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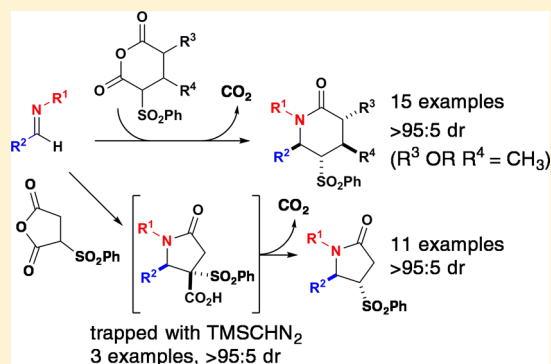
Diastereoselective Synthesis of γ - and δ -Lactams from Imines and Sulfone-Substituted Anhydrides

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S Supporting Information

ABSTRACT: Sulfone-substituted γ - and δ -lactams have been prepared in a single step with high diastereoselectivity. Sulfonylglutaric anhydrides produce intermediates that readily decarboxylate to provide δ -lactams with high diastereoselectivity. Substituents at the 3- or 4-position of the glutaric anhydride induce high levels of stereocontrol. Sulfonylsuccinic anhydrides produce intermediate carboxylic acids that can be trapped as methyl esters or allowed to decarboxylate under mild conditions. This method has been applied to a short synthesis of the pyrrolizidine alkaloid (\pm)-isoretroecanol.

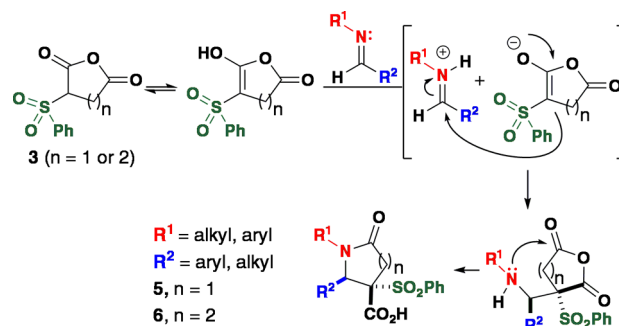


INTRODUCTION

The γ - and δ -lactam scaffolds are found in various biologically relevant compounds.^{1–3} Additionally, these core structures are crucial intermediates in the synthesis of various natural products as well as pharmaceuticals, prompting the development of new methods for the synthesis of these valuable structures.^{4–7} Our group has explored the synthesis of γ -lactams by the reactions of aryl-,^{8,9} thioaryl-,¹⁰ and cyano-substituted anhydrides.^{11,12} Furthermore, we have demonstrated that one-pot four-component reactions (4CRs) are possible in the case of thioaryl substitution.^{13,14} Recent computational studies of the cyanosuccinic anhydride reactions demonstrate that they proceed by a Mannich-like mechanism via the enol tautomer of the anhydride.¹⁵ Related reactions reported by Castagnoli, Cushman, and Haimova likely proceed by this mechanism as well.^{16–21} Castagnoli reported the first reactions of imines with succinic and glutaric anhydrides. Consistent with the proposed mechanism, those anhydrides are poorly enolizable and require forcing conditions. Two decades later, Cushman and Haimova reported analogous reactions with homophthalic anhydride, which is highly enolizable. The high reactivity of this anhydride at lower temperatures is consistent with the Mannich-like mechanism.

These results prompted us to explore Mannich-type reactions and related 4CRs of variously substituted anhydrides. Although aryl-substituted succinic anhydrides showed some variation in reactivity based on the substituents attached to the aromatic ring, direct attachment of an electron-withdrawing group resulted in higher reactivity.¹² Furthermore, in the case of cyanosuccinic anhydrides, the diastereoselectivity was reversed relative to the aryl and thioaryl cases and could be controlled by resident stereogenic centers.^{11,15} We envisioned

Scheme 1. Proposed Mechanism for the Formation of Sulfone-Substituted γ - and δ -Lactams



that the electron-withdrawing capability of a sulfone would impart the anhydride with similar reactivity as the nitrile-substituted anhydride, albeit with drastically different steric requirements (Scheme 1). Herein we report the development of anhydride Mannich reactions (AMRs) using sulfone-substituted anhydrides for the synthesis of γ - and δ -lactams as well as a six-step formal synthesis of (\pm)-isoretroecanol.^{22,23}

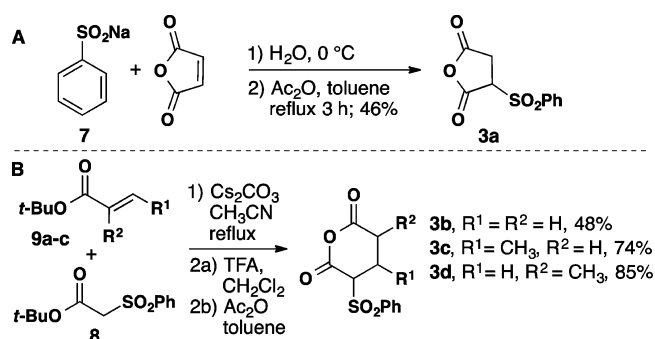
RESULTS AND DISCUSSION

Multigram-scale syntheses of anhydrides **3a–d** were achieved from readily available starting materials. Anhydride **3a** was synthesized by conjugate addition of benzenesulfinic acid sodium salt (**7**) to maleic anhydride to yield a diacid,²⁴ which was cyclized in one step (Scheme 2A). The syntheses of

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Scheme 2. Synthesis of (A) Sulfone Succinic Anhydride 3a and (B) Sulfone Glutaric Anhydrides 3b–d



anhydrides **3b–d** were achieved by Michael addition of sulfone acetate **8** to various *tert*-butyl acrylates followed by ester cleavage and cyclization (Scheme 2B).

Anhydride **3a** readily reacted with imines to form γ -lactams. As with previous AMRs, the carboxylic acid **5** (Table 1) is the first-formed product. Unlike all previous related intermediates, these carboxylic acids were prone to facile decarboxylation. Mild heating drove the decarboxylation to completion, allowing isolation of the sulfone-substituted lactams in high yields with only the *anti* diastereomer detectable by ^1H NMR spectroscopy. In all cases, non-enolizable substrates were well-tolerated. The lack of reactivity of ketones and enolizable aldehydes in the AMR probably stems from the rapid equilibration to the enamine tautomer, which is unreactive in the Mannich addition step.

Table 1. Scope of Sulfone-Substituted Anhydride **3a** in Reactions with Various Imines

entry	product	R ¹	R ²	yield
1	10a	Bn	Ph	83%
2	10b	CH ₃	Ph	83% ^b
3	10c	CH ₂ CCH	Ph	54%
4	10d	<i>n</i> -Pr	2-furyl	50%
5	10e	<i>n</i> -Pr	Ph	87%
6	10f	<i>n</i> -Pr	4-CNC ₆ H ₄	80% ^c
7	10g	<i>n</i> -Pr	2-MeOC ₆ H ₄	65%
8	10h	Bn	(<i>E</i>)-PhCHCH	82%
9	10i	<i>i</i> -Pr	Ph	70%
10	10j	CH ₂ CH=CH ₂	Ph	78%
11	10k	<i>n</i> -Pr	4-MeOC ₆ H ₄	84%

^aDetermined by ^1H NMR spectroscopy. ^bYield using commercially available imine. ^cDecarboxylation was done at room temperature.

The stereochemical configuration of the products was assigned by X-ray crystallography. Lactam **10e** has an *anti* configuration between the aromatic ring and the sulfonyl group. The other lactams were assigned by comparison of the coupling constants of the adjacent protons (e.g., **10f**; Figure 1A). Furthermore, acid intermediate **5f**, which leads to **10f** by decarboxylation, was also crystalline and was found to have an *anti* configuration between the sulfone and aromatic substituents (Figure 1B). Our previous mechanistic work on the

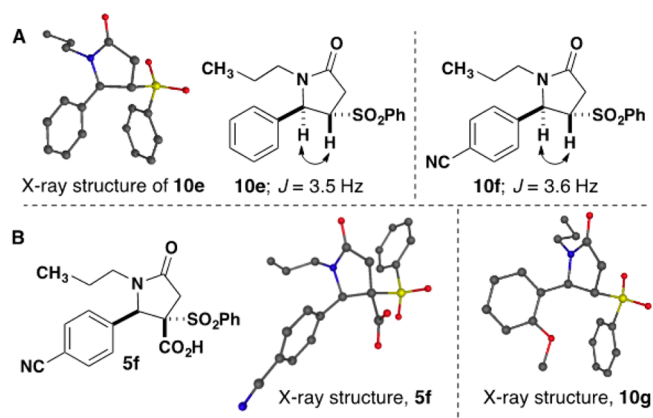
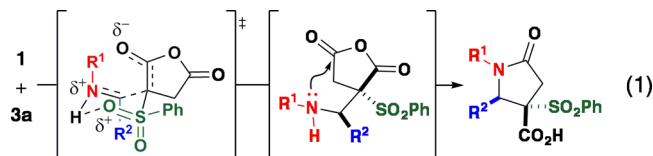


Figure 1. X-ray structures of **5f**, **10f**, and **10g** and *J* values for **10e** and **10j**.

ciano-substituted anhydrides suggests that the *anti*-configured carboxylic acids are the kinetic products of the AMRs.^{12,15} Subsequent decarboxylation leads to the *anti*-sulfones, which would also be expected to be thermodynamically preferred.

The stereochemical outcome of the reactions of imines with **3a** is adequately explained by a transition state that is analogous to what is operative for cyanosuccinic anhydrides (eq 1). The iminium ion is attacked by the enolate of the anhydride, and the cyclic transition state is stabilized by hydrogen bonding to the sulfone. After the Mannich reaction, subsequent rapid trans-annular acylation forms the lactam product.

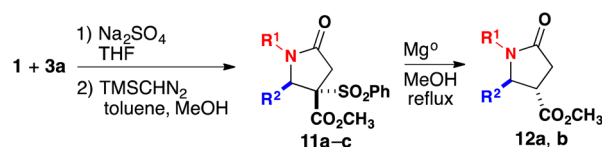


The carboxylic acid intermediates could be trapped with trimethylsilyldiazomethane (TMSCHN₂). Initial attempts at methylation using conventional methods (H₂SO₄/CH₃OH or CH₃I/K₂CO₃)²⁵ yielded only the decarboxylated products. After many esterification conditions were tried, treatment of crude mixtures of **5** with a commercially available solution of TMSCHN₂ resulted in reasonable yields of methyl esters **11a–c** (Table 2).²⁶ These intermediates could also be smoothly desulfonylated with magnesium in methanol to produce the corresponding esters **12** in good yield. Although this reaction was successful for **11a** and **11b**, no ester product was observed in the attempted desulfonylation of **11c**.²⁷

Sulfone-substituted glutaric anhydrides **3b–d** formed δ -lactams with high efficiency. The reactions initially formed carboxylic acids with modest (~80:20) diastereoselectivity. Unlike the analogous γ -lactams, these intermediates were impossible to isolate, thus preventing assignment of the configuration of the predominant diastereomer. Upon decarboxylation, sulfone lactams **13** were formed as single isomers in high yields (Table 3).

