=12.2, 2.0 Hz, 1H), 3.23 (dd, *J*=12.2, 2.0 Hz, 1H), 2.68 (ddd, *J*=14.0, 8.0, 6.0 Hz, 1H), 2.09 (ddd, *J*=14.1, 10.9, 7.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 135.6, 133.5, 123.0, 116.4, 86.6, 81.4, 70.2, 51.1, 50.0, 33.0; HRMS calculated for $C_{10}H_{13}NNaO_3S$ $(M+Na)^+$ 250.0514, found 250.0507.

*4.2.2. Sultam [(±) **5**]*

According to general procedure **A**, **1** (80 mg, 0.3 mmol), cat-**B** (30 mg, 0.03 mmol), and ethyl acrylate (3.2 mL, 30 mmol) were added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **(±) 5** [58 mg, 0.19 mmol, 65%] as a pale yellow solid. Mp 232 °C; FTIR (neat): 1716, 1350, 1269, 1167 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.85 (dd, *J*=15.6, 5.0 Hz, 1H), 6.30 (d, *J*=10.1 Hz, 1H), 6.04 (d, *J*=15.6 Hz, 1H), 5.57 (d, *J*=10.1 Hz, 1H), 5.02 (dd, *J*=6.7, 13.4 Hz, 1H), 4.24–4.16 (m, 3H), 3.82–3.75 (m, 1H), 3.75–3.69 (m, 1H), 3.62–3.56 (m, 1H), 3.30–3.25 (m, 1H), 2.83–2.74 (m, 1H), 2.21–2.12 (m, 1H), 1.32–1.27 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 165.9, 144.7, 134.0, 124.2, 121.7, 88.0, 80.0, 70.5, 60.8, 52.1, 51.0, 33.5, 14.2; HRMS calculated for $C_{13}H_{17}NNaO_5S$ $(M+Na)^+$ 322.0725, found 322.0698.

*4.2.3. Sultam [(±) **6**]*

According to general procedure **A**, **1** (80 mg, 0.3 mmol), cat-**B** (30 mg, 0.03 mmol), and methyl acrylate (2.7 mL, 30 mmol) were added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **(±) 6** [48 mg, 0.16 mmol, 56%] as a pale yellow solid. Mp 144 °C; FTIR (neat): 1722, 1350, 1340, 1167 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.86 (d, *J*=13.8 Hz, 1H), 6.30 (d, *J*=8.0 Hz, 1H), 6.05 (d, *J*=15.3 Hz, 1H), 5.56 (d, *J*=7.9 Hz, 1H), 5.02 (s, 1H), 4.19 (d, *J*=19.2 Hz, 1H), 3.85–3.53 (m, 6H), 3.28 (d, *J*=11.6 Hz, 1H), 2.78 (s, 1H), 2.16 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 166.3, 145.0, 133.9, 124.2, 121.2, 88.0, 80.0, 70.5, 52.1, 51.9, 50.9, 33.5; HRMS calculated for $C_{12}H_{15}NNaO_5S$ $(M+Na)^+$ 308.0569, found 308.0562.

*4.2.4. Sultam [(±) **7**]*

According to general procedure **A**, **1** (80 mg, 0.3 mmol), cat-**B** (30 mg, 0.03 mmol), and *tert*-butyl acrylate (4.3 mL, 30 mmol) were added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **(±) 7** [76 mg, 0.23 mmol, 78%] as a yellow oil. FTIR (neat): 2978, 1711, 1352, 1314, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 6.77 (dd, *J*=15.6, 5.0 Hz, 1H), 6.34 (d, *J*=10.2 Hz, 1H), 5.99 (d, *J*=15.6 Hz, 1H), 5.59 (d, *J*=10.3 Hz, 1H), 5.03 (s, 1H), 4.23 (d, *J*=19.6 Hz, 1H), 3.87–3.71 (m, 2H), 3.62 (d, *J*=12.5 Hz, 1H), 3.30 (d, *J*=12.2 Hz, 1H), 2.80 (s, 1H), 2.19 (ddd, *J*=14.0, 10.8, 6.6 Hz, 1H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 165.1, 143.4, 134.1, 124.2, 123.6, 88.0, 81.0, 80.1, 76.8, 70.6, 52.1, 50.9, 33.5, 31.0, 28.1; HRMS calculated for $C_{15}H_{21}NNaO_5S$ $(M+Na)^+$ 350.1038, found 350.1030.

*4.2.5. Sultam [(±) **8**]*

According to general procedure **A**, **1** (80 mg, 0.3 mmol), cat-**B** (30 mg, 0.03 mmol), and styrene (3.4 mL, 30 mmol) were added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **(±) 8** [73 mg, 0.24 mmol, 81%] as a brown liquid. FTIR (neat): 1348, 1338, 1164, 1132, 968, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.39 (dd, *J*=5.0, 3.4 Hz, 2H), 7.35–7.31 (m, 2H), 7.28 (dt, *J*=4.7, 1.9 Hz, 1H), 6.64 (d, *J*=15.8 Hz, 1H), 6.34 (dq, *J*=10.1, 2.1 Hz, 1H), 6.15 (dd, *J*=15.8, 7.0 Hz, 1H), 5.56 (dt, *J*=10.1, 2.5 Hz, 1H), 5.01 (q, *J*=7.2 Hz, 1H), 4.22 (dt, *J*=19.5, 2.5 Hz, 1H), 3.84–3.74 (m, 2H), 3.66 (dd, *J*=12.2, 2.0 Hz,

1H), 3.28 (dd, *J*=12.2, 2.0 Hz, 1H), 2.78 (ddd, *J*=13.9, 8.0, 5.7 Hz, 1H), 2.21 (ddd, *J*=14.2, 11.1, 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 135.9, 134.4, 132.8, 128.9, 128.3, 127.3, 126.7, 124.0, 87.5, 82.2, 71.3, 51.9, 51.0, 34.4; HRMS calculated for $C_{16}H_{17}NNaO_3S$ $(M+Na)^+$ 326.0827, found 326.0795.

