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

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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 (+)-isoretronecanol.

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 thiouyl 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 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 (+)-isoretronecanol.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 benzenesulfonic acid sodium salt (7) to maleic anhydride to yield a diacid,24 which was cyclized in one step (Scheme 2A). The syntheses of...
Scheme 2. Synthesis of (A) Sulfone Succinic Anhydride 3a and (B) Sulfone Glutaric Anhydrides 3b–d

The stereocchemical configuration of the products was assigned by X-ray crystallography. Lactam 10e has an anti configuration between the aromatic ring and the sulfonyle 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 cyano-substituted anhydrides suggests that the anti-configured carboxylic acids are the kinetic products of the AMRs. 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 transannular 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) 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). 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.

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. 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%),
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 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 (+)-isoretronecanol (Scheme 4). The reaction of imine 16 with 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 (+)-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 (+)-isoretronecanol in one step.22 While this second route is redox-inefficient,20 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.
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.19,21 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 glassware with magnetic stirring. Dry solvent was dispensed from a

**General Procedure A.** The amine and the aldehyde were dissolved in THF (0.10 M), and 3 equiv of triethyl orthofromate 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-phenoxy-(4-(phenylsulfonyl)pyrrolidin-2-one (10a).** General procedure A was used with sulfone anhydride 3a (0.24 g, 0.99 mmol), benzylation (109 µL, 0.99 mmol), and benzylationde (102 µL, 1.00 mmol) to yield 10a (0.32 g, 83%) as a foam (50:50 EtOAc/hex, Rf = 0.59). ¹H NMR (600 MHz, CDCl₃) δ 7.86–7.86 (m, 2H), 7.70–7.66 (m, 1H), 7.51 (d, J = 8.3, 7.2 Hz, 2H), 7.32 (d, J = 1.8 Hz, 1H), 6.27 (d, J = 3.3, 1.9 Hz, 1H), 6.19 (d, J = 3.3, 1.9 Hz, 1H), 5.07 (d, J = 4.1 Hz, 1H), 3.96 (d, J = 8.9, 6.1, 1.4 Hz, 1H), 3.40 (d, J = 13.9, 8.8, 7.1 Hz, 1H), 2.95–2.85 (m, 2H), 2.65 (d, 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). ³¹C NMR (75 MHz, CDCl₃) δ 169.9, 149.4, 143.5, 136.7, 134.5, 129.6, 126.8, 110.6, 109.8, 60.8, 55.2, 42.7, 31.2, 20.1, 11.1; IR (thin film) 1690 (C=O), 1414, 1322 (S=O) cm⁻¹; HRMS (ESI-TOF) m/z [M + Na]⁺ calcd for C₁₇H₁₇NO₄SNa 356.0932, found 356.0952.

**trans-5-(Furan-2-y1)-4-(phenylsulfonyl)-1-propylpyrrolidin-2-one (10d) General procedure A was used with sulfone anhydride 3a (0.24 g, 0.99 mmol), propylamine (82 µL, 0.99 mmol), and furan-2-carboxylic acid (83 µL, 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, Rf = 0.53). ¹H NMR (600 MHz, CDCl₃) δ 7.89 (m, 2H), 7.68 (t, J = 7.4 Hz, 1H), 7.60–7.55 (m, 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 (dd, J = 9.4, 4.1 Hz, 1H), 3.25–3.20 (m, 1H), 2.96 (dd, J = 18.2, 41.6 Hz, 1H), 2.89 (dd, J = 18.2, 41.6 Hz, 1H), 1.99 (t, J = 2.5 Hz, 1H). ³¹C NMR (150 MHz, CDCl₃) δ 169.9, 137.3, 136.6, 134.6, 129.6, 129.0, 128.9, 126.4, 63.4, 63.6, 31.0, 28.4; IR (thin film) 2014 (C=O), 1308 (S=O) cm⁻¹; HRMS (ESI-TOF) m/z [M + Na]⁺ calcd for C₁₇H₁₇NO₄SNa 356.0927, found 356.0813.

