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# Carbon−Carbon Bond-Forming Reactions of α-Thioaryl Carbonyl Compounds for the Synthesis of Complex Heterocyclic Molecules

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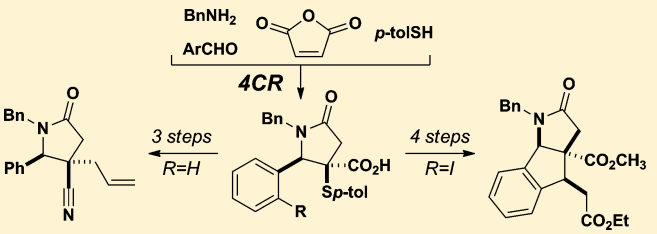
Supporting Information

**ABSTRACT:** Strategies for the formation of carbon−carbon bonds from the α-thioaryl carbonyl products of substituted lactams are described. Although direct functionalization is possible, a two step process of oxidation and magnesium-sulfoxide exchange has proven optimal. The oxidation step results in the formation of two diastereomers that exhibit markedly different levels of stability toward elimination, which is rationalized on the basis of quantum mechanical calculations and X-ray crystallography. Treatment of the sulfoxide with *i*-PrMgCl results in the formation of a magnesium enolate that will undergo an intramolecular Michael addition reaction to form two new stereogenic centers. The relationship between the substitution patterns of the sulfoxide substrate and the efficiency of the magnesium exchange reaction are also described.




## INTRODUCTION

Multicomponent reactions (MCRs) can form the starting point for highly efficient stereoselective syntheses.[1] We recently disclosed a new one-pot, four-component reaction (4CR) that produces highly substituted γ-lactams in high yield and with high diastereoselectivity for the formation of two or three stereogenic centers (eq 1).[2] We subsequently applied this reaction to the synthesis of the γ-lactam natural product heliotropamide, wherein the C−S bond in the 4CR product was cleaved to a C−H bond under conditions that initiate radical formation from the α-thioaryl ester.[3] In order to further exploit this functional unit within the 4CR products, we have investigated radical and anionic conditions for the formation of C−C bonds to generate quaternary stereogenic centers (Scheme 1A). Herein, we provide a detailed account of these studies as they were applied to the preparation of a model system possessing the connectivity of the core of nakadomarin A (Scheme 1B). The techniques described could also prove useful for the preparation of core structures featured in several related alkaloids[4] with quaternary stereogenic centers at the 3-position of a pyrrolidine ring (Scheme 1B).

## RESULTS AND DISCUSSION

Carbon−sulfur bonds can be cleaved under a variety of conditions that result in carbon−carbon bond formation. C−S bond breakage under reducing conditions to produce an anion is relatively straightforward, depending on the stability of the anion that is formed. In the case of enolate formation, recent examples of reducing agents for this process include lithium-di-*tert*-butyl biphenyl (LiDBB)[5] and $SmI_2$.[6] We also set out to explore the possibility of using the sulfide group of 4CR products as a radical precursor. Although bromides, iodides, and selenides undergo intermolecular carbon−carbon bond-forming reactions readily,[7] the reactions of sulfides are often limited to cyclizations[8] and reductions.[9] At the outset of our studies, there were only isolated examples of *inter*molecular trapping of radicals derived from sulfides to yield new C−C bonds.[10] These two potential reaction manifolds are complementary in their chemistry and produce similar substitution patterns, i.e., quaternary stereogenic centers adjacent to a carbonyl. The use of sulfides as precursors to carbocations that are trapped with nucleophilic alkenes is also possible with substrates that, unlike **6**, have electron-donating groups attached to the reacting carbon.[11] The ability of thioethers to serve as precursors to cations, anions, and radicals places this class of functional group among the most versatile functionalities in organic synthesis.

**Carbon−Carbon Bond-Formation via Radical Intermediates.** Radicals generated from 4CR products were initially investigated in intermolecular reactions with alkenes. The propensity of these substrates to form radicals was well-established by our previous studies that employed tris(trimethylsilyl)silane or tributyltin hydride to quench radicals formed under thermal conditions with AIBN as an initiator.[12] We first attempted to intercept the radical with *t*-butylacrylate and observed only reduction product **17**, suggesting that the radical intermediate was bypassing the alkene (eq 1). Lactam **17** is formed with high diastereoselectivity in accord with our previous results, which we attribute to delivery of the hydrogen atom from the face of the radical opposite to the neighboring phenyl ring.[2] The slow rate of alkene addition can be