*4.2.6. Sultam [(±) **9**]*

According to general procedure, **1** (80 mg, 0.3 mmol), cat-**B** (30 mg, 0.03 mmol), and 4-bromostyrene (3.9 mL, 30 mmol) were added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **(±) 9** [87 mg, 0.23 mmol, 80%] as a white solid. Mp 140 °C; FTIR (neat): 1487, 1350, 1338, 1164, 744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.48–7.43 (m, 2H), 7.25 (dt, *J*=9.0, 2.2 Hz, 2H), 6.58 (d, *J*=15.8 Hz, 1H), 6.33 (dq, *J*=10.1, 2.1 Hz, 1H), 6.14 (dd, *J*=15.8, 6.9 Hz, 1H), 5.57 (dt, *J*=10.1, 2.5 Hz, 1H), 4.99 (q, *J*=7.1 Hz, 1H), 4.22 (dt, *J*=19.5, 2.5 Hz, 1H), 3.84–3.73 (m, 2H), 3.65 (dd, *J*=12.2, 2.0 Hz, 1H), 3.28 (dd, *J*=12.2, 2.0 Hz, 1H), 2.77 (ddd, *J*=13.9, 8.0, 5.7 Hz, 1H), 2.19 (ddd, *J*=114.2, 11.1, 7.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 134.8, 134.3, 131.8, 131.5, 128.2, 128.1, 124.1, 122.1, 87.6, 81.9, 71.2, 51.9, 51.0, 34.3; HRMS calculated for $C_{16}H_{16}BrNNaO_3S$ $(M+Na)^+$ 403.9932, found 403.9619.

*4.2.7. Sultam [(±) **10**]*

According to general procedure **A**, **1** (80 mg, 0.3 mmol), cat-**B** (30 mg, 0.03 mmol), and acrylonitrile (1.9 mL, 30 mmol) was added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **(±) 10** [50 mg, 0.20 mmol, 67%] as a white solid. Mp 170 °C; FTIR (neat): 1338, 1164, 1114 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.67 (dd, *J*=16.2, 4.3 Hz, 1H), 6.28 (dq, *J*=10.1, 2.1 Hz, 1H), 5.67 (dd, *J*=1.9, 16.2 Hz, 1H), 5.60 (dt, *J*=10.1, 2.5 Hz, 1H), 5.03–4.96 (m, 1H), 4.21 (dt, *J*=19.6, 2.5 Hz, 1H), 3.80 (dt, *J*=19.6, 2.2 Hz, 1H), 3.72 (ddd, *J*=10.8, 6.4, 1.9 Hz, 1H), 3.58 (dd, *J*=2.0, 12.3 Hz, 1H), 3.29 (dd, *J*=2.0, 12.3 Hz, 1H), 2.86–2.79 (m, 1H), 2.16 (ddd, *J*=14.1, 10.9, 6.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 149.9, 132.3, 123.5, 115.4, 99.4, 87.1, 78.4, 69.1, 50.9, 49.9, 32.2; HRMS calculated for $C_{11}H_{12}N_2NaO_3S$ $(M+Na)^+$ 275.0466, found 275.0468.

*4.2.8. Sultam [(±) **12**]*

According to general procedure **A**, **2** (80 mg, 0.3 mmol) and cat-**B** (30 mg, 0.03 mmol) were added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **(±) 12** [63 mg, 0.23 mmol, 75%] as a brown liquid. FTIR (neat): 2927, 1597, 1311, 1150, 931 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.36 (dd, *J*=17.7, 11.1 Hz, 1H), 5.99 (dd, *J*=17.0, 10.6 Hz, 1H), 5.81 (ddd, *J*=17.2, 10.3, 6.9 Hz, 1H), 5.57–5.44 (m, 2H), 5.33 (dd, *J*=17.2, 1.1 Hz, 1H), 5.28–5.16 (m, 5H), 4.71–4.65 (m, 1H), 4.15 (d, *J*=13.8 Hz, 1H), 3.53 (d, *J*=8.6 Hz, 1H), 3.47 (d, *J*=13.8 Hz, 1H), 3.28 (d, *J*=10.9 Hz, 1H), 3.10 (d, *J*=10.9 Hz, 1H), 2.70 (dd, *J*=5.0, 13.7 Hz, 1H), 2.00 (ddd, *J*=8.7, 10.8, 13.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 139.4, 137.3, 136.2, 136.0, 119.9, 118.1, 116.4, 115.7, 85.7, 81.8, 66.6, 56.7, 44.7, 35.1; HRMS calculated for $C_{14}H_{19}NNaO_3S$ $(M+Na)^+$ 304.0983, found 304.0947.