This change in diastereoselectivity upon decarboxylation suggests the formation of a planar anion followed by selective protonation from one face of the anion. This result is in accordance with experimental data and models of sulfone anions proposed by Corey.^{28,29} Similar to our results with the succinic anhydride, the reaction tolerated a variety of non-enolizable aldehydes and a variety of alkylamines and anilines. While some of our initial reactions gave low yields (40–50%),

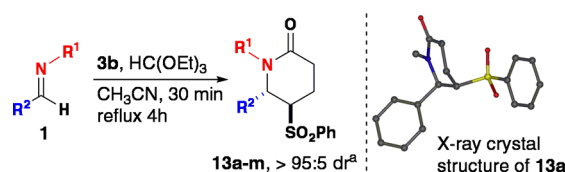
Table 2. Formation of 11 and Desulfonylation To Give 12



entry	R ¹	R ²	11, yield (dr)	12, yield (dr)
1	Bn	Ph	11a, 66% (>95:5)	12a, 76% (>95:5)
2	<i>n</i> -Pr	3,5-(MeO) ₂ C ₆ H ₃	11b, 57% (>95:5)	12b, 77% (90:10)
3	CH ₃	Ph	11c, 67% (>95:5)	12c, – ^a

^aDesulfonylation of 11c yielded a mixture of products as determined by NMR spectroscopy.

Table 3. Scope of Sulfone-Substituted Glutaric Anhydride 3b with Various Imines



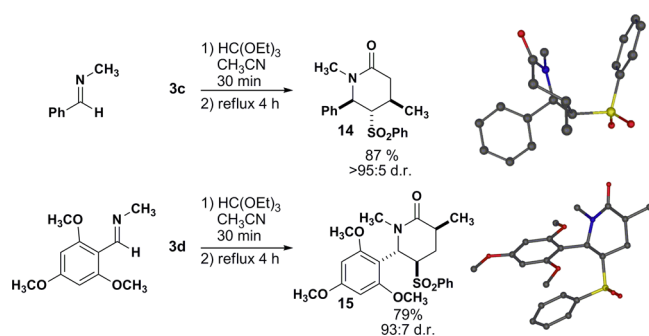
entry	product	R ¹	R ²	yield
1	13a	CH ₃	Ph	80% ^b
2	13b	<i>i</i> -Pr	Ph	84%
3	13c	Bn	Ph	85% ^b
4	13d	CH ₂ CCH	Ph	74% ^b
5	13e	CH ₂ CH=CH ₂	Ph	89% ^b
6	13f	Ph	Ph	72% ^b
7	13g	<i>n</i> -Pr	Ph	91% ^b
8	13h	<i>i</i> -Pr	(<i>E</i>)-PhCHCH	68%
9	13i	<i>n</i> -Pr	4-MeOC ₆ H ₄	69%
10	13j	<i>n</i> -Pr	4-ClC ₆ H ₄	87% ^b
11	13k	<i>n</i> -Pr	2-EtC ₆ H ₄	61% ^b
12	13l	<i>n</i> -Pr	3,5-(MeO) ₂ C ₆ H ₃	64%
13	13m	<i>n</i> -Pr	2-furyl	75%

^aDetermined by ¹H NMR spectroscopy. ^bYield using commercially available or purified imine.

the use of commercially available imines or those purified by distillation significantly increased the yields of the lactam products.

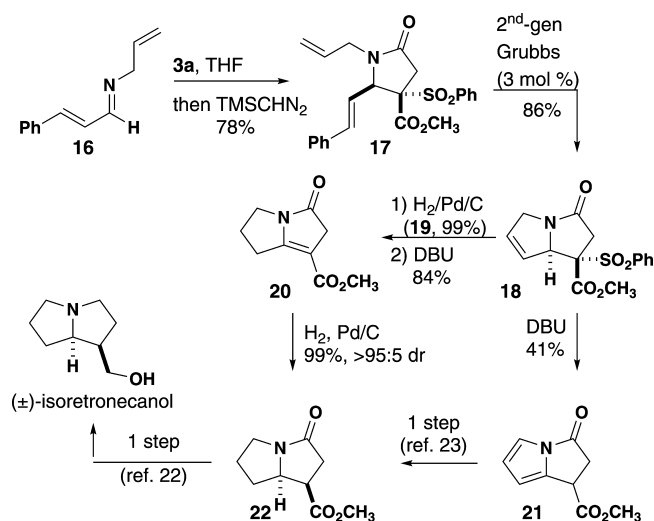
Methyl-substituted anhydrides 3c and 3d provided trisubstituted δ -lactams in high yields with good diastereomeric ratios (Scheme 3). These results suggest that substitution on the anhydride provides excellent facial selectivity, resulting in the formation of only two diastereomers of the intermediate carboxylic acids. Again, decarboxylation seemed to enable the

Scheme 3. AMRs with Methyl-Substituted Sulfone Glutaric Anhydrides and X-ray Crystal Structures of the Products



formation of a preferred stereoisomer. Studies are ongoing in our laboratory to develop an enantioselective Michael addition with sulfone acetate 8 to provide the anhydrides as single enantiomers, which would presumably provide enantiomerically pure lactam products.

This new AMR was applied to a formal synthesis of (\pm)-isoretronecanol (Scheme 4). The reaction of imine 16 with

Scheme 4. Formal Synthesis of (\pm)-Isoretronecanol

anhydride 3a followed by ring-closing metathesis provides the pyrrolizidine core of the natural product from cinnamaldehyde, allylamine, and 3a in two steps. The elimination of 18 yields 21, which has been converted to (\pm)-isoretronecanol in two steps in low yield.²³ Alternatively, reduction and elimination provides lactam 20. Further reduction yields lactam ester 22, which has been converted to (\pm)-isoretronecanol in one step.²² While this second route is redox-inefficient,³⁰ it provides material in a much higher yield and avoids the high-pressure conditions necessary to reduce pyrrole 21. This synthetic route showcases the versatility of the anhydride Michael reaction of the sulfone-substituted anhydride, exemplifying its usefulness in the assembly of heterocyclic targets. This synthesis demonstrates that the AMR of sulfone-substituted anhydrides will be useful for the assembly of many heterocyclic targets, natural and otherwise.

CONCLUSION

In summary, we have successfully synthesized various sulfone-substituted γ - and δ -lactams in good yields with high diastereoselectivities (>95:5) by an anhydride Mannich

reaction. We have previously studied the reactivity of several different substituted succinic anhydrides, but these are the first new results employing glutaric anhydrides since the original work of Castagnoli.^{20,21} Unlike previous reactions of this type to date, the carboxylic acid products were prone to decarboxylation. Although the γ -lactam acids derived from the substituted succinic anhydride could be trapped as esters, the analogous δ -lactam products could not be intercepted. Another important difference was observed in the diastereoselectivity of the initial Mannich-type reaction. Although the reactions of succinic anhydrides were very selective, the acid products derived from the glutaric anhydrides were generally formed as diastereomeric mixtures. In both cases, high selectivity was observed for the decarboxylation process. We have shown that this methodology is highly robust and have showcased it in the formal synthesis of a biologically active natural product. Further studies into the synthesis of additional natural product targets are underway.

EXPERIMENTAL SECTION

General Information. Unless otherwise specified, all commercially available reagents were used as received. All reactions using dried solvents were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Dry solvent was dispensed from a solvent purification system that passes solvent through two columns of dry neutral alumina. ¹H NMR spectra and proton-decoupled ¹³C NMR spectra were obtained on a 400 or 600 MHz NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent (CHCl₃, s, δ 7.26). Multiplicities are given as s (singlet), d (doublet), t (triplet), dd (doublet of doublets), m (multiplet), br m (broad multiplet), or br s (broad singlet); ¹³C NMR chemical shifts are reported relative to CDCl₃ (t, δ 77.23) unless otherwise noted. High-resolution mass spectra were recorded in positive ESI mode in methanol or acetonitrile. Silica gel chromatographic purifications were performed by flash chromatography with silica gel packed in glass columns. The eluting solvent for each purification was determined by thin-layer chromatography (TLC) on glass plates coated with silica gel and visualized by UV light or by staining with ceric ammonium molybdate (CAM) followed by gentle heating. The following abbreviations are used throughout: ethyl acetate (EtOAc), hexanes (hex), dichloromethane (DCM), triethylamine (TEA), diisopropylethylamine (DIPEA).

3-(Phenylsulfonyl)dihydrofuran-2,5-dione (3a). Benzenesulfonic acid sodium salt (10.0 g, 60.9 mmol) was dissolved in 100 mL of H₂O at 0 °C. Maleic anhydride (5.97 g, 60.9 mmol) was added. The reaction mixture was allowed to warm slowly overnight. Then 10% HCl was added, and the mixture was extracted two times with EtOAc. The combined organic layers were dried over Na₂SO₄, and the solvent was removed in vacuo to yield a white solid, which was dissolved in 50 mL of toluene. Ac₂O (70 mL, 20 mmol) was added, and the reaction mixture was heated at reflux for 3 h. The solvent was evaporated in vacuo, and the resulting brown solid was washed several times with cold DCM and collected in a fritted funnel, yielding a white to light-brown solid (6.8 g, 46% yield over the two steps). Mp 132.4–133.1 °C (dec.); ¹H NMR (400 MHz, CDCl₃) δ 7.96 (dd, J = 8.4, 1.3 Hz, 2H), 7.86–7.76 (m, 1H), 7.72–7.63 (m, 2H), 4.52 (dd, J = 10.3, 4.4 Hz, 1H), 3.68 (dd, J = 19.9 (gem), 4.4 Hz, 1H), 3.39 (dd, J = 19.7 (gem), 10.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 166.0, 162.9, 135.8, 135.4, 129.9, 129.7, 64.4, 30.1; IR (neat) 1782, 1739 (C=O), 1169 (S=O) cm⁻¹; HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₁₀H₉O₅S 241.0171, found 241.0165.