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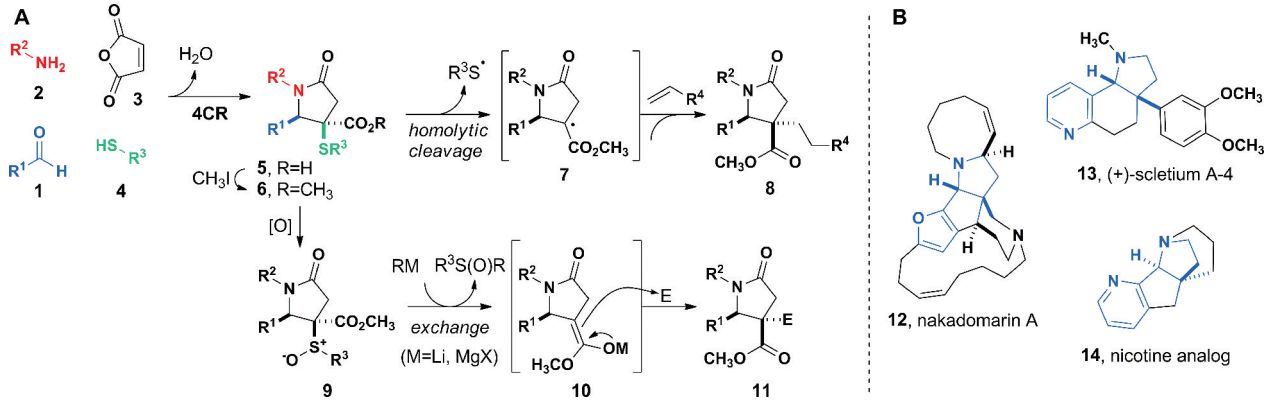
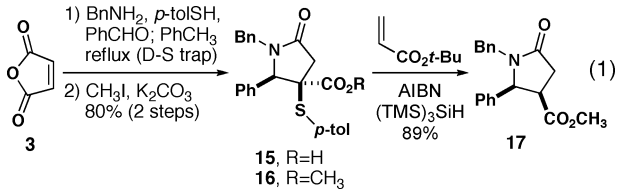
**Scheme 1. (A) Thioaryl-Substituted Gamma Lactams from a 4CR as Substrates for C−C Bond-Forming Reactions and (B) Targets with Arylpyrrolidine Substructures Accessible by a 4CR-Alkylation Sequence**



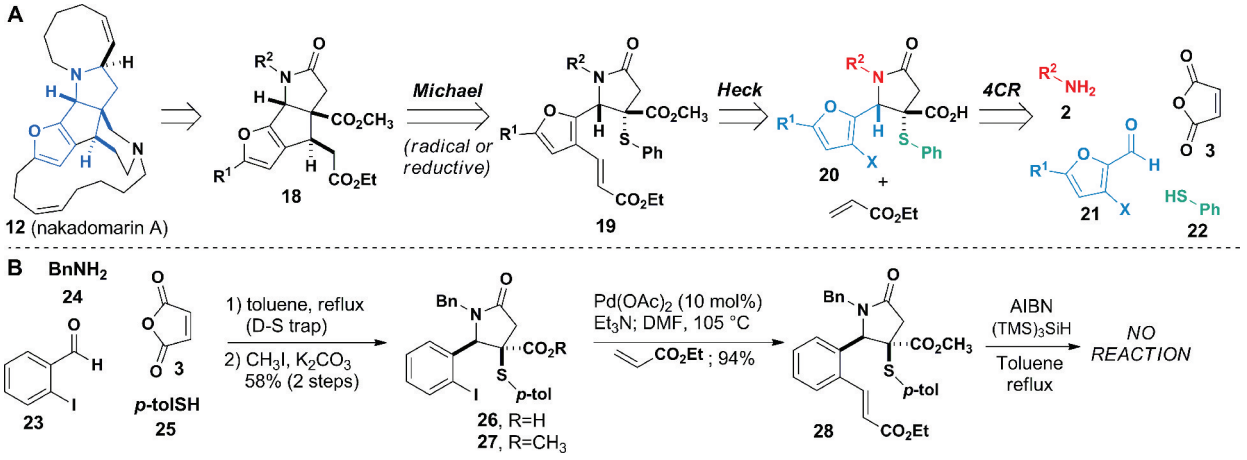




rationalized by a prohibitively high LUMO−SOMO energy gap between the electron-withdrawing group substituents on both the alkene and the radical. A related example with a secondary radical and *t*-butyl acrylate produces modest yield of the addition product.[10c] In that case, the radical is not stabilized by a carbonyl group and is expected to exhibit a more nucleophilic character.

We elected to study the possibility of cyclization in the context of an intramolecular radical-based Michael-type reaction that would provide an entry into the stereoselective synthesis of polycyclic products, e.g., the core of nakadomarin A. This hexacyclic marine alkaloid was first isolated in 1997[4c] and has subsequently been the subject of intense synthetic effort, culminating in several total syntheses.[13] Retrosynthetic analysis reveals that the tetracyclic core could emerge from a Michael reaction of susbstrate **19**, which is available in three steps by 4CR, methylation, and Heck reaction (Scheme 2A). For this study, we opted for a model system in which the furan ring is replaced with a phenyl ring. 2-Iodobenzaldehyde is commercially available and can be prepared on large scale using IBX to oxidize the much more cost-effective 2-iodobenzyl alcohol. The 4CR followed by esterification proceeds smoothly to produce lactam **27** in 58% yield. Heck reaction with ethyl acrylate produced substrate **28** in high yield (Scheme 2B). Use of several different potential catalysts revealed that $Pd(OAc)_2$ provided the most consistently high conversions.[14] Unfortunately, when **28** was treated with AIBN and $(TMS)_3SiH$ (or $Bu_3SnH$, not shown) and heated to reflux, only starting material was recovered, demonstrating that making the reaction intramolecular was not sufficient to favor propagation of the radical process. This result was surprising, given the similarity to a related "radical Michael" reaction reported by Posner,[8a] albeit on a less sterically demanding substrate. The increased steric demand of the neighboring ortho-substituted phenyl ring could be hindering the approach of the propagating reagent, i.e., the radicals formed from either $Bu_3SnH$ or $(TMS)_3SiH$.

Intermolecular reactions with a nucleophilic alkene were also attempted. Literature examples of secondary and tertiary radicals formed from phenyl sulfides suggested that this strategy could be applied to the 4CR lactams.[10] When ester **16** was treated with AIBN and allyltributyltin under thermal conditions, the starting material was recovered unchanged (Scheme 3A). We next explored the analogous nitrile **30**, which is easily formed in two steps from acid **15** (Scheme 3B).