*4.2.9. Sultam [(±) **13**]*

To a flame dried flask containing dry toluene (0.5 mL) were added diene **12** (30 mg, 0.1 mmol) and *N*-phenylmaleimide (0.23 g, 0.13 mmol). The reaction mixture was heated at 85 °C for 24 h. The crude reaction mixture was concentrated under reduced pressure and purified by flash chromatography (3:2 hexane/EtOAc) to yield **13** (38 mg, 8.3×10^{-5} mol, 83% yield) as a yellow oil. FTIR (neat): 1709, 1498, 1383, 1309, 1147 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.43 (dd, *J*=8.0, 16.5 Hz, 2H), 7.36 (dd, *J*=7.5, 15.2 Hz, 1H), 7.32–7.27 (m, 1H), 7.22 (d, *J*=7.3 Hz, 1H), 5.94 (td, *J*=10.8, 16.7 Hz, 2H), 5.80 (dddd, *J*=6.8, 10.4, 13.4, 17.0 Hz, 1H), 5.56–5.47 (m, 1H), 5.37 (dd, *J*=17.2, 22.0 Hz, 1H), 5.28–5.13 (m, 2H), 4.79–4.71 (m, 1H), 3.81 (d, *J*=14.1 Hz, 1H), 3.52 (d, *J*=8. Hz, 1H), 3.42–3.22 (m, 3H), 3.16 (dd, *J*=5.5, 10.8 Hz, 1H), 3.06 (dd, *J*=3.0, 10.8 Hz, 1H), 2.76–2.64 (m, 3H), 2.47–2.32 (m, 2H), 2.00 (ddd, *J*=7.7, 14.1, 17.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 178.8, 178.7, 178.4 (2), 137.3, 137.2, 136.3, 136.2, 134.4, 134.0, 131.9 (2), 129.1, 129.0, 128.6, 128.5, 126.4 (2), 125.7, 125.6, 118.2, 117.8, 116.6, 116.5, 86.0, 85.7, 82.2, 81.7, 66.7 (2), 57.9, 57.0, 49.5, 49.2, 39.4, 39.0, 38.9 (2), 34.9, 34.8, 25.6 (2), 24.3, 24.1; HRMS calculated for $C_{24}H_{26}N_2NaO_5S$ $(M+Na)^+$ 477.1460, found 477.1436.

*4.2.10. Sultam [(±) **15**]*

To a flame dried flask under argon were added furfural (1.72 mL, 20.8 mmol), 4-methoxybenzylamine (2.7 mL, 20.8 mmol), $MgSO_4$ (3.0 g), and dry CH_2Cl_2 (20 mL). After stirring at rt for 6 h, the crude reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude was dissolved in THF (20 mL) to which was added allyl magnesium bromide (5.57 mL, 11.15 mmol). The reaction mixture was stirred for 5 h. after which time NH_4Cl (satd aq, 10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (4×20 mL) and the combined organic layer was dried ($MgSO_4$). The crude reaction mixture **14** (1.2 g) was solvated in dry toluene (5 mL) and heated at reflux for 12 h. After such time the crude reaction mixture concentrated under reduced pressure and purified by flash chromatography (1:1 hexane/EtOAc) to provide the desired compound (95% yield) as a yellow liquid. FTIR (neat): 1612, 1514, 1301, 1247, 1137 cm^{-1}. [Mixture of diastereoisomers (1:1)] ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.37 (d, *J*=8.6 Hz, 1H), 7.32 (d, *J*=8.6 Hz, 1H), 6.95–6.81 (m, 4H), 6.52 (dd, *J*=5.8, 1.7 Hz, 1H), 6.47–6.38 (m, 3H), 6.18 (d, *J*=5.7 Hz, 1H), 5.93–5.78 (m, 1H), 5.74–5.58 (m, 1H), 5.28 (dd, *J*=4.5, 1.5 Hz, 1H), 5.22–5.14 (m, 2H), 5.09–4.97 (m, 2H), 4.51 (d, *J*=15.7 Hz, 1H), 4.41 (d, *J*=15.3 Hz, 1H), 4.28 (dd, *J*=15.5, 8.7 Hz, 2H), 3.81 (dd, *J*=8.9, 5.6 Hz, 6H), 3.72 (t, *J*=5.3 Hz, 1H), 3.24 (dd, *J*=7.9, 3.2 Hz, 1H), 3.13 (dd, *J*=7.8, 3.3 Hz, 1H), 2.74–2.59 (m, 1H), 2.56–2.48 (m, 1H), 2.45 (t, *J*=7.2 Hz, 1H), 1.80 (td, *J*=12.4, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.3, 159.2, 139.7, 137.9, 135.3, 132.9, 132.6, 132.1, 130.0, 129.9, 127.6, 127.3, 119.4, 118.9, 114.1, 114.1, 94.5, 92.2, 79.4, 78.8, 60.4, 59.7, 58.6, 58.4, 55.3, 55.3, 46.6, 46.0, 34.6, 33.8, 30.1, 29.5; HRMS calculated for $C_{18}H_{21}NNaO_4S$ $(M+Na)^+$ 370.1089, found 370.1075.