**trans-5-(Furan-2-y1)-4-(phenylsulfonyl)pyrrolidin-2-one (10e) General procedure A was used with sulfone anhydride 3a (0.3 g, 1.2 mmol), propylamine (100 µL, 1.2 mmol), and benzylationde (126 µL, 1.2 mmol) to yield 10e (0.36 g, 87%) as a solid (50:50 EtOAc/
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, Rf = 0.35). 1H NMR (600 MHz, CDCl3) δ 7.89 (dt, J = 8.5, 1.8 Hz, 2H), 7.69–7.54 (m, 3H), 7.43–7.24 (m, 3H), 7.13–6.98 (m, 2H), 7.09 (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, 2H).

HRMS (ESI-TOF) m/z [M – H]+ calculated for C18H16NO3S 334.1164, found 342.1155.

4-(trans-5-Oxo-3-(phenylsulfonyl)-1-propylpyrrolidin-2-yl)benzonitrile (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 (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, Rf = 0.27). 1H NMR (600 MHz, CDCl3) δ 7.92–7.86 (d, J = 7.8 Hz, 2H), 7.69 (m, 1H), 7.58 (d, 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 (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), 1.52 (m, 1H), 1.51–1.22 (m, 2H), 0.88–0.79 (t, J = 7.3 Hz, 3H); 13C NMR (150 MHz, CDCl3) δ 170.4, 159.9, 136.9, 134.4, 130.3, 129.6, 128.8, 127.4, 114.7, 64.1, 58.5, 53.3, 42.5, 31.1, 20.1, 11.1; IR (thin film) 1692 (C=O), 1445, 1412 (S=O) cm−1; HRMS (ESI-TOF) m/z [M + Na]+ calculated for C30H27NO5SNa 536.1245, found 536.1252.

trans-1-Benzyl-5-oxo-2,2-phenyl-3-(phenylsulfonyl)-pyrrolidine-3-carboxylate (11a). N-Benzylidenethiophenylamine (0.1 mL, 0.53 mmol) was added to a round-bottom flask containing Na2SO4 (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 stirred at 80 °C for 3 h, then cooled to 0 °C and stirred for an additional 1 h. The Na2SO4 was filtered o

the solvent was removed in vacuo. The residue was stirred in EtOAc, filtered through a Separatory funnel, and washed with HCl (1 M or 10%) and brine. The combined organic layers were dried over Na2SO4 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. The cold solution, TMSCHN2 (0.53 mL, 1.1 mmol, 2 mL 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, Rf = 0.47). 1H NMR (600 MHz, CDCl3) 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), 3.38–3.20 (m, 2H), 3.13 (s, 3H); 13C NMR (150 MHz, CDCl3) δ 170.0, 164.9, 134.9, 134.8, 134.4, 134.1, 131.1, 129.6, 129.5, 129.0, 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 [M + Na]+ calculated for C33H27NO5SNa 572.1195, found 572.1176.
Methyl trans-1-Methyl-5-oxo-2-phenyl-3-(phenylsulfonfonyl)-pyrrolidine-3-carboxylate (11c). N-Benzylideneethylamine (0.1 mL, 0.81 mmol) was added to a round-bottom flask containing Na2SO4 (0.57 g, 4.0 mmol) and THF (8 mL), and then sulfone

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\text{1}^1\text{H NMR (100 MHz, CDCl}_3) \delta 2.3 (\text{H}, s), 2.94 (\text{H}, s), 3.01 (d, \text{J} = 7.0 \text{Hz}, 1\text{H}), 2.61 (\text{ddd}, \text{J} = 13.8, 8.7, 5.2 \text{Hz}, 1\text{H}), 1.65–1.32 (\text{m}, 2\text{H}), 0.84 (t, \text{J} = 7.3 \text{Hz}, 3\text{H}); \text{1}^3\text{C NMR (150 MHz, CDCl}_3) \delta 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 [M + Na]\(^+\) calcd for C26H22NO5Na 484.1406, found 484.1404.
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Di-tert-butyl 2-(Phenylsulfonfonyl)acetate (8). To a 500 mL round-bottom flask were added benzensulfonic 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 EtO (150 mL) and washed with water (2 × 150 mL) and brine (150 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo to yield 8 (6.3 g, 96%) as a clear oil. \text{1}^1\text{H NMR} (300 MHz, CDCl3) \delta 7.90 (m, 2H), 7.68 (m, 1H), 7.55 (m, 2H), 4.03 (s, 2H), 1.33 (s, 9H); \text{1}^3\text{C NMR (75 MHz, CDCl}_3) \delta 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-(Phenylsulfonfonyl)pentanediol (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 × 100 mL). The combined organic layers were dried over Na2SO4 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. \text{1}^1\text{H NMR} (300 MHz, CDCl3) \delta 7.89 (d, J = 7.3 Hz, 2H), 7.68 (m, 1H), 7.57 (d, J = 8.4, 6.9 Hz, 2H), 3.99 (m, 1H), 2.24 (m, 4H), 1.42 (s, 9H), 1.35 (s, 9H); \text{1}^3\text{C NMR (75 MHz, CDCl}_3) \delta 170.9, 164.4, 157.4, 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 [M + Na]\(^+\) calcd for C31H34O6SNa 507.1504, found 507.1502.