**Scheme 2. (A) Retrosynthetic Analysis of Nakadomarin A and (B) Synthesis of Radical Michael Reaction Precursor and Attempted Cyclization**





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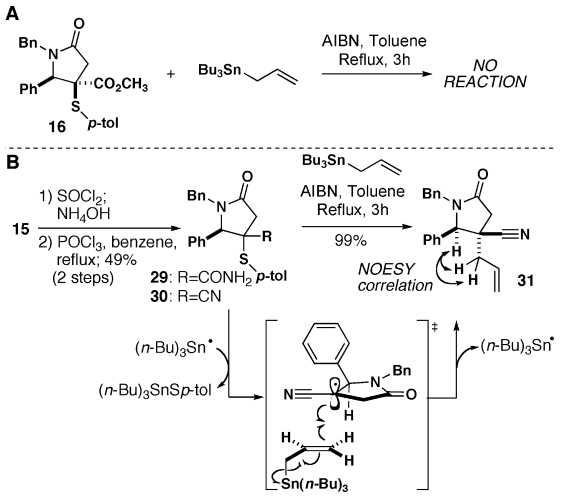
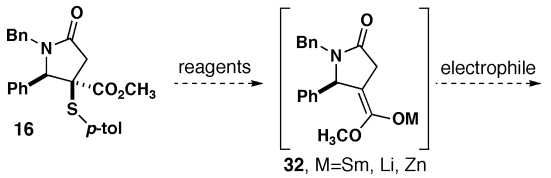
**Scheme 3. (A) Attempted Formation of a Radical from Ester 16 and Trapping with Allyltributyltin and (B) Synthesis, Radical Formation, and Trapping of Nitrile 30**




Conversion of acid **15** to amide **29** resulted in epimerization to a nearly 50:50 mixture of epimers, which was converted to a similar mixture of nitrile diastereomers. When nitrile **30** was treated with AIBN and allyltributylstannane, allylated product **31** was formed as a single diastereomer (>95:5 selectivity). The relative anti-configuration between the allyl group and the phenyl ring was established by NOESY correlation. This reaction demonstrates that steric effects play an important role in propagation of the radical process, i.e., in the accessibility of the tributyltin radical to the C−S bond, which is easier in the case of the nitrile when compared to the more sterically demanding ester. Although this reaction successfully installed the quaternary center needed for the core of nakadomarin A, the steps necessary to form the cyclopentene ring detracted from the viability of this route. Current studies are exploring related cyclization reactions to form larger rings.

**Reductive Enolate Formation.** We initially explored the ability of reducing agents to cleave the C−S bonds of 4CR lactam products to form enolates that could react with electrophiles. The most widely used protocol for the reductive formation of organolithium reagents from thioethers was originally reported by Cohen[15,16] and Screttas,[17] each of whom has also reported subsequent refinements.[18] Following the examples of Gleason, whose protocol is specifically for enolate generation,[5a] we treated lactam **16** with LiDBB and observed decomposition of the starting material after attempted trapping with electrophiles or protonation (Table 1). Close inspection of the proline-derived substrates used by Gleason revealed that most were devoid of multiple-bonded functionality that might be more easily reduced than the desired C−S bond.[5,19] We next attempted $SmI_2$ and observed no reaction.[6] The authors of ref 6 note that related reactions of γ-lactams were unsuccessful, suggesting that the additional inductive stabilization in a succinimide enolate intermediate facilitates the reduction by $SmI_2$ in that case. We also observed no reaction between **16** and $ZnBr_2$ or *p*-TsOH in the presence of $PPh_3$, as was used for the reduction of oxindoles resulting from the Gassman synthesis.[20] In the case of 3-thiomethyloxindoles, the resultant anion is quasi-aromatic and, thus, more stable by many orders of magnitude than enolate **32**. Other conditions for which isolated examples have been documented were not attempted.[21]

**Table 1. Attempted Reductive Enolate Generation Using Various Reported Reducing Conditions**

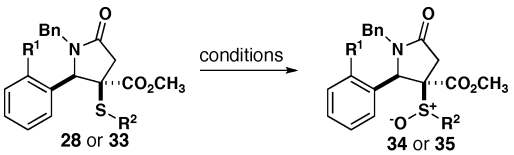



| entry | reagent(s) | solvent | temp (°C) | result |
|---|---|---|---|---|
| 1 | $SmI_2$ HMPA, *i*-PrCHO | THF | −78 | no reaction |
| 2 | LiDBB/MeI | THF | −78 | decomp |
| 3 | LiDBB/allylBr | THF | −78 | decomp |
| 4 | LiCl/$PPh_3$ | THF | 23 | no reaction |
| 5 | $Zn(OTf)_2$/$PPh_3$ | DCM | 23 | no reaction |

In contrast to sulfides, aryl sulfoxides undergo rapid exchange reactions at low temperatures with alkyl Grignard reagents to produce an aryl-alkyl sulfoxide and a new Grignard reagent. This reaction has been used in both capacities, i.e., for the unsymmetrical synthesis of sulfoxides[22] and for the preparation of complex Grignard reagents.[23,24] In addition, Hoffmann showed that the exchange reaction could be used for the synthesis of configurationally defined organomagnesium halides.[25] Among Satoh's reports of preparing magnesium carbenoids was one example of using magnesium-sulfoxide exchange for the preparation of α-halogenated enolates.[26] Although this sequence would require two steps for our system, the ease with which sulfides can be oxidized to sulfoxides in the presence of a variety of functional groups made this route attractive.