*4.2.11. Sultam [(±) **16**]*

According to general procedure **A**, **15** (0.06 g, 0.17 mmol), cat-**B** (0.015 g, 0.017 mmol) in ethylene degassed CH_2Cl_2 (35 mL) and the crude reaction mixture were purified by flash chromatography (2:1 hexane/EtOAc) to provide **16** (32 mg, 54%) and **17** (10 mg, 16%). FTIR (neat): 1612, 1514, 1305, 1249, 1149 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.42–7.22 (m, 2H), 7.11–6.74 (m, 2H), 6.10–5.87 (m, 1H), 5.80 (ddd, *J*=17.1, 10.4, 6.6 Hz, 1H), 5.72 (dt, *J*=5.7, 2.2 Hz, 1H), 5.30 (dt, *J*=17.2, 1.2 Hz, 1H), 5.23–5.15 (m, 1H), 4.52–4.38 (m, 2H), 4.05 (d, *J*=14.4 Hz, 1H), 3.82 (d, *J*=5.2 Hz, 3H), 3.64–3.54 (m, 2H), 2.75 (ddd, *J*=13.8, 5.5, 2.0 Hz, 1H), 2.64–2.43 (m, 2H), 2.12 (dt, *J*=13.8, 9.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.5, 135.9, 135.1, 130.4, 130.2, 126.8, 118.0, 114.1, 97.3, 80.1, 64.6, 63.8, 55.3, 45.4, 35.5, 35.2; HRMS calculated for $C_{18}H_{21}NNaO_4S$ $(M+Na)^+$ 370.1089, found 370.1087.

*4.2.12. Sultam [(±) **17**]*

FTIR (neat): 1514, 1303, 1247, 1145 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.31 (d, *J*=8.7 Hz, 2H), 6.90–6.85 (m, 2H), 5.97–5.81 (m, 2H), 5.72 (dddd, *J*=11.7, 9.5, 7.5, 6.4 Hz, 1H), 5.56–5.48 (m, 1H), 5.39 (ddd, *J*=12.5, 4.3, 3.1 Hz, 2H), 5.27–5.20 (m, 1H), 5.00–4.92 (m, 2H), 4.76 (dd, *J*=11.0, 5.9 Hz, 1H), 4.42 (d, *J*=15.8 Hz, 1H), 4.10 (d, *J*=15.8, 1H), 3.84–3.78 (s, 3H), 3.55 (d, *J*=8.4 Hz, 1H), 3.38 (dd, *J*=7.4, 5.2 Hz, 1H), 2.75 (ddd, *J*=13.6, 5.1, 0.9 Hz, 1H), 2.47–2.38 (m, 1H), 2.34–2.26 (m, 1H), 2.02 (ddd, *J*=13.6, 10.8, 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.5, 139.1, 136.8, 129.8, 118.1, 118.1, 117.1, 114.3, 88.5, 82.4, 66.9, 66.1, 55.7, 46.0, 35.1, 32.5; HRMS calculated for $C_{20}H_{25}NNaO_4S$ $(M+Na)^+$ 398.1402, found 398.1401.

*4.2.13. Sultam [(±) **18**]*

According to general procedure **A**, **15** (80 mg, 0.3 mmol), cat-**B** (30 mg, 0.03 mmol), and ethyl acrylate (3.0 mL, 30 mmol) were added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **(±) 18** [61 mg, 0.147 mmol, 49%] as a yellow oil. FTIR (neat): 1718, 1514, 1303, 1149 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.28–7.24 (m, 2H), 6.90–6.82 (m, 3H), 6.01 (ddd, *J*=9.7, 7.9, 1.9 Hz, 2H), 5.71 (dt, *J*=2.2, 5.7 Hz, 1H), 4.65–4.60 (m, 1H), 4.46 (d, *J*=14.4 Hz, 1H), 4.19 (q, *J*=7.1 Hz, 2H), 4.04 (d, *J*=14.4 Hz, 1H), 3.81 (s, 3H), 3.63 (dd, *J*=9.7, 1.9 Hz, 1H), 3.59 (dd, *J*=7.2, 3.7 Hz, 1H), 2.63–2.44 (m, 3H), 2.14 (dt, *J*=13.8, 9.9 Hz, 1H), 1.28 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 165.9, 159.5, 144.1, 135.4, 130.2, 130.1, 126.7, 122.2, 114.2, 97.8, 76.8, 64.6, 63.6, 60.7, 55.3, 45.5, 35.3, 35.2, 14.2; HRMS calculated for $C_{21}H_{25}NNaO_6S$ $(M+Na)^+$ 442.1300, found 442.1283.

*4.2.14. Sultam [(±) **19**]*

According to general procedure **A**, **15** (80 mg, 0.3 mmol), cat-**B** (30 mg, 0.03 mmol), and *tert*-butyl acrylate (4.3 mL, 30 mmol) were added to argon degassed, dry CH_2Cl_2 (85 mL, 0.005 M) to yield **(±) 19** [69 mg, 0.156 mmol, 52%] as a yellow oil. FTIR (neat): 2978, 1710, 1514, 1308, 1151 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.27–7.23 (m, 2H), 6.90–6.85 (m, 2H), 6.74 (dd, *J*=15.7, 5.3 Hz, 1H), 6.01–5.98 (m, 1H), 5.94 (dd, *J*=15.7, 1.4 Hz, 1H), 5.71 (dt, *J*=5.7, 2.2 Hz, 1H), 4.59 (dd, *J*=7.3, 2.7 Hz, 1H), 4.46 (d, *J*=14.4 Hz, 1H), 4.03 (d, *J*=14.4 Hz, 1H), 3.81 (s, 3H), 3.62 (dd, *J*=19.7, 1.9 Hz, 1H), 3.57 (dd, *J*=7.2, 3.8 Hz, 1H), 2.80 (ddd, *J*=13.8, 5.8, 2.0 Hz, 1H), 2.60–2.46 (m, 1H), 2.13 (dt, *J*=13.8, 9.9 Hz, 1H), 1.87–1.82 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 165.2, 159.5, 142.9, 135.4, 130.2, 130.1, 126.7, 124.1, 114.2, 97.7, 80.8, 76.8, 64.6, 63.6, 55.3, 45.4, 35.2, 35.2, 28.1; HRMS calculated for $C_{23}H_{29}NNaO_6S$ $(M+Na)^+$ 470.1613, found 470.1601.