Di-tert-butyl 3-Methyl-2-(phenylsulfonfonyl)pentanediol (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 × 100 mL). The combined organic layers were dried over Na2SO4 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: \text{1}^1\text{H NMR} (600 MHz, CDCl3) \delta 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); \text{1}^3\text{C NMR (150 MHz, CDCl}_3) \delta 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 [M + Na]\(^+\) calcd for C25H25O5SNa 421.1661, found 421.1653.

Di-tert-butyl 2-Methyl-4-(phenylsulfonfonyl)pentanediol (3db). 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 × 100 mL). The combined organic layers were dried over Na2SO4 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: \text{1}^1\text{H NMR} (400 MHz, CDCl3) \delta 7.89 (m, 2H), 7.69 (m, 1H), 7.58 (m, 2H), 4.03 (d, J = 11.9, 3.3 Hz, 1H), 2.28 (m, 2H), 1.99 (m, 1H), 1.43 (s, 9H), 3.37 (s, 9H), 1.16 (d, J = 6.6 Hz, 3H); \text{1}^3\text{C NMR (100 MHz, CDCl}_3) \delta 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 [M + Na]\(^+\) calcd for C26H25O5SNa 421.1661, found 421.1662.

3-(Phenylsulfonyl)diidro-2-H-pyran-2,6(3H)-dione (3b). To a dry 250 mL flask were added 3b (4.91 g, 12.7 mmol), CH2Cl2 (50 mL), and trifluoroacetic acid (50 mL). The reaction mixture was stirred for 1 h and then concentrated in vacuo and acetoxytrifluoroacetate with CH2Cl2 (3 × 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 × 10 mL). Filtering the off-white solid with diethyl ether yielded 3b (3.01 g, 93%) as a white solid. Mr 1222.2–1228.8 °C; \text{1}^1\text{H NMR (600 MHz, CDCl}_3) \delta 7.97 (m, 2H), 7.83 (m, 1H), 7.70 (m, 2H), 4.55 (m,
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, CDCl_3) 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, 3H), 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, CDCl_3) δ 169.0, 138.8, 137.0, 136.1, 134.0, 129.5, 129.3, 128.6, 128.5, 127.7, 125.9, 63.9, 57.2, 47.6, 28.3, 16.1; IR (thin film) 3058, 2936, 1642, 1307, 1144 cm⁻¹; HRMS (ESI-TOF) m/z [M + Na⁺] calcd for C_{20}H_{21}NO_{3}SNa 378.1140, found 378.1136.

trans-1-Propyl-6-(phenylsulfonyl)-1-propylpiperidin-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, CDCl_3) δ 7.99 (m, 2H), 7.69 (m, 9H), 7.59 (m, 2H), 7.36 (s, 1H), 3.31 (s, 1H), 1.94 (s, 1H), 1.54 (s, 2H), 0.87 (t, J = 7.4 Hz, 2H), 0.69 (d, J = 7.4 Hz, 2H). 13C NMR (150 MHz, CDCl_3) δ 169.1, 138.9, 137.0, 136.4, 134.1, 129.8, 128.6, 128.4, 128.0, 127.4, 126.6, 63.9, 57.2, 47.6, 28.3, 16.1; IR (thin film) 3055, 2988, 1641, 1307, 1148 cm⁻¹; HRMS (ESI-TOF) m/z [M + Na⁺] calcd for C_{20}H_{21}NO_{3}SNa 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, CDCl_3) δ 7.92 (m, 2H), 7.67 (t, J = 7.5 Hz, 1H), 7.56 (m, 2H), 7.32 (m, 2H), 7.27 (m, 1H), 7.19 (m, 5H), 5.54 (s, 1H), 3.48 (m, 1H), 2.95 (m, 1H), 2.26 (dd, J = 18.1 (gem), 6.2 Hz, 1H), 2.20 (m, 2H). 13C NMR (150 MHz, CDCl_3) δ 169.8, 142.3, 139.7, 137.2, 134.4, 129.6, 129.2, 128.6, 128.4, 128.0, 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 C_{24}H_{24}NO_{3}SNa 414.1140, found 414.1133.