General Procedure A. The amine and the aldehyde were dissolved in THF (0.10 M), and 3 equiv of triethyl orthoformate was added. The reaction mixture was allowed to stir for 3 h or overnight. The anhydride was added, and then the reaction mixture was allowed to stir for 3 h. Water was added to the mixture (final concentration 0.05 mmol), followed by the addition of 3 equiv of

K₂CO₃ and heating at reflux for 4 h, unless otherwise stated. The reaction mixture was allowed to cool to rt and then extracted two times with EtOAc. The combined organic layers were washed with brine and dried over Na₂SO₄. The solvent was evaporated in vacuo, and the crude mixture was purified by flash chromatography using an EtOAc/30–50% gradient, unless otherwise stated.

trans-1-Benzyl-5-phenyl-4-(phenylsulfonyl)pyrrolidin-2-one (10a). General procedure A was used with sulfone anhydride 3a (0.24 g, 0.99 mmol), benzylamine (109 μ L, 0.99 mmol), and benzaldehyde (102 μ L, 1.0 mmol) to yield 10a (0.32 g, 83%) as a foam (50:50 EtOAc/hex, R_f = 0.59). ¹H NMR (600 MHz, CDCl₃) δ 7.68–7.64 (m, 2H), 7.62 (tt, J = 7.5, 1.3 Hz, 1H), 7.48–7.41 (m, 2H), 7.32–7.23 (m, 6H), 7.09–7.06 (m, 2H), 6.83–6.79 (m, 2H), 5.09 (d, J = 14.9 Hz, 1H), 4.70 (d, J = 3.3 Hz, 1H), 3.66 (ddd, J = 9.9, 4.4, 3.3 Hz, 1H), 3.44 (d, J = 14.9 Hz, 1H), 3.03 (dd, J = 18.2 (gem), 4.3 Hz, 1H), 2.95 (ddd, J = 18.2 (gem), 9.9, 1.2 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 170.5, 137.7, 136.4, 134.7, 134.4, 129.5, 129.3, 128.9, 128.7, 128.7, 128.4, 127.8, 126.1, 63.5, 60.6, 44.5, 30.7; IR (thin film) 1692 (C=O), 1322 (S=O) cm⁻¹; HRMS (ESI-TOF) m/z [M + Na]⁺ calcd for C₂₃H₂₁NO₃Na 414.1140, found 414.1120.

trans-1-Methyl-5-phenyl-4-(phenylsulfonyl)pyrrolidin-2-one (10b). General procedure A was used with sulfone anhydride 3a (0.30 g, 1.26 mmol) and (*E*)-*N*-methyl-1-phenylmethanimine (156 μ L, 1.26 mmol). Because the commercially available imine was used in this experiment, the anhydride was added immediately after the imine was dissolved instead of waiting for 3 h or overnight. The reaction yielded 10b (0.332 g, 83%) as a foam (50:50 EtOAc/hex, R_f = 0.35). ¹H NMR (600 MHz, CDCl₃) δ 7.89 (d, J = 7.5 Hz, 2H), 7.69 (t, J = 7.5 Hz, 1H), 7.58 (t, J = 7.8 Hz, 2H), 7.36–7.31 (m, 3H), 7.06–7.02 (m, 2H), 4.97 (d, J = 3.5 Hz, 1H), 3.66 (dt, J = 9.8, 4.1 Hz, 1H), 2.90 (dd, J = 18.1 (gem), 4.7 Hz, 1H), 2.82 (dd, J = 18.1 (gem), 9.8 Hz, 1H), 2.64 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 170.6, 138.2, 136.8, 134.6, 129.7, 129.5, 129.0, 128.9, 126.1, 64.3, 63.6, 31.0, 28.4; IR (thin film) 1690 (C=O), 1308 (S=O) cm⁻¹; HRMS (ESI-TOF) m/z [M + Na]⁺ calcd for C₁₇H₁₇NO₃Na 338.0827, found 338.0818.

trans-5-Phenyl-4-(phenylsulfonyl)-1-(prop-2-yn-1-yl)pyrrolidin-2-one (10c). General procedure A was used with sulfone anhydride 3a (0.240 g, 1.00 mmol), prop-2-yn-1-amine (64.0 μ L, 1.00 mmol), and benzaldehyde (102 μ L, 1.00 mmol) to yield 10c (0.182 g, 54%) as a foam. The residue was purified by flash column chromatography (50:50 EtOAc/hex, R_f = 0.53). ¹H NMR (600 MHz, CDCl₃) δ 7.89 (m, 2H), 7.68 (t, J = 7.4 Hz, 1H), 7.60–7.53 (t, 2H), 7.35–7.29 (m, 3H), 7.07–7.02 (m, 2H), 5.23 (d, J = 4.0 Hz, 1H), 4.51 (dd, J = 17.6, 2.6 Hz, 1H), 3.75 (ddd, J = 9.4, 5.1, 4.0 Hz, 1H), 3.25–3.20 (m, 1H), 2.96 (dd, J = 18.2 (gem), 5.1 Hz, 1H), 2.89 (ddd, J = 18.2 (gem), 9.8, 1.1 Hz, 1H), 2.25 (t, J = 2.5 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 169.9, 137.3, 136.6, 134.6, 129.6, 129.4, 129.0, 128.9, 126.4, 76.2, 73.3, 63.9, 60.9, 31.1, 30.5; IR (thin film) 1699 (C=O), 1414, 1322 (S=O) cm⁻¹; HRMS (ESI-TOF) m/z [M + Na]⁺ calcd for C₁₉H₁₇NO₃Na 362.0827, found 362.0831.

trans-5-(Furan-2-yl)-4-(phenylsulfonyl)-1-propylpyrrolidin-2-one (10d). General procedure A was used with sulfone anhydride 3a (0.24 g, 0.99 mmol), propylamine (82 μ L, 0.99 mmol), and furan-2-carbaldehyde (83 μ L, 1.00 mmol) to yield 10d (0.167 g, 50%) as a foam. The residue was purified by flash column chromatography (50:50 EtOAc/hex, R_f = 0.47). ¹H NMR (600 MHz, CDCl₃) δ 7.90–7.86 (m, 2H), 7.70–7.65 (m, 1H), 7.57 (dd, J = 8.3, 7.2 Hz, 2H), 7.32 (d, J = 1.8 Hz, 1H), 6.27 (dd, J = 3.3, 1.9 Hz, 1H), 6.19 (d, J = 3.3 Hz, 1H), 5.07 (d, J = 4.1 Hz, 1H), 3.96 (ddd, J = 8.9, 6.1, 4.1 Hz, 1H), 3.40 (ddd, J = 13.9, 8.8, 7.1 Hz, 1H), 2.95–2.85 (m, 2H), 2.65 (ddd, J = 13.9, 8.6, 5.2 Hz, 1H), 1.47–1.37 (m, 1H), 1.33–1.24 (m, 1H), 0.82 (t, J = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 169.9, 149.4, 143.5, 136.7, 134.5, 129.6, 128.6, 110.6, 109.8, 60.8, 55.2, 42.7, 31.2, 20.1, 11.1; IR (thin film) 1690 (C=O), 1416, 1308 (S=O) cm⁻¹; HRMS (ESI-TOF) m/z [M + Na]⁺ calcd for C₁₇H₁₉NO₄Na 356.0932, found 356.0929.

trans-5-Phenyl-4-(phenylsulfonyl)-1-propylpyrrolidin-2-one (10e). General procedure A was used with sulfone anhydride 3a (0.3 g, 1.2 mmol), propylamine (100 μ L, 1.2 mmol), and benzaldehyde (126 μ L, 1.2 mmol) to yield 10e (0.36 g, 87%) as a solid (50:50 EtOAc/

hex, $R_f = 0.36$). Mp 149.8–150.4 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.89 (dt, $J = 8.5, 1.4$ Hz, 2H), 7.76–7.54 (m, 3H), 7.43–7.24 (m, 3H), 7.13–6.98 (m, 2H), 5.09 (d, $J = 3.5$ Hz, 1H), 3.70–3.56 (m, 2H), 2.97–2.76 (m, 2H), 2.54 (dddd, $J = 13.7, 8.4, 5.1, 1.1$ Hz, 1H), 1.55–1.31 (m, 2H), 0.85 (td, $J = 7.3, 1.2$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 170.6, 138.4, 136.7, 134.5, 129.6, 129.3, 128.8, 128.7, 126.0, 63.8, 61.1, 42.6, 30.9, 19.9, 11.1; IR (thin film) 1688 (C=O) cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_3\text{S}$ 342.1164, found 342.1155.

4-(trans-5-Oxo-3-(phenylsulfonyl)-1-propylpyrrolidin-2-yl)-benzotrile (10f). General procedure A (except that the decarboxylation was performed at room temperature overnight) was used with sulfone anhydride **3a** (0.3 g, 1.2 mmol), propylamine (102 μL , 1.2 mmol), and 4-cyanobenzaldehyde (0.164 g, 1.3 mmol) to yield **10f** (0.36 g, 80%) as a foam (50:50 EtOAc/hex, $R_f = 0.35$). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.89 (dt, $J = 8.5, 1.8$ Hz, 2H), 7.77–7.54 (m, 5H), 7.26 (m, 2H), 5.20 (d, $J = 3.6$ Hz, 1H), 3.67 (dt, $J = 13.7, 8.0$ Hz, 1H), 3.57 (dt, $J = 10.0, 4.3$ Hz, 1H), 2.88 (dd, $J = 18.2$ (gem), 4.5 Hz, 1H), 2.76 (dd, $J = 18.1$ (gem), 10.0 Hz, 1H), 2.52 (ddd, $J = 13.8, 8.6, 5.0$ Hz, 1H), 1.44 (m, 2H), 0.87 (t, $J = 7.3$ Hz, 3H); $^{13}\text{C NMR}$ (600 MHz, CDCl_3) δ 170.7, 144.1, 136.6, 134.9, 133.3, 129.9, 128.9, 127.2, 118.1, 113.1, 63.8, 60.6, 43.1, 31.3, 20.1, 11.2; IR (thin film) 1692 (C=O), 1445, 1412 (S=O) cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3\text{SNa}$ 391.1092, found 391.1098.

trans-5-(2-Methoxyphenyl)-4-(phenylsulfonyl)-1-propylpyrrolidin-2-one (10g). General procedure A was used with sulfone anhydride **3a** (88 mg, 0.36 mmol), propylamine (30 μL , 0.36 mmol), and aldehyde (50 mg, 0.37 mmol) to yield **10g** (87 mg, 65%) as a solid (50:50 EtOAc/hex, $R_f = 0.17$). Mp 125.3–126.1 °C; $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.92–7.86 (m, 2H), 7.69–7.62 (m, 1H), 7.55 (t, $J = 7.9$ Hz, 2H), 7.28 (m, 1H), 6.93–6.82 (m, 3H), 5.16 (s, 1H), 3.80 (d, $J = 9.8$ Hz, 1H), 3.69 (s, 3H), 3.49 (dt, $J = 13.5, 8.1$ Hz, 1H), 2.96 (dd, $J = 17.9$ (gem), 4.0 Hz, 1H), 2.85 (dd, $J = 17.9$ (gem), 9.9 Hz, 1H), 2.48 (ddd, $J = 13.7, 8.5, 5.2$ Hz, 1H), 1.46–1.28 (m, 2H), 0.82 (t, $J = 7.3$ Hz, 3H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 171.2, 157.5, 137.7, 134.2, 130.5, 129.5 (2C), 129.0 (2C), 125.7, 121.1, 111.5, 62.8, 55.6, 42.8, 31.7, 20.3, 11.3; IR (thin film) 1681 (C=O) cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_4\text{SNa}$ 396.1245, found 396.1252.