*4.2.15. tert-Butyl (2S)-1-(furan-2-yl)-1-hydroxy-3-phenylpropan-2-ylcarbamate (**20**)*

To a stirring suspension of imidazole (12.8 g, 188 mmol) in CH_2Cl_2 (40 mL) was added a solution of $PhOP(O)Cl_2$ (5.61 mL, 37.7 mmol) in CH_2Cl_2 (40 mL). After stirring for 1 h, the reaction mixture was cooled to 0 °C and a solution of Boc-phenylalanine (10.0 g, 37.7 mmol) in CH_2Cl_2 (28 mL) was added and the reaction mixture stirred for 1 h. After such time, Weinreb amine (3.68 g, 37.7 mmol) was added and the reaction mixture stirred at rt for 14 h. The reaction was quenched with citric acid (2 M aq, 80 mL) and the organic layer washed with $NaHCO_3$ (1 M aq, 80 mL) and brine (80 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to generate the desired intermediate as a clear oil (crude NMR analysis).

A portion of the crude (6.59 g, 25.3 mmol) in THF (84.5 mL) was cooled to −40 °C and stirred for 30 min. In a separate round bottom flask, a solution of furan (4.6 mL, 63.3 mmol) in THF (110 mL) was cooled to −78 °C to which ^{n}BuLi (26.3 mL) was added slowly and upon completion was stirred for 30 min. After such time, this solution was added slowly to the crude mixture at −40 °C and the reaction mixture was subsequently stirred for an additional 6 h. After such time the reaction was quenched with NH_4Cl (satd aq, 80 mL) and the reaction mixture warmed to rt. The aqueous layer was extracted with EtOAc (3×120 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the desired intermediate as a clear oil (crude NMR analysis). A portion of the crude (1.0 g) in THF (12 mL)/MeOH (1.5 mL) was cooled to 0 °C and after stirring for 15 min, $NaBH_4$ (0.14 g, 3.8 mmol) was added and the reaction mixture stirred for 2 h at 0 °C. After such time the reaction mixture was warmed to rt and diluted with EtOAc (10 mL) followed by HCl (10% aq, 10 mL). After stirring for 15 min, the organic layer was washed with HCl (10% aq, 10 mL), H_2O (10 mL), $NaHCO_3$ (satd aq, 10 mL), and brine (10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield the desired intermediate as a white solid. Mp 144–146 °C; FTIR (neat) 1716, 1454, 1292, 1172, 1132 cm^{-1}. [Major isomer] ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.43 (m, 1H), 7.34–7.17 (m, 5H), 6.38–6.29 (m, 2H), 4.80 (d, *J*=19.2 Hz, 1H), 4.70–4.78 (m, 1H), 4.27 (br s, 1H), 3.55 (br s, 1H), 2.80 (d, *J*=6.3 Hz, 2H), 1.35 (s, 9H). [Minor isomer] ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.16–7.35 (m, 5H), 6.43–6.38 (m, 2H), 4.89 (s, 1H), 4.75 (s, 1H), 4.14 (s, 1H), 3.08 (s, 1H), 2.88–2.99 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 154.6, 154.0, 142.3, 142.0, 137.9, 137.6, 129.3, 129.3, 128.5, 128.5, 126.5, 126.5, 110.3, 107.8, 106.8, 80.0, 79.7, 77.3, 77.0, 76.7, 70.1, 68.7, 56.5, 55.4, 37.6, 36.6, 28.3; HRMS calculated for $C_{18}H_{23}NO_4Na$ $(M+Na)^+$ 340.1525, found 340.1520 (TOF MS ES^+).

*4.2.16. **7**H-4a,7-Epoxy-2H-1,2-benzothiazin-4-ol, 3,4,8,8a-tetrahydro-3-(phenylmethyl)-, 1,1-dioxide, (3S,4R) (**21**)*