Initial attempts at oxidation of thioaryl-substituted lactams proceeded in highly variable yields (Table 2). Initial use of

**Table 2. Entries 1−5 Converted 28 to 34, Whereas Entries 5−13 Converted 33 to 35**




**28**, **34**: $R^1$ = $CHCHCO_2Et$, $R^2$ = *p*-tol;
**33**, **35**: $R^1$ = H, $R^2$ = *p*-$Ch_3OC_6H_4$ (PMP)

| entry | oxidant | solvent | temp (°C) | yield (%) |
|---|---|---|---|---|
| 1 | 1 equiv *m*-CPBA | DCM | −42 to 23 | 24 |
| 2 | 1 equiv *m*-CPBA | DCM | −78 to −10 | 33 |
| 3 | 1 equiv Oxone, $Al_2O_3$ | DCM | reflux | NR |
| 4 | 1 equiv $NaIO_4$ | $CH_3OH$ | 0 to 23 | 15 |
| 5 | 1 equiv IBX, TBAB | DCM | 23 | NR |
| 6 | 1 equiv $H_2O_2$ | PhOH/$H_2O$ | 23 | 31 |
| 7 | 0.5 equiv *m*-CPBA | DCM | −78 | 14 |
| 8 | 1 equiv $MnO_2$ | $CHCl_3$ | 23 | NR |
| 9 | 1 equiv *m*-CPBA, $PhCO_2H$ | DCM | −78 | NR |
| 10 | 1 equiv $MnO_2$, 3 equiv HCl | $CH_3OH$ | 23 | NR |
| 11 | 10 equiv $MnO_2$, 20 equiv HCl | $CH_3OH$ | 23 | NR |
| 11 | 1 equiv *m*-CPBA | THF | 0 | 45 |
| 12 | 1 equiv *m*-CPBA | ether | 0 | 43 |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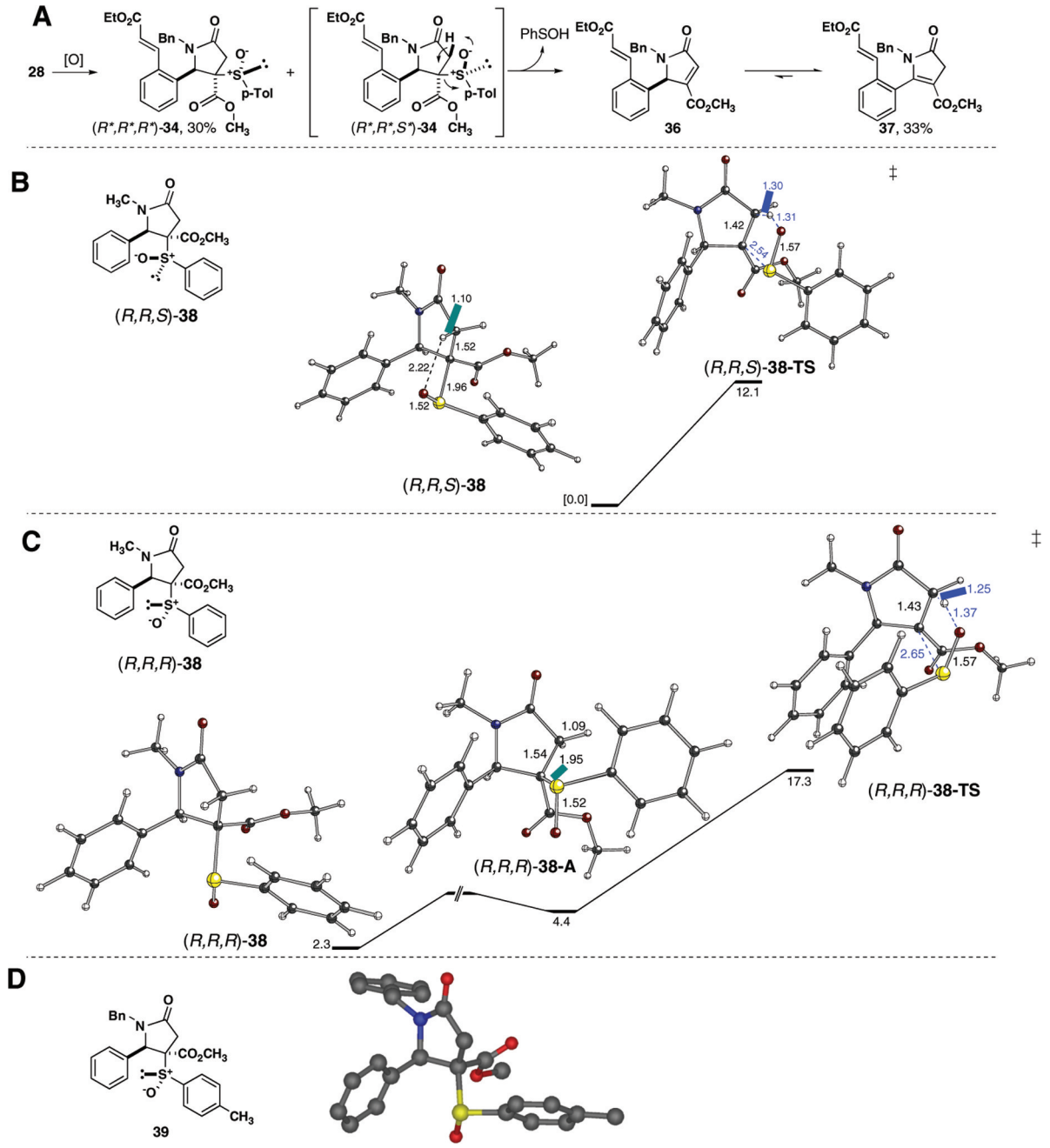


**Figure 1.** (A) Proposed mechanism for the formation of **37** from (*R**,*R**,*R**)-**34**. (B) Computed structures and relative energies for the elimination of (*R*,*R*,*S*)-**38**. (C) Computed structures and relative energies for the elimination of (*R*,*R*,*R*)-**38**. Energies (kcal/mol) shown for A and B are all relative to the energy of the lowest energy conformer of (*R*,*R*,*S*)-**38** and are Gibbs free energies calculated at 25 °C. Selected bond lengths are shown in Å. (D) Crystal structure of sulfoxide **39**.