trans-1-Benzyl-4-(phenylsulfonyl)-5-((E)-styryl)pyrrolidin-2-one (10h). General procedure A was used with sulfone anhydride **3a** (0.18 g, 0.73 mmol), benzylamine (76 μL , 0.69 mmol), and aldehyde (0.1 mL, 0.79 mmol) to yield **10h** (0.25 g, 82%) as a foam (50:50 EtOAc/hex, $R_f = 0.36$). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.81–7.74 (m, 2H), 7.65–7.14 (m, 13H), 6.12 (d, $J = 15.8$ Hz, 1H), 5.74 (dd, $J = 15.6, 8.5$ Hz, 1H), 4.93 (d, $J = 15.0$ Hz, 1H), 4.38 (dd, $J = 8.8, 4.3$ Hz, 1H), 3.90 (d, $J = 15.0$ Hz, 1H), 3.65 (dt, $J = 9.9, 5.1$ Hz, 1H), 3.01 (dd, $J = 18.0$ (gem), 5.5 Hz, 1H), 2.86 (dd, $J = 18.1$ (gem), 10.0 Hz, 1H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 170.1, 136.8, 135.3, 135.2, 135.0, 134.4, 129.5, 128.8, 128.7, 128.7, 128.4, 127.7, 126.8, 126.7, 125.3, 61.7, 59.9, 44.7, 30.8; IR (thin film) 1690 (C=O), 1146 (S=O) cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{23}\text{NO}_3\text{SNa}$ 440.1296, found 440.1282.

trans-1-Isopropyl-5-phenyl-4-(phenylsulfonyl)pyrrolidin-2-one (10i). General procedure A was used with sulfone anhydride **3a** (0.3 g, 1.26 mmol), isopropylamine (100 μL , 1.22 mmol), and benzaldehyde (128 μL , 1.26 mmol) to yield **10i** (0.297 g, 70%) as a foam (50:50 EtOAc/hex, $R_f = 0.42$). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.98–7.86 (m, 2H), 7.72 (tt, $J = 7.2, 1.5$ Hz, 1H), 7.68–7.56 (m, 2H), 7.40–7.26 (m, 3H), 7.17–6.97 (m, 2H), 5.10 (d, $J = 2.3$ Hz, 1H), 4.20–3.98 (m, 1H), 3.57 (ddd, $J = 9.6, 2.6, 2.1$ Hz, 1H), 2.93 (ddd, $J = 18.2$ (gem), 9.6, 1.9 Hz, 1H), 2.88–2.75 (m, 1H), 1.21 (dd, $J = 6.8, 2.0$ Hz, 3H), 0.85 (dd, $J = 6.9, 1.9$ Hz, 3H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 170.7, 140.7, 136.6, 134.5, 129.6, 129.2, 128.8, 128.7, 125.9, 64.5, 60.1, 45.5, 31.2, 20.8, 19.5; IR (thin film) 1693 (C=O), 1145 (S=O) cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_3\text{SNa}$ 366.1140, found 366.1147.

trans-1-Allyl-5-phenyl-4-(phenylsulfonyl)pyrrolidin-2-one (10j). General procedure A was used with sulfone anhydride **3a** (0.30 g, 1.26 mmol), allylamine (93 μL , 1.24 mmol), and benzaldehyde (128

μL , 1.26 mmol) to yield **10j** (0.33 g, 78%) as a foam (50:50 EtOAc/hex, $R_f = 0.42$). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.88 (dt, $J = 8.5, 2.0$ Hz, 2H), 7.77–7.67 (m, 1H), 7.59 (m, 2H), 7.43–7.27 (m, 3H), 6.99 (m, 2H), 5.55 (dddd, $J = 17.6, 10.0, 7.8, 4.3$ Hz, 1H), 5.23–5.15 (m, 1H), 5.14–5.02 (m, 2H), 4.40 (ddt, $J = 15.4, 3.9, 1.9$ Hz, 1H), 3.75–3.65 (m, 1H), 2.95 (m, 3H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 170.42, 138.2, 136.8, 134.5, 131.0, 129.7, 129.5, 129.4, 128.9, 126.2, 119.0, 63.9, 60.7, 43.4, 31.0; IR (thin film) 1691 (C=O), 1145 (S=O) cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_3\text{SNa}$ 364.0983, found 364.0974.

trans-5-(4-Methoxyphenyl)-4-(phenylsulfonyl)-1-propylpyrrolidin-2-one (10k). General procedure A was used with sulfone anhydride **3a** (0.30 g, 1.2 mmol), propylamine (100 μL , 1.2 mmol), and 4-methoxybenzaldehyde (151 μL , 1.2 mmol) to yield **10k** (0.38 g, 84%) as a foam (50:50 EtOAc/hex, $R_f = 0.27$). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.92–7.86 (d, $J = 7.8$ Hz, 2H), 7.69 (m, 1H), 7.58 (t, $J = 7.8$ Hz, 2H), 6.96 (dd, $J = 9.2, 2.5$ Hz, 2H), 6.84 (dd, $J = 9.0, 2.5$ Hz, 2H), 5.04 (d, $J = 3.5$ Hz, 1H), 3.80 (sharp s, 3H), 3.66–3.53 (m, 2H), 2.90 (dd, $J = 18.2$ (gem), 4.7 Hz, 1H), 2.85–2.76 (dd, $J = 18.2$ (gem), 10.2 Hz, 1H), 2.52 (m, 1H), 1.51–1.32 (m, 2H), 0.88–0.79 (t, $J = 7.8$ Hz, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 170.4, 159.9, 136.9, 134.4, 130.3, 129.6, 128.8, 127.4, 114.7, 64.1, 60.7, 55.3, 42.5, 31.1, 20.0, 11.1; IR (thin film) 1687 (C=O), 1354, 1144 (S=O) cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_4\text{SNa}$ 396.1245, found 396.1252.

Methyl trans-1-Benzyl-5-oxo-2-phenyl-3-(phenylsulfonyl)pyrrolidine-3-carboxylate (11a). *N*-Benzylidenebenzylamine (0.1 mL, 0.53 mmol) was added to a round-bottom flask containing Na_2SO_4 (0.37 g, 2.6 mmol) and THF (6 mL), and then sulfone anhydride **3a** (0.13 g, 0.54 mmol) was added. The reaction mixture was allowed to stir for 1.5 h, after which the Na_2SO_4 was removed by filtration and the solvent was removed in vacuo. The residue was redissolved in EtOAc, transferred to a separatory funnel, and washed with HCl (1.2 M or 10%) and brine. The combined organic layers were dried over Na_2SO_4 , and the solvent removed in vacuo. The resulting acid was redissolved in a mixture of toluene and methanol (12 mL:7 mL) and cooled to 0 °C. To the cold solution, TMSCHN_2 (0.53 mL, 1.1 mmol, 2 M solution in hexanes) was added dropwise over a period of 5 min. The reaction was monitored by TLC for the disappearance of starting material. After ~2 h the solvent was removed in vacuo, and the resulting material was purified by column chromatography (30–60% EtOAc:hex) to yield **11a** (0.157 g, 66% over the two steps) as an amorphous solid (50:50 EtOAc/hex, $R_f = 0.47$). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.64–7.18 (m, 15H), 5.21 (d, $J = 14.5$ Hz, 1H), 4.89 (s, 1H), 3.70 (d, $J = 18.7$ (gem) Hz, 1H), 3.38–3.30 (m, 2H), 3.13 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 170.0, 164.9, 134.9, 134.8, 134.8, 134.4, 131.1, 129.6, 129.5, 129.5, 129.0, 128.9, 128.9, 128.2, 76.2, 63.9, 52.7, 44.9, 35.0; IR (thin film) 1783, 1784 (C=O), 1124 (S=O) cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{23}\text{NO}_5\text{SNa}$ 472.1195, found 472.1176.

Methyl trans-2-(3,5-Dimethoxyphenyl)-5-oxo-3-(phenylsulfonyl)-1-propylpyrrolidine-3-carboxylate (11b). Propylamine (68 μL , 0.83 mmol) and 3,5-dimethoxybenzaldehyde (0.14 g, 0.84 mmol) were dissolved in THF (8 mL). Na_2SO_4 (0.59 g, 4.2 mmol) was added, and the mixture was allowed to stir for 1.5 h. Sulfone anhydride **3a** (0.20 g, 0.83 mmol) was added, and the reaction was allowed to stir for an additional 1 h. The Na_2SO_4 was filtered off, and the solvent was removed in vacuo. The residue was redissolved in EtOAc, transferred to a separatory funnel, and washed with HCl (1.2 M or 10%) and brine. The combined organic layers were dried over Na_2SO_4 , and the solvent was removed in vacuo. The resulting crude acid was dissolved in a mixture of toluene and methanol (13 mL:7 mL) and cooled to 0 °C. To the cold solution, TMSCHN_2 (0.83 mL, 1.7 mmol, 2 M solution in hexanes) was added dropwise over a period of 5 min, and the reaction was monitored by TLC for the disappearance of starting material. After ~2 h the solvent was removed in vacuo, and the resulting material was purified by column chromatography (30–60% EtOAc:hex) to yield **11b** (0.22 g, 57% over the two steps) as an amorphous solid (50:50 EtOAc/hex, $R_f = 0.31$). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 8.01–7.83 (m, 2H), 7.81–7.68 (m,

1H), 7.68–7.52 (m, 2H), 6.39 (d, $J = 2.3$ Hz, 1H), 6.22 (s, 2H), 5.38 (s, 1H), 3.74 (s, 6H), 3.66–3.59 (m, 1H), 3.55 (d, $J = 18.4$ (gem) Hz, 1H), 3.26 (m, 3H), 3.14 (d, $J = 18.5$ (gem) Hz, 1H), 2.58 (ddd, $J = 13.8, 8.7, 5.2$ Hz, 1H), 1.65–1.32 (m, 2H), 0.92 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 169.9, 164.7, 160.9, 137.3, 135.3, 134.9, 130.4, 129.2, 100.8, 76.7, 64.3, 55.4, 52.8, 43.2, 35.8, 20.2 (2C), 11.3; IR (thin film) 1748, 1702 (C=O), 1144, 1457 (S=O) cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_7\text{SNa}$ 484.1406, found 484.1404.