Carbamate **20** (2.0 g, 6.3 mmol) was dissolved in CH_2Cl_2 (32 mL), cooled to 0 °C, and after stirring for 15 min TFA (1.95 mL, 25.2 mmol) was added cautiously. After stirring at rt for 3 h, the reaction mixture was cooled to 0 °C and NaOH (10% aq, 35 mL) was added. The reaction mixture was diluted with CH_2Cl_2 (32 mL), the aqueous layer extracted with CH_2Cl_2 (2×30 mL), and the combined organic dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the desired carbamate intermediate as a white solid. The crude product (1.78 g) was dissolved in EtOH (40 mL) and NaOH (1 M aq, 40 mL) was added. After stirring at reflux for 14 h, the organic solvent was removed under reduced pressure. The resulting aqueous layer was extracted with CH_2Cl_2 (3×30 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to produce the desired amino alcohol intermediate as a yellow oil. The crude material was dissolved in CH_2Cl_2 (11.7 mL), to which was added Et_3N (1.58 mL, 91 mmol) and the reaction mixture was cooled to 0 °C. After stirring for 10 min, 2-chloroethanesulfonyl chloride (0.52 mL, 4.89 mmol) was added drop wise over 5 min. The reaction mixture was warmed to rt and stirred for 12 h. After which time the crude mixture was concentrated and purified by flash chromatography (1:2 hexane/EtOAc) to yield **21** (1.0 g, 3.2 mmol, 52%) as a white solid. FTIR (neat) 3480, 3350, 2358, 1448, 1305, 1139 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.28 (m, 2H), 7.28–7.19 (m, 3H), 6.55 (dd, *J*=5.7, 1.5 Hz, 1H), 6.34 (d, *J*=5.7 Hz, 1H), 5.19 (dd, *J*=4.7, 1.5 Hz, 1H), 4.64 (d, *J*=10.6 Hz, 1H), 4.07 (dd, *J*=16.4, 9.7 Hz, 1H), 3.90 (s, 1H), 3.21 (dd, *J*=7.9, 3.2 Hz, 1H), 3.10 (dd, *J*=13.9, 6.6 Hz, 1H), 2.92 (dd, *J*=13.8, 8.9 Hz, 1H), 2.61–2.52 (m, 1H), 2.35 (s, 1H), 1.77 (dd, *J*=12.2, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.1, 136.1, 133.4, 129.1, 129.0, 127.2, 91.2, 79.5, 64.2, 56.2, 55.6, 37.0, 28.8; HRMS calculated for $C_{15}H_{17}NO_4SNa$ $(M+Na)^+$ 330.0776, found 330.2017 (TOF MS ES^+).

*4.2.17. Sultam [**22**]*

Into a 1 dram vial were added **21** (85 mg, 0.27 mmol), DMF (0.6 mL, 0.46 M), Cs_2CO_3 (0.18 g, 0.55 mmol), and allyl bromide (25 μL, 0.30 mmol). The reaction mixture was heated at 50 °C and stirred for 4 h after which time the crude mixture was filtered and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (1:2 hexane/EtOAc) to yield **22** (86 mg, 2.48 mmol, 92%) as a yellow oil. FTIR (neat) 3386, 3249, 2358, 1336, 1315, 1152 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.30 (m, 2H), 7.25 (dd, *J*=7.2, 5.2 Hz 3H), 6.57 (dt, *J*=5.6, 2.8 Hz, 1H), 6.27 (d, *J*=5.7, 1H), 6.04–5.94 (m, 1H), 5.33 (ddq, *J*=20.2, 10.4, 1.4 Hz, 2H), 5.21 (dd, *J*=4.7, 1.6 Hz, 1H), 4.71 (d, *J*=12.1 Hz, 1H), 4.31 (dt, *J*=5.5, 1.4 Hz, 2H), 4.14 (dddd, *J*=12.1, 8.3, 7.1, 1.0 Hz, 1H), 3.64 (s, 1H), 3.20 (dd, *J*=7.9, 3.3 Hz, 1H), 3.11 (dd, *J*=14.3, 7.1 Hz, 1H), 2.90 (dd, *J*=14.3, 8.5 Hz, 1H), 2.60 (ddd, *J*=12.2, 4.6, 3.4 Hz, 1H), 1.78 (dd, *J*=12.1, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 136.5, 133.6, 133.4, 129.1, 129.0, 127.1, 118.2, 91.0, 79.5, 74.9, 72.5, 56.7, 56.1, 37.4, 29.0;

HRMS calculated for $C_{18}H_{21}NO_5SNa$ $(M+Na)^+$ 370.1089, found 370.1087 (TOF MS ES^+).

4.2.18. Sultam [**23**]

According to general procedure **A**, sultam **22** (20 mg) underwent ROM–RCM–CM with ethylene to yield **23** (18 mg, 90%) as a clear oil. FTIR (neat): 3481, 2975, 1724 1445, 1308, 1139 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.17 (m, 3H), 7.14 (ddd, J=9.5, 6.6, 3.4 Hz, 2H), 6.46 (d, J=5.7 Hz, 1H), 6.37 (dd, J=5.7, 1.6 Hz, 1H), 5.75 (dddd, J=17.2, 10.0, 7.6, 5.7 Hz, 1H), 5.16 (ddd, J=13.6, 11.0, 1.1 Hz, 2H), 5.02 (dd, J=4.6, 1.6 Hz, 1H), 4.03–3.90 (m, 3H), 3.80–3.70 (m, 2H), 3.25–3.16 (m, 2H), 3.01 (dd, J=13.4, 5.1 Hz, 1H), 2.18 (dt, J=12.7, 4.4 Hz, 1H), 1.87 (dd, J=12.7, 8.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.9, 137.3, 135.3, 134.9, 129.4, 128.6, 126.7, 118.6, 91.6, 78.4, 64.2, 62.9, 57.3, 53.6, 37.1, 30.8; HRMS calculated for $C_{18}H_{21}NO_4SNa$ $(M+Na)^+$ 370.1089, found 370.1087 (TOF MS ES^+).