*m*-CPBA (Table 2, entry 12) was encouraging, producing the desired product in 45% yield. A scan of oxidants known to produce sulfoxides from sulfides in the presence of alkenes was evaluated.[27] Yields comparable to that of *m*-CPBA could be obtained with $H_2O_2$/phenol (Table 2, entry 6). Extensive variation of the oxidant revealed that the yield could never be increased above 50%. In addition, we noted that **34** or **35** was formed as a single diastereomer in all cases, despite related precedent indicating that the diastereoselectivity of this process was often modest.

The inescapably low yield paired with the inexplicably high diastereoselectivity prompted us to more carefully scrutinize the byproduct of this reaction. Upon careful purification of the reaction mixture from *m*-CPBA oxidation, unsaturated lactam **37** was isolated in 33% yield (Figure 1A). This product would seem to emerge from elimination of the sulfoxide or perhaps sulfone arising from overoxidation. We favored the former explanation from the outset, as it would be adequately explained by preferential elimination of one diastereomer over the other, thus explaining both the low yield of sulfoxide *and* the high apparent diastereoselectivity of this process. Furthermore, sulfones are far less prone to elimination when compared to sulfoxides.[28] In fact, alkyl sulfides have often served as synthetic equivalents for alkenes by virtue of the efficient oxidation/elimination sequence that can reveal the double bond.[29]


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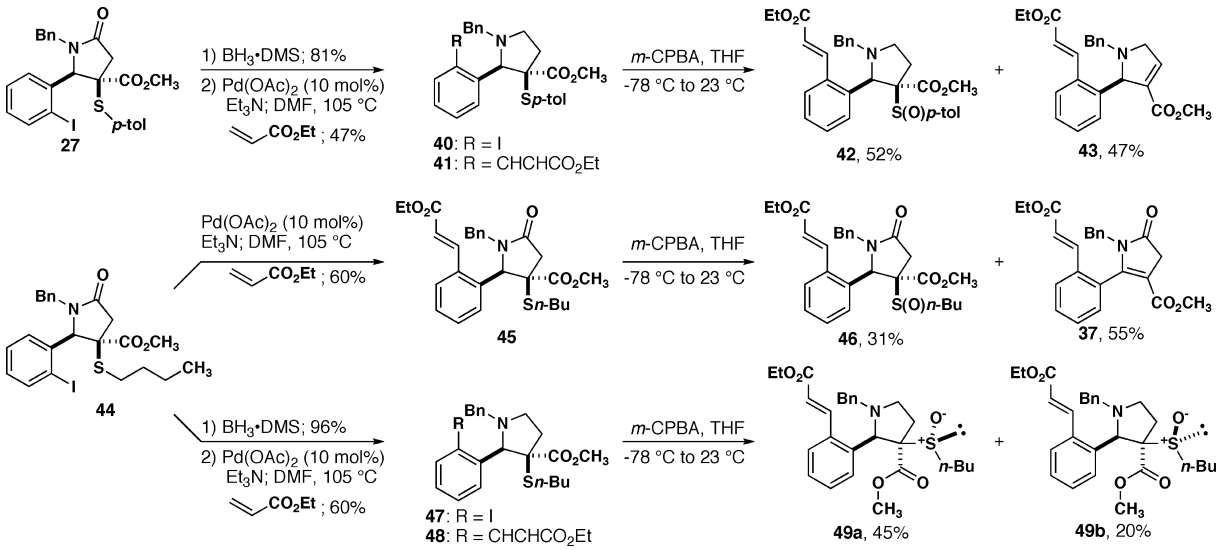
**Scheme 4. Synthesis of Sulfoxide Substrates to Avoid Elimination**