Methyl *trans*-1-Methyl-5-oxo-2-phenyl-3-(phenylsulfonyl)pyrrolidine-3-carboxylate (11c). *N*-Benzylidenemethylamine (0.1 mL, 0.81 mmol) was added to a round-bottom flask containing Na_2SO_4 (0.57 g, 4.0 mmol) and THF (8 mL), and then sulfone anhydride **3a** (0.19 g, 0.80 mmol) was added. The reaction mixture was allowed to stir for 1.5 h, after which the Na_2SO_4 was removed by filtration and the solvent removed in vacuo. The residue was redissolved in EtOAc, transferred to a separatory funnel, and washed with HCl (1.2 M or 10%) and brine. The combined organic layers were dried over Na_2SO_4 , and the solvent was removed in vacuo. The crude acid was redissolved in a mixture of toluene and methanol (13 mL:7 mL) and cooled to 0 °C. To the cold solution, TMSCHN_2 (0.81 mL, 1.6 mmol, 2 M solution in hexanes) was added dropwise over a period of 5 min, and the reaction was monitored by TLC for the disappearance of starting material. After ~2 h the solvent was removed in vacuo, and the resulting material was purified by column chromatography (30–60% EtOAc:hex) to yield **11c** (0.20 g, 67% over the two steps) as an amorphous solid (50:50 EtOAc/hex, $R_f = 0.28$). ^1H NMR (400 MHz, CDCl_3) δ 7.88 (dt, $J = 8.6, 2.2$ Hz, 2H), 7.72–7.63 (m, 1H), 7.64–7.50 (m, 2H), 7.36–7.23 (m, 4H), 7.05 (d, $J = 7.2$ Hz, 2H), 5.31 (s, 1H), 3.49 (d, $J = 18.4$ (gem) Hz, 1H), 3.15 (d, $J = 2.3$ Hz, 3H), 3.01 (d, $J = 18.5$ (gem) Hz, 1H), 2.58 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.75, 164.51, 135.32, 135.1, 134.3, 130.2, 129.4, 129.3, 128.7, 127.6, 76.7, 66.5, 52.9, 35.5, 28.3; IR (thin film) 1736, 1690 (C=O), 1177, 1360 (S=O) cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_5\text{SNa}$ 396.0882, found 396.0887.

Methyl *trans*-1-Benzyl-5-oxo-2-phenylpyrrolidine-3-carboxylate (12a). Ester **11a** (0.104 g, 0.23 mmol) was dissolved in anhydrous MeOH (12 mL), and magnesium turnings (169 mg, 6.9 mmol, flame-dried under argon) were added to the reaction mixture. The mixture was heated to 50 °C for 15 min and then to 64 °C for 1.5 h, cooled to rt, poured into an Erlenmeyer flask containing 10% HCl (20 mL), and extracted with diethyl ether. The organic layer was dried over Na_2SO_4 , and the solvent was removed in vacuo. Purification by flash chromatography (30–50% EtOAc/hex) yielded **12a** as an oil (0.54 g, 76%). ^1H NMR data for the major diastereomer (600 MHz, CDCl_3): δ 7.41–7.33 (m, 4H), 7.30–7.23 (m, 3H), 7.18–7.13 (m, 1H), 7.05–7.01 (m, 2H), 5.11 (d, $J = 14.7$ Hz, 1H), 4.63–4.56 (d, $J = 5.4$ Hz, 1H), 3.64 (s, 3H), 3.48 (d, $J = 14.9$ Hz, 1H), 3.07 (m, 1H), 2.94–2.75 (m, 2H). The ^1H NMR data are in accordance with the literature.⁶

Methyl *trans*-2-(3,5-Dimethoxyphenyl)-5-oxo-1-propylpyrrolidine-3-carboxylate (12b). Ester **11b** (75.4 mg, 0.163 mmol) was dissolved in anhydrous MeOH (12 mL), and magnesium turnings (162 mg, 6.67 mmol, flame-dried under argon) were added to the reaction mixture. The mixture was heated to 50 °C for 15 min and then to 64 °C for 1.5 h, cooled to rt, poured into an Erlenmeyer flask containing 10% HCl (30 mL), and extracted with diethyl ether. The organic layer was dried over Na_2SO_4 , and the solvent was removed in vacuo. Purification by flash chromatography (30–50% EtOAc/hex) yielded **12b** as an oil (0.35 g, 67%). ^1H NMR (400 MHz, CDCl_3) δ 6.42 (t, $J = 2.2$ Hz, 1H), 6.35 (d, $J = 2.3$ Hz, 2H), 4.83 (d, $J = 5.3$ Hz, 1H), 3.79 (s, 6H), 3.74 (s, 3H), 3.66 (dt, $J = 13.6, 8.1$ Hz, 1H), 3.04 (ddd, $J = 9.6, 7.0, 5.2$ Hz, 1H), 2.84 (dd, $J = 17.2, 9.8$ Hz, 1H), 2.76 (d, $J = 7.0$ Hz, 1H), 2.61 (ddd, $J = 13.6, 8.3, 5.2$ Hz, 1H), 1.54–1.37 (m, 2H), 0.84 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.1, 172.7, 161.5, 142.0, 104.5, 100.1, 64.2, 55.5, 52.6, 45.9, 42.5, 33.8, 20.2, 11.3; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_5\text{Na}$ 344.1474, found 344.1465.

***tert*-Butyl 2-(Phenylsulfonyl)acetate (8).** To a 500 mL round-bottom flask were added benzenesulfonic acid sodium salt (5.1 g, 30.8 mmol), *tert*-butyl bromoacetate (3.8 mL, 25.6 mmol), and 170 mL of ethanol. The reaction mixture was refluxed for 4 h and then concentrated in vacuo. The crude mixture was suspended in Et_2O (150 mL) and washed with water (2 \times 150 mL) and brine (150 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo to yield **8** (6.31 g, 96%) as a clear oil. ^1H NMR (300 MHz, CDCl_3) δ 7.90 (m, 2H), 7.68 (m, 1H), 7.55 (m, 2H), 4.03 (s, 2H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 161.2, 138.8, 134.1, 129.1, 128.5, 83.6, 62.0, 27.6. These data are in accordance with the literature.³¹

***Di-tert*-butyl 2-(Phenylsulfonyl)pentanedioate (3ba).** To a dry 250 mL round-bottom flask were added **8** (6.31 g, 24.6 mmol), cesium carbonate (400 mg, 1.23 mmol), *tert*-butyl acrylate (3.6 mL, 24.6 mmol), and 80 mL of acetonitrile. The reaction mixture was heated to 50 °C overnight and then diluted with water and extracted with ethyl acetate (3 \times 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified on silica gel (20:80 EtOAc/hex) to yield **3ba** (4.91 g, 52%) as an amorphous solid. ^1H NMR (300 MHz, CDCl_3) δ 7.89 (d, $J = 7.3$ Hz, 2H), 7.68 (m, 1H), 7.57 (dd, $J = 8.4, 6.9$ Hz, 2H), 3.99 (m, 1H), 2.24 (m, 4H), 1.42 (s, 9H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.9, 164.4, 137.4, 134.1, 129.4, 129.0, 83.5, 81.0, 70.1, 32.1, 28.0, 27.7, 22.3; IR (thin film) 2979, 1730, 1309, 1138 cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{28}\text{O}_6\text{SNa}$ 407.1504, found 407.1502.

***Di-tert*-butyl 3-Methyl-2-(phenylsulfonyl)pentanedioate (3ca).** To a dry 250 mL round-bottom flask were added **8** (3.00 g, 11.7 mmol), cesium carbonate (382 mg, 1.17 mmol), *tert*-butyl crotonate (1.90 mL, 11.7 mmol), and 40 mL of acetonitrile. The reaction mixture was heated to reflux overnight and then diluted with water and extracted with ethyl acetate (3 \times 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified on silica gel (20:80 EtOAc/hex) to yield **3ca** (3.75 g, 80%) as an amorphous solid (mixture of diastereomers). NMR data for one diastereomer: ^1H NMR (600 MHz, CDCl_3) δ 7.90 (m, 3H), 7.64 (m, 2H), 7.53 (m, 3H), 4.10 (d, $J = 8.0$ Hz, 1H), 2.71 (m, 2H), 2.43 (m, 1H), 1.42 (s, 16H, overlap with minor diastereomer), 1.27 (s, 14H, overlap with minor diastereomer), 1.12 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 170.7, 164.4, 138.4, 134.0, 129.2, 128.9, 83.3, 80.8, 73.7, 39.9, 29.6, 28.1, 27.6, 17.1; IR (thin film) 2980, 1729, 1325, 1135 cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{30}\text{O}_6\text{SNa}$ 421.1661, found 421.1653.

***Di-tert*-butyl 2-Methyl-4-(phenylsulfonyl)pentanedioate (3da).** To a dry 250 mL round-bottom flask were added **8** (3.00 g, 11.7 mmol), cesium carbonate (382 mg, 1.17 mmol), *tert*-butyl methacrylate (1.90 mL, 11.7 mmol), and 40 mL of acetonitrile. The reaction mixture was heated to reflux for 48 h and then diluted with water and extracted with ethyl acetate (3 \times 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified on silica gel (20:80 EtOAc/hex) to yield **3da** (4.20 g, 90%) as an amorphous solid (mixture of diastereomers). NMR data for one diastereomer: ^1H NMR (400 MHz, CDCl_3) δ 7.89 (m, 2H), 7.69 (m, 1H), 7.58 (m, 2H), 4.03 (dd, $J = 11.9, 3.3$ Hz, 1H), 2.28 (m, 2H), 1.99 (m, 1H), 1.43 (s, 9H), 1.37 (s, 9H), 1.16 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 174.2, 164.7, 137.6, 134.3, 129.5, 129.2, 83.6, 81.1, 69.6, 38.2, 30.6, 28.2, 27.8, 18.4; IR (thin film) 2978, 2936, 1727, 1325, 1138 cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{30}\text{O}_6\text{SNa}$ 421.1661, found 421.1662.

3-(Phenylsulfonyl)dihydro-2H-pyran-2,6(3H)-dione (3b). To a dry 250 mL flask were added **3ba** (4.91 g, 12.7 mmol), CH_2Cl_2 (50 mL), and trifluoroacetic acid (50 mL). The reaction mixture was stirred for 1 h and then concentrated in vacuo and azeotropically distilled with CH_2Cl_2 (3 \times 10 mL). The crude mixture was taken up in 45 mL of trifluoroacetic anhydride and stirred overnight. The reaction mixture was concentrated in vacuo and azeotroped with toluene (3 \times 10 mL). Filtering the off-white solid with diethyl ether yielded **3b** (3.01 g, 93%) as a white solid. Mp 122.2–122.8 °C; ^1H NMR (600 MHz, CD_3CN) δ 7.97 (m, 2H), 7.83 (m, 1H), 7.70 (m, 2H), 4.55 (m,

1H), 3.06 (m, 1H), 2.87 (m, 1H), 2.50 (m, 2H); ¹³C NMR (150 MHz, CD₃CN) δ 165.3, 160.7, 137.3, 135.0, 129.5, 129.0, 63.4, 27.1, 17.1; IR (thin film) 3098, 2929, 1816, 1746 1322, 1152 cm⁻¹; HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for C₁₁H₁₀O₅SNa 277.0147, found 277.0145.