4.2.19. Sultam [**24**]

To a stirring solution of sultam **21** (50 mg, 0.16 mmol), Et_3N (45 μL, 0.32 mmol), and CH_2Cl_2 (0.35 mL) in a 1 dram vial was added acryloyl chloride (17 μL, 0.21 mmol). After stirring for 4 h at rt, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography (1:1 hexane/EtOAc) to yield **24** (53 mg, 0.14 mmol, 92%) as a yellow oil. FTIR (neat): 3470, 2980, 1726 1452, 1300, 1140 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.22 (m, 3H), 7.17 (dd, J=6.6, 5.0 Hz, 2H), 6.62 (dd, J=17.3, 1.0 Hz, 1H), 6.54 (dd, J=5.8, 1.6 Hz, 1H), 6.27 (dd, J=17.3, 10.4 Hz, 1H), 6.06 (dd, J=10.4, 1.0 Hz, 1H), 5.95 (d, J=5.8 Hz, 1H), 5.48 (d, J=19.2 Hz, 1H), 5.22 (dd, J=4.7, 1.6 Hz, 1H), 4.64 (d, J=11.6 Hz, 1H), 4.21 (dtd, J=11.6, 7.3, 1.0 Hz, 1H), 3.19 (dd, J=7.9, 3.2 Hz, 1H), 2.84 (qd, J=14.3, 7.3 Hz, 2H), 2.67–2.57 (m, 1H), 1.79 (dd, J=12.2, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 137.2, 135.3, 134.9, 129.4, 128.6, 126.7, 118.6, 91.6, 78.4, 64.2, 62.9, 57.3, 53.6, 37.1, 30.8; HRMS calculated for $C_{18}H_{19}NO_5SNa$ $(M+Na)^+$ 384.0882, found 384.0886 (TOF MS ES^+).

4.2.20. Sultam [**25**]

According to general procedure **A**, sultam **24** (18 mg) underwent ROM–RCM–CM with ethylene to yield **25** (16 mg, 85%) as a clear oil. FTIR (neat): 3480, 2982, 1726, 1448, 1305, 1139 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (t, J=7.3 Hz, 2H), 7.16 (dd, J=15.3, 7.9 Hz, 1H), 7.11 (d, J=7.1 Hz, 2H), 6.43 (dd, J=17.2, 0.9 Hz, 1H), 6.08 (dd, J=17.2, 10.4 Hz, 1H), 5.91 (dd, J=10.4, 0.9 Hz, 1H), 5.77–5.69 (m, 1H), 5.66 (dd, J=17.4, 10.8 Hz, 1H), 5.26 (d, J=17.4 Hz, 1H), 5.19 (dd, J=13.9, 7.4 Hz, 2H), 5.09 (d, J=10.2 Hz, 1H), 5.07 (s, 1H), 4.93 (dd, J=16.2, 7.8 Hz, 1H), 4.36 (d, J=12.1 Hz, 1H), 4.27–4.19 (m, 1H), 3.63 (d, J=6.6 Hz, 1H), 2.73–2.60 (m, 3H), 2.03 (ddd, J=14.0, 9.5, 6.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 138.9, 138.3, 135.6, 133.2, 129.1, 128.7, 127.0, 127.0, 118.2, 118.1, 87.1, 81.4, 77.3, 61.8, 54.7, 37.5, 32.8; HRMS calculated for $C_{20}H_{23}NO_5SNa$ $(M+Na)^+$ 412.1195, found 412.1190 (TOF MS ES^+).

4.2.21. *N*-Allyl-*N*-(furan-2-ylmethyl)methanesulfonamide (**26**)[23]

Into a flame dried flask under argon were added methanesulfonyl chloride (2.03 mL, 26.2 mmol), Et_3N (4.4 mL, 31.6 mmol), and dry CH_2Cl_2 (70 mL). After cooling down to 0 °C, furfurylamine (2.32 mL, 26.1 mmol) was added and the reaction flask stirred at rt for 5 h. After such time, the crude reaction mixture was washed with water and the organic layer dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield a yellow oil. The crude material was subsequently dissolved in CH_3CN (100 mL), to which K_2CO_3 (7.27 g, 52.6 mmol) and allyl bromide (3.0 mL, 34.6 mmol) were added. After stirring at 60 °C for 12 h, the crude reaction mixture was filtered through a pad of Celite and washed with CH_2Cl_2. The crude mixture was concentrated under reduced pressure and purified by flash chromatography (4:1 hexane/EtOAc) to provide **26** (5.35 g, 24.8 mmol, 95% yield) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.43–7.40 (m, 1H), 6.36 (dd, J=3.1, 1.9 Hz, 1H), 6.31 (d, J=3.2 Hz, 1H), 5.78 (ddt, J=16.4, 10.1, 6.3 Hz, 1H), 5.30 (ddd, J=10.9, 8.7, 1.3 Hz, 2H), 4.42 (s, 2H), 3.82 (d, J=6.2 Hz, 2H), 2.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 149.7, 142.9, 132.6, 119.4, 110.5, 110.0, 49.3, 42.5, 39.4; HRMS calculated for $C_9H_{13}NNaO_3S$ $(M+Na)^+$ 238.0514, found 238.0510.