trans-1-(3-Isoamyl)-6-phenyl-5-(phenylsulfonyl)piperidin-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, CDCl_3) δ 7.91 (m, 2H), 7.69 (m, 1H), 7.59 (t, J = 7.8 Hz, 2H), 7.31 (d, 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 (dd, 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, CDCl_3) δ 169.2, 139.7, 137.4, 134.3, 129.6, 129.2, 128.5, 128.0, 127.4, 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 C_{26}H_{25}NO_{3}SNa 430.1290, found 430.1290.

trans-1-(3-Isoamyl)-6-(6-ethyl)-5-(phenylsulfonyl)piperidin-2-one (13h). General procedure C. The residue was purified by flash column chromatography (70:30 EtOAc/hex, R_f = 0.40) to yield 13h as a foam (117 mg, 84%). 1H NMR (300 MHz, CDCl_3) δ 7.92 (m, 2H), 7.74–
trans-6-(4-Methoxyphenyl)-5-(phenylsulfonyl)-1-propylpiperidin-2-one (13j). General procedure B. The residue was purified by flash column chromatography (60:40 EtOAc/hex, Rf = 0.42) to yield 13j as a foam (96 mg, 69%). 1H NMR (600 MHz, CDCl3) 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 (s, 3H), 3.37 (m, 2H), 2.81 (m, 1H), 2.45 (m, 2H), 2.01 (m, 2H), 1.61 (m, 2H), 0.88 (m, J = 7.1 Hz, 3H); 13C NMR (150 MHz, CDCl3) δ 169.2, 159.1, 134.5, 132.9, 129.8, 128.8, 128.6, 126.5, 63.5, 51.8, 47.3, 29.1, 20.7, 20.2, 18.78; IR (thin film) 3059, 2975, 1639, 1463, 1305, 1145 cm⁻¹; HRMS (ESI-TOF) m/z [M + Na]⁺ calcd for C23H23NO5SNa 448.1195, found 448.1195.
	rans-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, Rf = 0.42) to yield 13k as a foam (92 g, 61%). 1H NMR (600 MHz, CDCl3) 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 (m, J = 7.8 Hz, 1H), 5.51 (s, 1H), 3.91 (m, 3H), 3.14 (m, 2H), 2.94 (m, 1H), 2.53 (m, J = 183 (gm), 7.4 Hz, 1H), 2.42 (m, 2H), 2.34 (m, 2H), 2.07 (m, 1H), 1.98 (m, 1H), 1.69 (m, 2H), 1.14 (m, J = 7.5 Hz, 3H); 13C NMR (150 MHz, CDCl3) δ 169.2, 138.3, 133.2, 133.2, 129.6, 128.5, 127.5, 64.7, 57.5, 48.0, 28.1, 20.3, 17.9, 11.3; IR (thin film) 2964, 2920, 1633, 1250, 1144 cm⁻¹; HRMS (ESI-TOF) m/z [M + Na]⁺ calcd for C23H23NO5SNa 448.1195, found 448.1195.

trans-6-(3,5-Dimethoxyphenyl)-5-(phenylsulfonyl)-1-propylpiperidin-2-one (13l). General procedure C. The residue was purified by flash column chromatography (80:20 EtOAc/hex, Rf = 0.35) to yield 13l as a white solid (169 mg, 79%). Mp 143.7–144.3 °C. 1H NMR (600 MHz, CDCl3) 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), 5.80 (2H), 5.31 (d, J = 9.5 Hz, 1H), 4.22 (d, J = 13.4, 8.5, 3.6 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 6H), 2.48 (s, 4H, NCH3 and 1 methylene), 2.69 (s, 1H), 1.84 (m, 1H), 1.27 (d, J = 6.9 Hz, 3H); 13C NMR (150 MHz, CDCl3) δ 173.1, 161.4, 158.8, 137.4, 133.2, 125.8, 124.8, 106.8, 90.6, 61.9, 55.6, 55.2, 51.9, 30.5, 31.8, 29.3, 17.1; IR (thin film) 3006, 2939, 1614, 1286, 1134 cm⁻¹; HRMS (ESI-TOF) m/z [M + H⁺] calcd for C23H22NO5SNa 434.1637, found 434.1649.