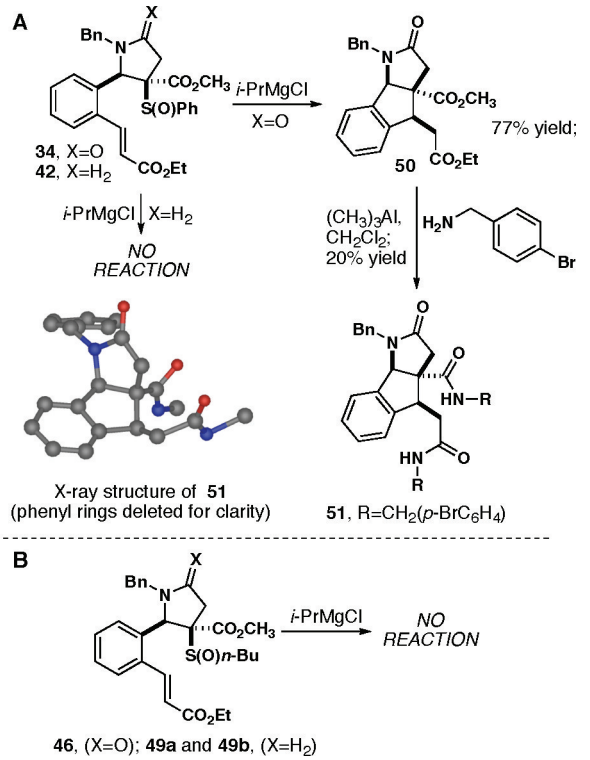



Our hypothesis regarding preferential elimination of one isomer of sulfoxide is supported by quantum chemical calculations and X-ray crystallography. Calculation of the structures of the two possible isomers of sulfoxide (B3LYP/6-31G+(d,p))[30] indicates that they differ in energy by several kcal/mol (Figure 1). Nonetheless, both could likely be formed under the reaction conditions. The preferred isomer, (*R**,*R**,*R**)-**38**, positions the sulfoxide oxygen distal to the $\alpha$-proton of the ester, while isomer (*R**,*R**,*S**)-**38** positions the sulfoxide oxygen directly over the $\alpha$-proton, preorganizing the molecule for elimination. Significant differences in the barriers to elimination are predicted, with elimination preferred for (*R**,*R**,*S**)-**38**. We were able to obtain a single crystal of **39**, the structure of which has the same relative configuration of isomer (*R**,*R**,*R**)-**38**. The structural similarity of **39** and (*R**,*R**,*R**)-**38** is consistent with the hypothesis that this isomer is less likely to undergo elimination on the basis of conformational preferences conferred by the sulfoxide stereogenic center. Although an enantioselective catalyst for sulfoxide formation might conceivably provide a solution to this problem, it would not be easy to test on a racemic mixture of lactams and may be investigated on an enantiomerically pure substrate when it becomes available. In addition, most chiral catalysts to date do not function well on hindered sulfoxides, e.g., those with one tertiary substituent.[31]

Two strategies for avoiding elimination were evaluated. First, we prepared a substrate with the carbonyl group of the lactam core removed to reduce the acidity of the proton that is implicated in the sulfoxide elimination. Lactam **27** reacted smoothly with $BH_3$·DMS to produce substituted pyrrolidine **40**, which was carried on through the Heck reaction in modest yield (Scheme 4). Subsequent oxidation proceeded smoothly without affecting the tertiary amine. Unfortunately, elimination product **43** was still observed along with a single diastereomer of **42**, suggesting the course of the reaction was similar to that of the lactam. Interestingly, the product of pyrrolidine elimination was pyrroline **43**, in which there was no isomerization of the alkene into conjugation with the nitrogen. We next hypothesized that an aliphatic, rather than aromatic, sulfoxide would be less prone to elimination. Heck product **45** was prepared in analogy to **28** and was shown to give similar results in the oxidation. Finally, combining these two modifications in the form of *n*-butyl substituted pyrrolidines **49a** and **49b** effectively avoided elimination. A mixture of diastereomers of the two sulfoxides was obtained in 65% combined yield.

Sulfoxides **34**, **42**, **46**, **49a**, and **49b** were examined in magnesium exchange reactions. **34** reacted smoothly with *i*-PrMgCl to produce tricyclic product **50** in high yield and with high diastereoselectivity (Scheme 5). The relative configuration

**Scheme 5. (A) Cyclization of Lactam Sulfoxide 34 to 50 by Magnesium-Sulfoxide Exchange/Michael Addition and X-ray Crystal Structure of Amide Derivative 51 and (B) Attempted Cyclizations of *n*-Butyl Sulfoxides 46, 49a, and 49b**




of the product was established through X-ray crystallography after conversion to the bis-*p*-bromobenzyl amide **51** using the method of Weinreb.[32] The relative stereochemistry for the ring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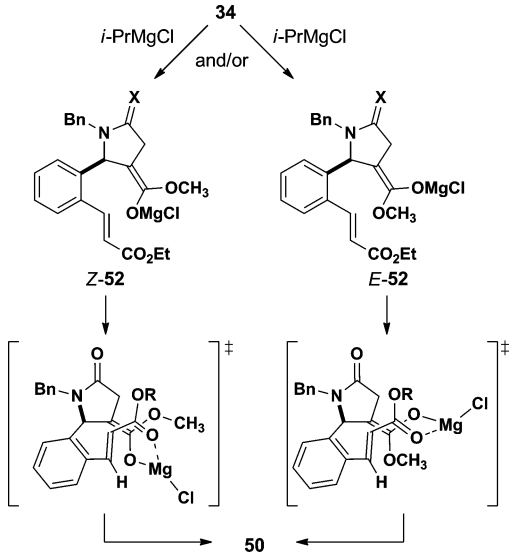
junction was cis, as expected; however, the stereogenic center arising from facial selectivity on the Michael acceptor was syn to the ring juncture, counter to our expectation and opposite in configuration to the analogous position on nakadomarin A. The analogous pyrrolidine sulfoxide **42** did not undergo efficient cyclization. The origin of this lack of reactivity is unclear, potentially arising from a result of conformation preferences, complexation of the basic nitrogen to the Grignard reagent, reduced enolate stability of the pyrrolidine relative to the lactam, or some other effect. Although aromatic sulfoxides are almost universally employed in the exchange reactions that have been performed to date, we investigated *n*-butyl sulfoxide-substituted substrates because of their superior stability when compared to the aromatic sulfoxides. Neither lactam **46** nor pyrrolidines **49a** and **49b** underwent cyclization.

The diastereoselectivity of the intramolecular Michael addition reaction probably originates from chelate organization of the magnesium enolate and the unsaturated ester carbonyl. Although we have no insight as to the geometry of the presumed enolate intermediate, or even whether or not there is a preponderance of one isomer, we propose that the syn diastereoselection could originate from either *Z*- or *E*-enolate (*Z*-**52**, *E*-**52**, Scheme 6). Previous mechanistic proposals by

**Scheme 6. Proposed Transition State Model to Explain Stereochemical Outcome of the Michael Addition from the Two Possible Enolate Isomers Indicated *Z*-52 and *E*-52**




Heathcock[33] and recent computational evidence from Evans[34] suggest a closed transition state for the Michael addition, in which the acceptor carbonyl is activated by the enolate metal. Application of these models to either *E*- or *Z*-**52** explains the observed formation of **50**.