4-Methyl-3-(phenylsulfonyl)dihydro-2H-pyran-2,6(3H)-dione (3c). To a dry 250 mL flask were added **3ca** (3.73 g, 9.30 mmol), CH₂Cl₂ (50 mL), and trifluoroacetic acid (50 mL). The reaction mixture was stirred for 1 h and then concentrated in vacuo and azeotropically distilled with CH₂Cl₂ (3 × 10 mL). To the crude mixture was added acetic anhydride (33 mL), and the mixture was taken up in 100 mL of toluene and stirred overnight. The mixture was concentrated in vacuo and azeotroped with benzene (3 × 10 mL). Trituration with diethyl ether afforded **3c** (2.31 g, 92%) as a solid (mixture of diastereomers). NMR data for one diastereomer: ¹H NMR (600 MHz, CD₃CN) δ 7.93 (m, 2H), 7.84 (m, 1H), 7.70 (m, 2H), 4.40 (m, 1H), 3.29 (m, 1H), 3.03 (m, 1H), 2.75 (m, 1H), 1.18 (m, 3H); ¹³C NMR (151 MHz, CD₃CN) δ 164.8, 160.4, 135.2, 129.6, 129.3, 128.9, 69.6, 33.9, 24.4, 19.4; IR (thin film) 2991, 2957, 1814, 1758, 1311, 1146 cm⁻¹; HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for C₁₂H₁₂O₅SNa 291.0293, found 291.0303.

3-Methyl-5-(phenylsulfonyl)dihydro-2H-pyran-2,6(3H)-dione (3d). To a dry 250 mL flask were added **3da** (4.00 g, 10.0 mmol), CH₂Cl₂ (50 mL), and trifluoroacetic acid (50 mL). The reaction mixture was stirred for 1 h and then concentrated in vacuo and azeotropically distilled with CH₂Cl₂ (3 × 10 mL). To the crude mixture were added acetic anhydride (33 mL) and 100 mL of toluene, and the resulting mixture was stirred overnight, concentrated in vacuo, and azeotroped with benzene (3 × 10 mL). Trituration with diethyl ether afforded **3d** (2.53 g, 94%) as a solid (mixture of diastereomers). NMR data for one diastereomer: ¹H NMR (400 MHz, CDCl₃) δ 7.90 (m, 2H), 7.74 (m, 1H), 7.62 (m, 3H, overlap with minor diastereomer), 4.22 (dd, *J* = 3.0, 9.0 Hz, 1H), 2.95 (ddd, *J* = 2.1, 6.1, 15.2 Hz, 1H), 2.76–2.58 (m, 1H), 2.13 (ddd, *J* = 6.2, 13.2, 15.2 Hz, 1H), 1.44 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 167.8, 160.3, 137.1, 135.2, 129.8, 129.4, 64.8, 32.6, 25.5, 16.4; IR (thin film) 3066, 2970, 1803, 1755, 1310, 1154 cm⁻¹; HRMS (ESI-TOF) *m/z* [M + H₂O + Na]⁺ calcd for C₁₂H₁₄O₆SNa 309.0409, found 309.0402.

General Procedures for the Glutaric Anhydride Mannich Reaction. *General Procedure B.* To a dry 10 mL flask were added 2 mL of acetonitrile, triethyl orthoformate (0.11 mL, 0.63 mmol), amine (0.39 mmol), and aldehyde (0.39 mmol). The reaction mixture was stirred overnight. Anhydride **3b** (0.39 mmol) in 2 mL of acetonitrile was added, and the reaction mixture was stirred for 30 min at room temperature and then refluxed for 4 h. The mixture was cooled to room temperature and concentrated in vacuo. The product was purified by flash column chromatography (conditions given for each compound).

General Procedure C. To a dry 10 mL flask was added 4 mL of acetonitrile, triethyl orthoformate (0.11 mL, 0.63 mmol), the prepared imine (0.39 mmol), and anhydride **3b–d** (0.39 mmol). The reaction mixture was stirred for 30 min at room temperature and then refluxed for 4 h. The mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by flash column chromatography (conditions given for each compound).

trans-1-Methyl-6-phenyl-5-(phenylsulfonyl)piperidin-2-one (13a). General procedure C. The residue was purified by flash column chromatography (70:30 EtOAc/hex, *R_f* = 0.40) to yield **13a** as a solid (105 mg, 80%). Mp 152.6–153.1 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.91 (m, 2H), 7.69 (m, 1H), 7.59 (m, 2H), 7.32 (m, 3H), 7.04 (m, 2H), 5.10 (s, 1H), 3.36 (ddd, *J* = 5.0, 4.9, 2.3 Hz, 1H), 2.84 (s, 3H), 2.73 (m, 1H), 2.45 (ddd, *J* = 17.9 (gem), 6.6, 4.6 Hz, 1H), 2.08 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 169.3, 139.0, 137.3, 134.4, 129.6, 129.3, 128.6, 128.4, 126.0, 65.0, 60.7, 34.4, 27.9, 17.8; IR (thin film) 3057, 2930, 1635, 1302, 1142 cm⁻¹; HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for C₁₈H₁₉NO₃SNa 352.0983, found 352.0973.

trans-1-Isopropyl-6-phenyl-5-(phenylsulfonyl)piperidin-2-one (13b). General procedure B. The residue was purified by flash column chromatography (60:40 EtOAc/hex, *R_f* = 0.40) to yield **13b** as a foam (117 mg, 84%). ¹H NMR (300 MHz, CDCl₃) δ 7.92 (m, 2H), 7.74–

7.64 (m, 1H), 7.60 (m, 2H), 7.30 (m, 3H), 7.15 (m, 2H), 5.40 (s, 1H), 4.68 (m, 1H), 3.28 (m, 1H), 2.78 (m, 1H), 2.49 (ddd, *J* = 12.3, 11.9, 9.8 Hz, 1H), 1.92 (m, 2H), 1.31 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 169.7, 141.6, 137.5, 134.3, 129.6, 129.0, 128.6, 128.0, 126.0, 65.0, 53.8, 47.6, 28.5, 20.3, 20.1, 17.5; IR (thin film) 2967, 2945, 1641, 1303, 1143 cm⁻¹; HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for C₂₀H₂₃NO₃SNa 380.1296, found 380.1306.

trans-1-Benzyl-6-phenyl-5-(phenylsulfonyl)piperidin-2-one (13c). General procedure C. The residue was purified by flash column chromatography (70:30 EtOAc/hex, *R_f* = 0.48) to yield **13c** as a foam (130 mg, 85%). ¹H NMR (600 MHz, CDCl₃) δ 7.63 (t, *J* = 7.4 Hz, 1H), 7.39 (m, 7H), 7.30 (m, 3H), 7.25 (t, *J* = 6.1 Hz, 2H), 6.79 (m, 2H), 5.76 (d, *J* = 14.6 Hz, 1H), 4.69 (s, 1H), 3.22 (d, *J* = 14.6 Hz, 1H), 3.17 (m, 1H), 3.07 (m, 1H), 2.67 (dd, *J* = 18.1 (gem), 6.8 Hz, 1H), 2.43 (m, 1H), 2.18 (m, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 169.0, 138.8, 137.0, 136.1, 134.0, 129.5, 129.4, 129.3, 128.6, 128.6, 128.5, 127.7, 125.9, 63.9, 57.2, 47.6, 28.3, 16.1; IR (thin film) 3059, 2936, 1642, 1307, 1144 cm⁻¹; HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for C₂₄H₂₃NO₃SNa 428.1296, found 428.1303.

trans-6-Phenyl-5-(phenylsulfonyl)-1-(prop-2-yn-1-yl)piperidin-2-one (13d). General procedure C. The residue was purified by flash column chromatography (60:40 EtOAc/hex, *R_f* = 0.40) to yield **13d** as a foam (103 mg, 75%). ¹H NMR (600 MHz, CDCl₃) δ 7.99 (m, 2H), 7.69 (m, 1H), 7.59 (m, 2H), 7.30 (m, 3H), 6.98 (dd, *J* = 7.3, 2.0 Hz, 2H), 5.40 (d, *J* = 2.4 Hz, 1H), 4.95 (dd, *J* = 17.5, 2.6 Hz, 1H), 3.38 (td, *J* = 5.0, 2.5 Hz, 1H), 3.30 (dd, *J* = 17.5, 2.5 Hz, 1H), 2.81 (ddd, *J* = 17.7, 10.5, 6.9 Hz, 1H), 2.52 (ddd, *J* = 18.0 (gem), 6.7, 4.3 Hz, 1H), 2.28 (m, 1H), 2.12 (m, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 168.7, 138.4, 137.3, 134.4, 129.5, 129.3, 128.9, 128.6, 126.2, 77.7, 73.1, 64.6, 57.9, 34.3, 28.3, 17.3; IR (thin film) 3303, 3055, 1650, 1267, 1148 cm⁻¹; HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for C₂₀H₁₉NO₃SNa 376.0983, found 376.0977.

trans-1-Allyl-6-phenyl-5-(phenylsulfonyl)piperidin-2-one (13e). General procedure C. The residue was purified by flash column chromatography (60:40 EtOAc/hex, *R_f* = 0.40) to yield **13e** as a foam (124 mg, 89%). ¹H NMR (600 MHz, CDCl₃) δ 7.92 (m, 2H), 7.71 (m, 1H), 7.60 (m Hz, 2H), 7.29 (m, 3H), 6.96 (dd, *J* = 7.5, 1.9 Hz, 2H), 5.83 (dddd, *J* = 17.7, 10.5, 8.2, 4.3 Hz, 1H), 5.21 (m, 2H), 5.11 (s, 1H), 4.86 (ddd, *J* = 15.0, 4.3, 2.0 Hz, 1H), 3.31 (td, *J* = 4.7, 1.8 Hz, 1H), 3.00–2.82 (m, 2H), 2.54 (ddd, *J* = 18.0 (gem), 6.8, 3.7 Hz, 1H), 2.19 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 169.1, 139.1, 137.3, 134.4, 132.4, 129.5, 129.3, 128.7, 128.4, 126.0, 118.8, 64.4, 57.2, 47.9, 28.0, 17.1; IR (thin film) 3054, 2988, 1641, 1307, 1148 cm⁻¹; HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for C₂₀H₂₁NO₃SNa 378.1140, found 378.1136.

trans-1,6-Diphenyl-5-(phenylsulfonyl)piperidin-2-one (13f). General procedure C. The residue was purified by flash column chromatography (70:30 EtOAc/hex, *R_f* = 0.40) to yield **13f** as a foam (110 mg, 72%). ¹H NMR (600 MHz, CDCl₃) δ 7.92 (m, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.56 (m, 2H), 7.32 (m, 2H), 7.27 (m, 3H), 7.19 (m, 5H), 5.54 (s, 1H), 3.48 (m, 1H), 2.95 (m, 1H), 2.66 (dt, *J* = 18.1 (gem), 6.2 Hz, 1H), 2.20 (m, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 169.8, 142.3, 139.7, 137.2, 134.4, 129.6, 129.2, 129.1, 128.6, 128.3, 127.3, 127.0, 126.2, 64.9, 62.2, 28.8, 18.2; IR (thin film) 3066, 3008, 2946, 1654, 1304, 1143 cm⁻¹; HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for C₂₃H₂₁NO₃SNa 414.1140, found 414.1131.