4.2.22. Sultam [(±) **28**]

To a flame dried flask were added **26** (2 g, 9.29 mmol), diethyl chlorophosphate (1.6 mL, 11.1 mmol), and THF (40 mL). The reaction mixture was cooled to −78 °C and after stirring for 15 min, LHMDS (1.0 M solution in THF) was added. The resulting solution was warmed to 0 °C and maintained for 2 h. To another flame dried flask, ethyl glyoxalate (3.7 mL, 18.7 mmol) and THF (40 mL) were added at −78 °C. After stirring for 15 min, this solution was added to the anionic solution containing **26** via cannula. The resulting solution was stirred at −78 °C for 7 h and then warmed to rt and stirred for an additional 18 h. After such time, NH_4Cl (satd aq, 25 mL) was added and the mixture was extracted with CH_2Cl_2 (4×25 mL). The organic layer was dried ($MgSO_4$), filtrated, concentrated under reduced pressure, and purified by flash chromatography (7:1 hexane/EtOAc) to provide the mixture of Diels–Alder product **28** and precursor **27**. Addition of hexane and Et_2O followed by cooling at 0 °C, resulted in crystallization of the desired product **28** as a white solid (1.55 g, 5.2 mmol, 56%). FTIR (neat): 2983, 1736, 1301, 1141, 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.51 (d, J=5.7 Hz, 1H), 6.48 (dd, J=5.7, 1.5 Hz, 1H), 5.88 (ddt, J=16.6, 10.1, 6.4 Hz, 1H), 5.40 (dd, J=4.7, 1.4 Hz, 1H), 5.34 (dd, J=17.1, 1.3 Hz, 1H), 5.29 (dd, J=10.1, 1.0 Hz, 1H), 4.20–4.12 (m, 2H), 3.84 (dd, J=9.9, 5.9 Hz, 2H), 3.81–3.77 (m, 2H), 3.62 (d, J=11.5 Hz, 1H), 3.55 (d, J=3.7 Hz, 1H), 1.27 (t, J=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 168.8, 137.4, 135.6, 132.2, 119.9, 91.8, 81.0, 63.4, 61.8, 48.8, 48.3, 47.7, 14.2; HRMS calculated for $C_{13}H_{17}NNaO_5S$ $(M+Na)^+$ 322.0725, found 322.0721.

4.2.23. Sultam [(±) **29**]

To a flame dried flask was added dry CH_2Cl_2 (50 mL, 0.005 M), which was degassed with ethylene for 30 min. After such time, sultam **28** (0.1 g, 0.33 mmol) and cat-**B** (0.03 g, 0.033 mmol) were added and the reaction mixture was refluxed at 40 °C for 1 h under ethylene (1 atm). After cooling to rt, the crude reaction mixture was concentrated under reduced pressure and purified by flash chromatography (6:1 hexane/EtOAc) to yield **29** (58 mg, 1.94 mmol, 59% yield) as a gray solid. Mp 155 °C; FTIR (neat): 2978, 1732, 1340, 1194, 999 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.34 (dq, J=10.1, 2.1 Hz, 1H), 5.73 (ddd, J=17.2, 10.4, 6.8 Hz, 1H), 5.58 (dt, J=2.5, 10.1 Hz, 1H), 5.39 (dt, J=17.1, 1.2 Hz, 1H), 5.27 (dt, J=10.4, 1.1 Hz 1H), 5.08 (dd, J=8.2, 7.4 Hz, 1H), 4.21 (ddd, J=6.7, 5.7, 1.9 Hz, 1H), 4.18–4.12 (m, 3H), 3.82–3.75 (m, 2H), 3.57 (dd, J=12.3, 2.0 Hz, 1H), 3.31 (dd, J=12.3, 2.0 Hz, 1H), 1.25 (t, J=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 168.9, 134.3, 132.7, 124.1, 119.3, 87.2, 84.2, 72.2, 61.8, 52.7, 51.0, 50.9, 14.1; HRMS calculated for $C_{13}H_{17}NNaO_5S$ $(M+Na)^+$ 322.0725, found 322.0716.

4.2.24. Sultam [(±) **30**]

Into a flame dried flask under argon sultam **29** (862 mg, 2.88 mmol), CH_3CN (11.5 mL, 0.25 M), and I_2 (730 mg, 2.88 mmol) were added. The resulting solution was stirred at rt for 24 h. The reaction was quenched with aqueous $NaHCO_3$ and the aqueous layer was extracted with EtOAc (3×10 mL). The organic layer was dried ($MgSO_4$) and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (6:1 hexane/EtOAc) to provide 78 mg (25% yield) of the desired compound. FTIR (neat): 2961, 1778, 1354, 1159, 1111 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.26 (dq, J=10.1, 2.1 Hz, 1H), 5.61 (dt, J=10.1, 2.5 Hz, 1H), 4.85 (d, J=6.6 Hz, 1H), 4.66 (dd, J=6.9, 3.4 Hz, 1H), 4.24 (dt,

J=19.7, 2.5 Hz, 1H), 3.99 (dd, J=6.6, 3.5 Hz, 1H), 3.87–3.82 (m, 2H), 3.59 (dd, J=12.4, 2.1 Hz, 1H), 3.43(dd, J=11.1, 3.5 Hz, 1H), 3.30 (dd, J=11.1, 6.9 Hz, 1H), 3.29 (dd, J=12.5, 1.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 173.5, 132.0, 125.0, 89.4, 85.0, 81.2, 73.1, 50.9, 50.9, 49.0, 3.6. HRMS calculated for $C_{11}H_{12}INNaO_5S$ $(M+Na)^+$ 419.9379, found 419.9344.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.03.080.

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16. The 1:1 ratio of diastereomers was indistinguishable by ^{1}H. However, ^{13}C NMR spectroscopy was able to distinguish both as reported in Supplementary data.
17. Diastereomeric ratio of 1.43:1.0 was determined by ^{1}H NMR analysis of crude **15**.
18. Previous results by both Hoffman and Howell have demonstrated higher selectivity with a series of serine-derived amino ketones: (a) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1998**, *63*, 3979–3985; (b) So, R. C.; Izmirian, D. P.; Richardson, S. K.; Guerrera, R. L.; Howell, A. R. *J. Org. Chem.* **2004**, *69*, 3233–3235; This selectivity could be increased up to ~4:1 using low temperature (−78 °C), however the yield of the reaction was reduced.
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