Tricyclic product **50** is also capable of undergoing a subsequent Dieckmann cyclization. In one run of the Michael addition of sulfoxide **34**, the reaction was quenched with methanol and left to stand at room temperature for several hours. A reduced yield of **50** was obtained along with 33% of a new product. NMR spectroscopy and mass spectrometry supported the assignment of keto amide **53**, and the structure was eventually confirmed by X-ray crystallography (Figure 2). Although a large body of literature surrounds the chemistry of fused triquinanes and related triquinacenes, i.e., the all-carbon

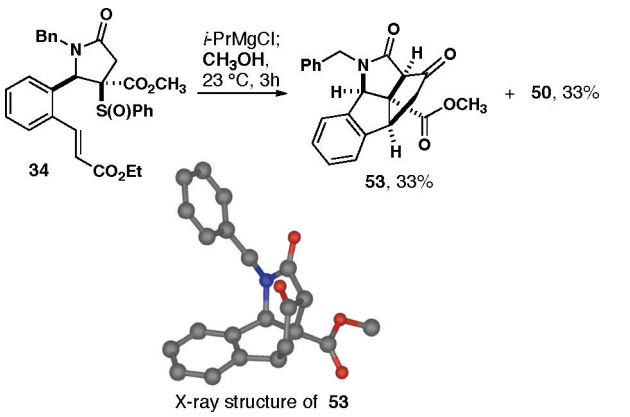



**Figure 2.** Michael reaction/Dieckmann cyclization of **34** to aza-triquinane **53** and X-ray crystal structure of **53**.

variant of the core of **53**, similar structures with nitrogen in the periphery are far less common.[35] Furthermore, there is only one case of a triquinane structure featuring an amide in direct analogy to **53**.[36]

The changes in sulfoxide structure that conferred stability suggested that modulation of the carbonyl group might allow stable arylsulfoxides to be accessed. An amide would be expected to be less electron-withdrawing than an ester and less likely to enable elimination. On the other hand, a nitrile would be comparably electron withdrawing and less sterically demanding than the ester. Starting with carboxylic acid **26**, the corresponding pyrrolidine amide and nitrile could be accessed in one or two steps, respectively. The Heck reaction was executed without incident in each case. Oxidation of the pyrrolidine amide resulted in exclusive recovery of the elimination product (Scheme 7), suggesting that the more easily eliminated diastereomer is formed preferentially or that both diastereomers undergo facile elimination due to conformational influences. Conversion of acid **26** into amide **59** and then into nitrile **60** was achieved under standard conditions. Unfortunately, oxidation to sulfoxide **61** was accompanied by a significant amount of elimination. Furthermore, treatment of the sulfoxide with *i*-PrMgCl did not result in any cyclization. Although this result was disappointing, there are few previous examples of nitrile-stabilized Grignard reagents formed from sulfoxide exchange, and in one case, the substrate benefits from additional stabilization from cyclopropyl substitution.[37]

## CONCLUSION

Several approaches to the construction of C−C bonds from thioethers that result in quaternary stereogenic centers have been explored. Although radical C−S bond cleavage for reduction is facile, the analogous process for C−C bond formation is more limited, requiring a nitrile substituent and more forcing conditions. The latter reaction exhibits high diastereoselection with the same sense of induction as was observed for reduction. Anionic methods were also explored, and the most productive emerged from magnesium-sulfoxide exchange. This method proved to be limited to ester-containing substrates and proceeded in high yield and with high diastereoselectivity. The lone drawback of this approach is a poor yield in the sulfoxidation step, which was traced to differential propensities for elimination of the diastereomeric sulfoxides that are formed. Future studies will explore the development of substrates for asymmetric oxidation that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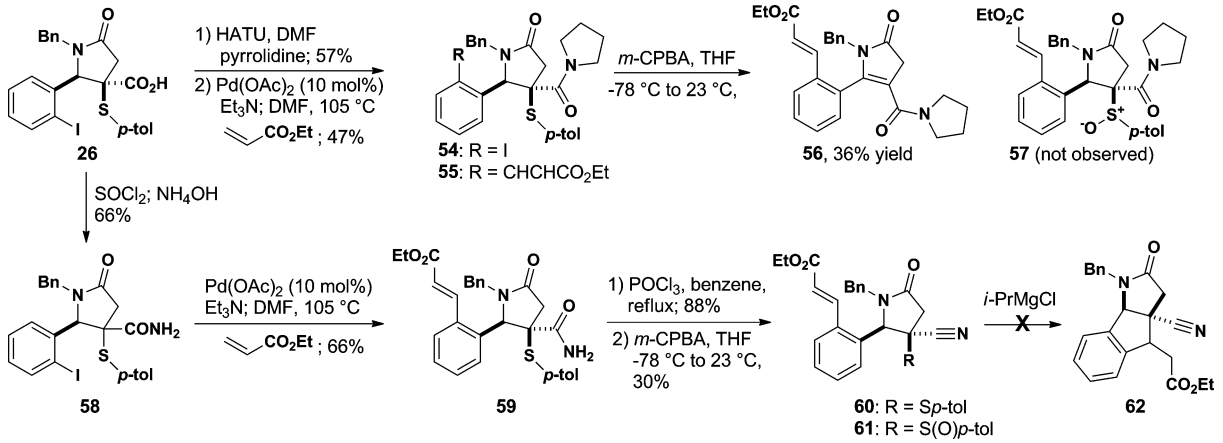
**Scheme 7. Attempted Preparation of Amide Sulfoxide 54 and Preparation and Attempted Cyclization of Nitrile Sulfoxide 61**




eschew the elimination problem. We anticipate that the strategies described herein will pave the way for the assembly of complex 5-arylpyrrolidine motifs as intermediates in the synthesis of alkaloid natural products and other biologically important organic molecules.