trans-6-Phenyl-5-(phenylsulfonyl)-1-propylpiperidin-2-one (13g). General procedure C. The residue was purified by flash column chromatography (70:30 EtOAc/hex, *R_f* = 0.46) to yield **13g** as a foam (126 mg, 91%). ¹H NMR (600 MHz, CDCl₃) δ 7.91 (m, 2H), 7.69 (m, 1H), 7.59 (t, *J* = 7.8 Hz, 2H), 7.31 (dd, *J* = 8.4, 6.6 Hz, 2H), 7.25 (m, 1H), 7.05 (d, *J* = 7.4 Hz, 2H), 5.22 (s, 1H), 3.95 (dtd, *J* = 13.6, 6.8, 3.3 Hz, 1H), 3.32 (td, *J* = 5.0, 2.0 Hz, 1H), 2.81 (m, 1H), 2.43 (m, 2H), 1.99 (m, 2H), 1.61 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 169.2, 139.7, 137.4, 134.3, 129.6, 129.2, 128.5, 128.3, 126.1, 64.7, 57.9, 48.0, 28.0, 20.3, 17.6, 11.3; IR (thin film) 2967, 2929, 2871, 1639, 1308, 1147 cm⁻¹; HRMS (ESI-TOF) *m/z* [M + Na]⁺ calcd for C₂₀H₂₃NO₃SNa 380.1296, found 380.1290.

trans-1-Isopropyl-5-(phenylsulfonyl)-6-(*E*-styryl)piperidin-2-one (13h). General procedure B. The residue was purified by flash column

chromatography (60:40 EtOAc/hex, $R_f = 0.50$) to yield **13h** as an orange amorphous solid (101 mg, 68%). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.93 (dd, $J = 7.2, 1.6$ Hz, 2H), 7.70 (m, 1H), 7.60 (dd, $J = 8.2, 6.6$ Hz, 2H), 7.32 (m, 5H), 6.37 (dd, $J = 16.0, 1.2$ Hz, 1H), 6.07 (dd, $J = 15.8, 6.4$ Hz, 1H), 4.94 (dt, $J = 6.6, 1.6$ Hz, 1H), 4.66 (m, 1H), 3.35 (td, $J = 6.4, 2.0$ Hz, 1H), 2.68 (dt, $J = 17.2, 7.0$ Hz, 1H), 2.40 (dt, $J = 17.2, 7.1$ Hz, 1H), 2.09 (dt, $J = 14.4, 7.2$ Hz, 1H), 1.99 (dt, $J = 14.4, 7.2$ Hz, 1H), 1.33 (d, $J = 6.8$ Hz, 3H), 1.18 (d, $J = 6.9$ Hz, 3H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 169.7, 137.6, 135.4, 134.2, 132.0, 129.8, 129.6, 128.8, 128.6, 128.4, 126.5, 63.5, 51.8, 47.3, 29.1, 20.7, 20.2, 18.78; IR (thin film) 3059, 2975, 1639, 1446, 1305, 1145 cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{25}\text{NO}_3\text{SNa}$ 406.1453, found 406.1447.

trans-6-(4-Methoxyphenyl)-5-(phenylsulfonyl)-1-propylpiperidin-2-one (13i). General procedure B. The residue was purified by flash column chromatography (60:40 EtOAc/hex, $R_f = 0.42$) to yield **13i** as a foam (96 mg, 69%). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.92 (d, $J = 8.4$ Hz, 2H), 7.69 (t, $J = 7.4$ Hz, 1H), 7.60 (t, $J = 7.8$ Hz, 2H), 6.97 (d, $J = 8.6$ Hz, 2H), 6.84 (m, 2H), 5.18 (m, 1H), 3.93 (m, 1H), 3.77 (s, 3H), 3.30 (m, 1H), 2.81 (m, 1H), 2.45 (m, 2H), 2.01 (m, 2H), 1.61 (m, 2H), 0.88 (t, $J = 7.5$ Hz, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 169.2, 159.5, 134.2, 131.5, 129.5, 128.6, 127.3, 114.5, 105.0, 64.9, 57.5, 55.3, 48.0, 28.1, 20.3, 17.6, 11.3; IR (thin film) 2964, 2920, 1633, 1250, 1144 cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_4\text{SNa}$ 410.1402, found 410.1400.

trans-6-(4-Chlorophenyl)-5-(phenylsulfonyl)-1-propylpiperidin-2-one (13j). General procedure C. The residue was purified by flash column chromatography (60:40 EtOAc/hex, $R_f = 0.40$) to yield **13j** as a foam (133 mg, 87%). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.89 (m, 2H), 7.69 (m, 1H), 7.59 (m, 2H), 7.28 (m, 2H), 7.01 (m, 2H), 5.21 (s, 1H), 3.92 (ddd, $J = 13.6, 9.0, 7.4$ Hz, 1H), 3.27 (td, $J = 5.1, 2.2$ Hz, 1H), 2.78 (ddd, $J = 17.4, 10.1, 6.8$ Hz, 1H), 2.41 (m, 2H), 1.96 (m, 2H), 1.59 (m, 2H), 0.86 (t, $J = 7.4$ Hz, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 169.2, 138.3, 137.2, 134.4, 134.2, 129.6, 129.4, 128.5, 127.5, 64.6, 57.5, 48.0, 28.1, 20.3, 17.9, 11.3; IR (thin film) 2964, 2937, 1641, 1306, 1146 cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{22}\text{ClNO}_3\text{SNa}$ 414.0907, found 414.0921.

trans-6-(2-Ethylphenyl)-5-(phenylsulfonyl)-1-propylpiperidin-2-one (13k). General procedure C. The residue was purified by flash column chromatography (60:40 EtOAc/hex, $R_f = 0.42$) to yield **13k** as a foam (92 g, 61%). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.95 (d, $J = 8.4$ Hz, 2H), 7.70 (t, $J = 7.4$ Hz, 1H), 7.61 (t, $J = 7.9$ Hz, 2H), 7.24 (m, 1H), 7.17 (m, 2H), 7.05 (d, $J = 7.8$ Hz, 1H), 5.51 (s, 1H), 3.97 (m, 1H), 3.14 (m, 1H), 2.94 (m, 1H), 2.53 (dd, $J = 18.3$ (gem), 7.4 Hz, 1H), 2.42 (m, 1H), 2.34 (m, 2H), 2.07 (m, 1H), 1.98 (m, 1H), 1.69 (m, 2H), 1.14 (t, $J = 7.5$ Hz, 3H), 0.92 (t, $J = 7.4$ Hz, 3H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 168.9, 141.1, 137.6, 136.1, 134.3, 129.63, 129.60, 128.63, 128.60, 126.5, 126.1, 62.5, 54.4, 48.2, 27.3, 24.3, 20.4, 16.3, 15.4, 11.5; IR (thin film) 3006, 2966, 1639, 1300, 1144 cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{27}\text{NO}_3\text{SNa}$ 408.1609, found 408.1620.

trans-6-(3,5-Dimethoxyphenyl)-5-(phenylsulfonyl)-1-propylpiperidin-2-one (13l). General procedure B. The residue was purified by flash column chromatography (80:20 EtOAc/hex, $R_f = 0.50$) to yield **13l** as a foam (104 mg, 64%). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.92 (m, 2H), 7.69 (t, $J = 7.1$ Hz, 1H), 7.60 (m, 2H), 6.32 (s, 1H), 6.16 (d, $J = 2.1$ Hz, 2H), 5.14 (d, $J = 2.1$ Hz, 1H), 3.95 (ddd, $J = 13.4, 9.6, 6.5$ Hz, 1H), 3.72 (s, 6H), 3.34 (td, $J = 4.8, 1.9$ Hz, 1H), 2.79 (m, 1H), 2.46 (m, 2H), 2.03 (m, 2H), 1.63 (m, 2H), 0.89 (t, $J = 7.4$ Hz, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 169.1, 161.5, 142.3, 137.4, 134.2, 129.6, 128.6, 104.2, 99.5, 64.6, 58.0, 55.4, 48.2, 28.0, 20.3, 17.7, 11.3; IR (thin film) 2962, 2937, 1641, 1594, 1306, 1145 cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{27}\text{NO}_5\text{SNa}$ 440.1508, found 440.1517.

trans-6-(Furan-2-yl)-5-(phenylsulfonyl)-1-propylpiperidin-2-one (13m). General procedure B. The residue was purified by flash column chromatography (70:30 EtOAc/hex, $R_f = 0.35$) to yield **13m** as a foam (101 mg, 75%). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.88 (d, $J = 7.2$ Hz, 2H), 7.65 (m, 1H), 7.56 (t, $J = 7.7$ Hz, 2H), 7.27 (dd, $J = 1.9, 1.0$ Hz, 1H), 6.24 (m, 1H), 6.10 (m, 1H), 5.16 (d, $J = 2.9$ Hz, 1H), 3.78 (ddd, $J = 13.6, 9.6, 6.4$ Hz, 1H), 3.59 (td, $J = 6.1, 3.1$ Hz, 1H), 2.71 (m, 2H),

2.43 (dt, $J = 17.5, 6.6$ Hz, 1H), 2.09 (m, 2H), 1.58 (m, 1H), 1.49 (m, 1H), 0.85 (t, $J = 7.4$ Hz, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 169.4, 151.3, 143.0, 137.3, 134.2, 129.5, 128.5, 110.6, 108.4, 61.8, 52.9, 47.8, 28.5, 20.4, 19.0, 11.3; IR (thin film) 2965, 2933, 2875, 1647, 1503, 1306, 1148 cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_4\text{SNa}$ 370.1089, found 370.1076.

rel-(4R,5S,6R)-1,4-Dimethyl-6-phenyl-5-(phenylsulfonyl)piperidin-2-one (14). General procedure C with anhydride **3c**. The residue was purified by flash column chromatography (70:30 EtOAc/hex, $R_f = 0.35$) to yield **14** as a solid (111 mg, 87%). Mp 127.4–128.1 °C; $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.99 (m, 2H), 7.74 (m, 1H), 7.65 (m, 2H), 7.35 (dd, $J = 8.4, 7.1$ Hz, 2H), 7.28 (m, 1H), 7.05 (d, $J = 6.8$ Hz, 2H), 5.21 (s, 1H), 3.45 (d, $J = 6.9$ Hz, 1H), 2.91 (s, 3H), 2.53 (m, 1H), 2.45 (dd, $J = 15.7, 5.3$ Hz, 1H), 2.11 (dd, $J = 15.8, 11.6$ Hz, 1H), 0.91 (d, $J = 6.7$ Hz, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 171.1, 139.3, 137.0, 134.5, 129.6, 129.4, 129.1, 127.9, 125.3, 73.7, 60.3, 38.1, 34.4, 29.1, 22.4; IR (thin film) 2912, 1658, 1305, 1130 cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_3\text{SNa}$ 366.1140, found 366.1145.

rel-(3S,5R,6S)-1,3-Dimethyl-5-(phenylsulfonyl)-6-(2,4,6-trimethoxyphenyl)piperidin-2-one (15). General procedure C with anhydride **3d**. The residue was purified by flash column chromatography (80:20 EtOAc/hex, $R_f = 0.35$) to yield **15** as a white solid (169 mg, 79%). Mp 143.7–144.3 °C; $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.70 (d, $J = 7.5$ Hz, 2H), 7.50 (t, $J = 7.4$ Hz, 1H), 7.37 (t, $J = 7.7$ Hz, 2H), 5.89 (s, 2H), 5.31 (d, $J = 9.5$ Hz, 1H), 4.22 (ddd, $J = 13.4, 9.5, 3.6$ Hz, 1H), 3.72 (s, 3H), 3.71 (s, 6H), 2.48 (m, 4H, NCH_3 and 1 methylene H), 2.40 (m, 1H), 1.84 (m, 1H), 1.27 (d, $J = 6.9$ Hz, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 173.1, 161.4, 158.6, 137.4, 133.4, 128.50, 128.48, 106.8, 90.6, 61.9, 55.6, 55.2, 51.9, 35.0, 31.8, 29.3, 17.1; IR (thin film) 3006, 2939, 1614, 1286, 1134 cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{28}\text{NO}_6\text{S}$ 434.1637, found 434.1649.