**Methyl trans-1-Allyl-5-oxo-3-(phenylsulfonyl)-2-[(E)-styryl]-pyrroline-3-carboxylate (17).** Allylamine (0.29 mL, 3.8 mmol) and trans-cinnamaldehyde (0.53 mL, 4.2 mmol) were added to a round-bottom flask containing THF (38 mL) and Na₂SO₄ (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 Na₂SO₄ was filtered off, and the solvent was evaporated in vacuo. The residue was redisolved in EtOAc and washed with 10% HCl and brine. The organic layer was dried over Na₂SO₄ 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 CHCl₃ (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 redisolved in anhydrous toluene and methanol (60 mL, 30 mL), and TMSCHN₂ (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, Rf = 0.44). 1H NMR (600 MHz, CDCl3) δ 7.98–8.79 (m, 2H), 7.81–7.56 (m, 3H), 7.41–7.24 (m, 3H), 6.49 (d, J = 15.8 Hz, 1H), 5.84–5.72 (m, 2H), 5.34–5.25 (m, 2H), 5.02 (d, J = 8.8 Hz, 1H), 4.40 (d, 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 (gm) Hz, 1H); 13C NMR (150 MHz, CDCl3) δ 169.4, 165.3, 156.7, 153.8, 153.2, 153.0, 131.7, 130.6, 129.3, 128.9, 128.6, 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 [M + Na]⁺ calcd for C31H26NO5SNa 548.1195, found 548.1195. The Journal of Organic Chemistry
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$_2$SO$_4$, and then purified by EtOAc/hexane (30–60%), yielding 18 (0.39 g, 86%) as an amorphous solid (50:50 EtOAc/hexane, R$_f$ = 0.16). $^1$H NMR (600 MHz, CDCl$_3$) δ 8.02–7.93 (m, 2H), 7.74 (d, J = 7.4, 1.3 Hz, 1H), 7.61 (t, J = 7.9 Hz, 2H), 5.90 (d, J = 6.0, 2.1 Hz, 1H), 5.55 (d, J = 6.2, 2.2 Hz, 1H), 5.38 (t, 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); $^1$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]$^+$ calc'd for C$_7$H$_7$NO$_2$SNa 220.4623, found 220.4621.

**Methyl trans-3-Oxo-1-phenylsulfonfyl/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/hexane, R$_f$ = 0.1). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.98–7.90 (m, 2H), 7.79–7.70 (m, 1H, 7H), 6.60 (d, 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, 1H, 2.91 (dd, J = 12.2, 6.0, 3.9 Hz, 1H), 1.25 (d, J = 12.6, 9.3 Hz, 1H); $^1$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, 25.8, IR (thin film) 1734, 1686 (C=O), 1146 (S=O) cm$^{-1}$; HRMS (ESI-TOF) m/z [M + Na]$^+$ calc'd for C$_{15}$H$_{17}$NO$_5$SNa 346.0725, found 346.0769.

**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/hexane, R$_f$ = 0.40) to yield 20 as a colorless oil (0.047 g, 84%). $^1$H 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); $^1$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).** Esters 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/hexane, R$_f$ = 0.45), yielding 21 as an oil (12 mg, 41%). $^1$H 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, 3.1 Hz, 1H), 3.78 (s, 3H), 3.48 (d, J = 19.8 Hz, 1H, 3.19 (dd, J = 18.6 Hz, 9 Hz, 1H); $^1$C NMR (150 MHz, CDCl$_3$) δ 170.6, 169.6, 136.1, 119.2, 112.3, 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%). $^1$H NMR (600 MHz, CDCl$_3$) δ 6.09 (d, J = 9.7, 9.1 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); $^1$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.$^{22,23}$
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