Methyl trans-1-Allyl-5-oxo-3-(phenylsulfonyl)-2-(E)-styrylpyrrolidine-3-carboxylate (17). Allylamine (0.29 mL, 3.8 mmol) and *trans*-cinamaldehyde (0.53 mL, 4.2 mmol) were added to a round-bottom flask containing THF (38 mL) and Na_2SO_4 (3.3 g, 23.0 mmol), and the mixture was allowed to stir for 1 h. The anhydride (0.92 g, 3.8 mmol) was added, and the resulting mixture was allowed to stir for 2 h. The Na_2SO_4 was filtered off, and the solvent was evaporated in vacuo. The residue was redissolved in EtOAc and washed with 10% HCl and brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was triturated with hexanes, transferred to a fritted funnel, and washed in portions with hexanes five times (5 mL) and two times with a 9:1 mixture of cold hexanes and CHCl_3 (10 mL total), yielding 1.2 g of an off-white solid, which was ~85% pure by NMR. A portion of the resulting acid (0.885 g, 2.2 mmol) was redissolved in anhydrous toluene and methanol (60 mL:30 mL), and TMSCHN_2 (2.2 mL, 4.4 mmol, 2 M in hexanes) was added at 0 °C dropwise over a period of 5 min. The mixture was allowed to stir for 1.5 h and monitored by TLC for disappearance of the starting material. The solvent was removed in vacuo, and the crude mixture was purified by flash column chromatography (EtOAc/hex 30–60%), yielding **17** (0.85 g, 92%) as an amorphous solid (50:50 EtOAc/hex, $R_f = 0.44$). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.98–7.89 (m, 2H), 7.81–7.56 (m, 3H), 7.41–7.24 (m, 5H), 6.54 (d, $J = 15.8$ Hz, 1H), 5.84–5.72 (m, 2H), 5.34–5.25 (m, 2H), 5.02 (d, $J = 8.4$ Hz, 1H), 4.40 (ddt, $J = 15.3, 4.7, 1.7$ Hz, 1H), 3.71–3.42 (m, 3H), 3.44–3.27 (m, 2H), 3.13 (d, $J = 18.2$ (gem) Hz, 1H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 169.4, 165.3, 136.7, 135.8, 135.2, 135.0, 131.7, 130.6, 129.3, 128.9, 128.9, 126.8, 121.9, 119.4, 76.1, 62.0, 53.4, 43.8, 35.6. IR (thin film) 1736, 1715, 1694 (C=O), 1309, 1148 (S=O) cm^{-1} ; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_5\text{SNa}$ 448.1195, found 448.1195.

Methyl trans-3-Oxo-1-(phenylsulfonyl)-2,3,5,7a-tetrahydro-1H-pyrrolizine-1-carboxylate (18). Ester **17** (0.602 g, 1.41 mmol) was dissolved in anhydrous benzene (114 mL), which was degassed by bubbling with argon for approximately 5 min. Then Grubbs second-generation catalyst (35 mg, 3 mol %) was added, and the mixture was heated to reflux for 9 h. The solvent was evaporated in vacuo, and the residue was redissolved in EtOAc (30 mL). Saturated NH_4Cl (10 mL)

was added, and the mixture was allowed to stir for 30 min. The mixture was transferred to a separatory funnel, and the organic layer was washed with brine, dried over Na_2SO_4 , and then purified (EtOAc/hex 30–60%), yielding **18** (0.39 g, 86%) as an amorphous solid (50:50 EtOAc/hex, $R_f = 0.16$). ^1H NMR (600 MHz, CDCl_3) δ 8.02–7.93 (m, 2H), 7.74 (td, $J = 7.4, 1.3$ Hz, 1H), 7.61 (t, $J = 7.9$ Hz, 2H), 5.90 (dq, $J = 6.0, 2.1$ Hz, 1H), 5.55 (dq, $J = 6.2, 2.2$ Hz, 1H), 5.38 (tt, $J = 4.3, 1.8$ Hz, 1H), 4.33 (ddt, $J = 15.7, 4.2, 2.1$ Hz, 1H), 3.78–3.67 (m, 2H), 3.62 (s, 3H), 3.00 (d, $J = 15.7$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 172.8, 165.7, 136.9, 134.9, 130.6, 130.3, 129.3, 129.2, 79.0, 70.1, 53.3, 50.7, 39.5; IR (thin film) 1735, 1716, 1687 (C=O), 1311, 1148 (S=O) cm^{-1} ; HRMS (ESI-TOF) m/z [M + Na] $^+$ calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_5\text{SNa}$ 344.0569, found 344.0568.

Methyl trans-3-Oxo-1-(phenylsulfonyl)hexahydro-1H-pyrrolizine-1-carboxylate (19). Alkene **18** (0.25 g, 0.77 mmol) was dissolved in anhydrous MeOH (30 mL), and the reaction mixture was degassed by bubbling with argon for 5 min. Then Pd/C (45 mg) was added and H_2 was bubbled into the reaction flask, and the mixture was allowed to stir for 3 h (monitored by TLC). The Pd/C was filtered off and washed with EtOAc (3×10 mL). The solvent was removed in vacuo, yielding **19** (0.246 g, 99%) as an amorphous solid (50:50 EtOAc/hex, $R_f = 0.1$). ^1H NMR (600 MHz, CDCl_3) δ 7.98–7.90 (m, 2H), 7.79–7.70 (m, 1H), 7.60 (dd, $J = 8.5, 7.3$ Hz, 2H), 4.61 (dd, $J = 9.7, 5.9$ Hz, 1H), 3.72 (s, 3H), 3.62–3.49 (m, 2H), 3.17 (d, $J = 17.1$ Hz, 1H), 3.15–3.05 (m, 1H), 2.07–1.93 (m, 2H), 1.91 (dtd, $J = 12.2, 6.0, 3.9$ Hz, 1H), 1.25 (dq, $J = 12.6, 9.3$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 170.6, 166.0, 134.9, 130.3, 130.2, 129.2, 75.6, 63.9, 53.4, 42.1, 39.4, 28.5, 25.8; IR (thin film) 1734, 1686 (C=O), 1146 (S=O) cm^{-1} ; HRMS (ESI-TOF) m/z [M + Na] $^+$ calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_5\text{SNa}$ 346.0725, found 346.0730.

Methyl 5-Oxo-2,3,5,6-tetrahydro-1H-pyrrolizine-7-carboxylate (20). To sulfone **19** (0.10 g, 0.31 mmol) dissolved in 3 mL of CHCl_3 was added DBU (70 μL , 0.46 mmol), and the reaction mixture was stirred overnight. The mixture was concentrated in vacuo and purified by flash chromatography (70:30 EtOAc/hex, $R_f = 0.40$) to yield **20** as a colorless oil (0.047 g, 84%). ^1H NMR (600 MHz, CDCl_3) δ 3.72 (s, 3H), 3.58 (t, $J = 7.1$ Hz, 2H), 3.52 (m, 2H), 2.93 (m, 2H), 2.40 (p, $J = 7.4$ Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 172.8, 164.0, 161.6, 98.6, 51.0, 41.5, 41.2, 26.6, 25.6. These data are in accordance with the literature.²³

Methyl 3-Oxo-2,3-dihydro-1H-pyrrolizine-1-carboxylate (21). Ester **18** (50 mg, 0.16 mmol) was dissolved in 2 mL of CHCl_3 , and DBU (36 μL , 0.24 mmol) was added. The reaction was monitored by TLC. After 90 min, the solvent evaporated in vacuo, and the crude mixture was purified by flash chromatography (20:80 EtOAc/hex, $R_f = 0.45$), yielding **21** as an oil (12 mg, 41%). ^1H NMR (600 MHz, CDCl_3) δ 7.04 (d, $J = 3.4$ Hz, 1H), 6.47 (t, $J = 3.5$ Hz, 1H), 6.17 (d, $J = 3.1$ Hz, 1H), 4.20 (dd, $J = 9, 3$ Hz, 1H), 3.78 (s, 3H), 3.48 (dd, $J = 19.8$ (gem), 3.6 Hz, 1H), 3.19 (dd, $J = 18.6$ (gem), 9 Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 170.6, 169.6, 136.1, 119.2, 112.2, 106.6, 52.9, 38.1, 38.0. These data are in accordance with the literature.²³

Methyl trans-3-Oxohexahydro-1H-pyrrolizine-1-carboxylate (22). Alkene **20** (47 mg, 0.25 mmol) was dissolved in 2.2 mL of methanol under an atmosphere of argon, and 10% Pd/C (14 mg) was added to the vial. The flask was purged with H_2 gas via a balloon, and the reaction mixture was stirred under an atmosphere of H_2 overnight. The reaction vessel was purged with argon, and then the mixture was filtered through Celite and concentrated to yield **22** as an oil (45 mg, 99%). ^1H NMR (600 MHz, CDCl_3) δ 4.09 (ddd, $J = 9.7, 9.1, 3.8$ Hz, 1H), 3.69 (s, 3H), 3.57 (q, $J = 9.3$ Hz, 1H), 3.38 (td, $J = 8.5, 4.8$ Hz, 1H), 3.03 (t, $J = 11.7$ Hz, 1H), 2.78 (d, $J = 8.9$ Hz, 2H), 2.05 (q, $J = 9.5$ Hz, 1H), 1.95 (m, 1H), 1.82 (m, 1H), 1.24 (m, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 174.0, 172.2, 62.7, 51.9, 41.8, 39.9, 36.0, 27.4, 26.0. These data are in accordance with the literature.^{22,23}

■ ASSOCIATED CONTENT

📄 Supporting Information

Copies of ^1H and ^{13}C NMR spectra and crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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