## EXPERIMENTAL SECTION

**4CR Ester 27.** To a solution of *para*-thiocresol (3.42 mL, 3.42 mmol, 1 M) in toluene were added melaic anhydride (0.335 g, 3.42 mmol), *o*-iodobenzaldehyde (0.793 g, 3.42 mmol), and benzylamine (0.37 mL, 3.42 mmol). The mixture was stirred for 24 h at reflux under a Dean−Stark trap and then cooled to 23 °C. Toluene was removed in vacuo to yield a yellow crude mixture. This was dissolved in acetone (5 mL) and $K_2CO_3$ (0.945 g, 6.83 mmol), and iodomethane (1.02 mL 13.668 mmol) was added. After stirring at 23 °C for 24 h, the resulting mixture was partitioned between water (25 mL) and DCM (15 mL). The layers were separated, and the aqueous layer was extracted with 2 × 20 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 3 g of a brown oil. The oil was purified by flash chromatography (15:85 EtOAc/hexanes) to yield the product as a yellow oil (1.109 g, 58%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.95 (d, $J$ = 7.3, 1H), 7.43 (t, $J$ = 7.6, 1H), 7.28 (dd, $J$ = 5.8, 7.7, 3H), 7.12 (dd, $J$ = 4.5, 12.0, 2H), 7.06−7.00 (m, 6H), 5.39 (s, 1H), 5.08 (d, $J$ = 14.5, 1H), 3.55 (s, 3H), 3.41 (d, $J$ = 14.0, 1H), 3.18 (d, $J$ = 17.0, 1H), 2.82 (dd, $J$ = 1.0, 17.0, 1H), 2.31 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 172.0, 171.6, 140.7, 140.4, 137.0, 136.5, 135.4, 130.9, 130.0, 129.0, 128.9, 128.8, 128.8, 128.3, 128.2, 128.1, 126.3, 105.0, 102.3, 70.5, 58.8, 53.2, 45.2, 41.0, 21.5; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{26}H_{24}INO_3S$ $(M + H)^+$ 558.0595, found 558.0595; IR (thin film) 1730, 1696 cm$^{-1}$; TLC (20% EtOAc/hexanes) $R_f$ = 0.15.

**Ester 28.** To a flame-dried flask were added palladium acetate (0.045 g, 0.199 mmol) and iodide **27** (1.11 g, 1.99 mmol) as a solution in DMF (10 mL). Next were added ethyl acrylate (0.84 mL, 7.96 mmol) and triethylamine (0.55 mL, 3.98 mmol). The mixture was heated to 105 °C under argon and a reflux condenser for 24 h and then cooled to 23 °C. The resulting mixture was partitioned between DCM (30 mL) and water (40 mL). The layers were separated, and the water layer was extracted with 2 × 20 mL DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 1.5 g of a bright red oil. The oil was purified by flash chromatography (20:80 EtOAc/hexanes) to yield the product as a red oil (0.990 g, 94%): $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.99 (d, $J$ = 15.7, 1H), 7.67−7.62 (m, 1H), 7.46 (pd, $J$ = 1.6, 7.3, 2H), 7.27−7.20 (m, 4H), 7.04−6.99 (m, 4H), 6.96−6.92 (m, 2H), 6.32 (t, $J$ = 12.6, 1H), 5.34 (s, 1H), 5.12 (d, $J$ = 6.6, 1H), 4.28−4.23 (m, 2H), 3.58 (s, 3H), 3.42 (d, $J$ = 14.6, 1H), 3.30 (d, $J$ = 14.6 1H), 2.89 (dd, $J$ = 1.1, 17.1, 1H), 2.29 (s, 3H), 1.35−1.32 (m, 3H); $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 172.0, 171.6, 166.5, 141.7, 140.4, 136.3, 136.2, 135.4, 133.4, 130.2, 130.0, 129.5, 128.9, 128.4, 128.0, 127.6, 127.3, 126.1, 121.7, 62.6, 60.7, 58.6, 53.2, 45.0, 41.3, 21.5, 14.6; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{31}H_{31}NO_5S$ $(M + H)^+$ 530.1996, found 530.1995; IR (thin film) 1731, 1699 cm$^{-1}$; TLC (20% EtOAc/hexanes) $R_f$ = 0.20.

**4CR Lactam Amide 29.** To a solution of *para*-thiocresol (30 mL, 30 mmol, 1 M) in toluene were added melaic anhydride (2.9418 g, 30 mmol), benzaldehyde (3.06 mL, 30 mmol), and benzylamine (3.28 mL, 30 mmol). The mixture was stirred for 24 h at reflux under a Dean−Stark trap and then cooled to 23 °C. Toluene was removed in vacuo to yield a yellow crude mixture. This was dissolved in benzene (40 mL) and cooled to 0 °C, at which time $SOCl_2$ (4.36 mL 60 mmol) was added and the mixture was heated to reflux for 12 h. After cooling to 23 °C, the solvent was removed in vacuo, and the residue was dissolved in DCM (40 mL). This was cooled to 0 °C, and $NH_4OH$ (12 mL, 300 mmol) was added slowly via syringe. After the addition was complete, the reaction was allowed to warm to 23 °C and stirred for 5 h. Finally, water was added, and the mixture was partitioned between water (25 mL) and DCM (40 mL). The layers were separated, and the aqueous layer was extracted with 2 × 50 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 15.3985 g of a brown oil. The oil was purified by flash chromatography (35:65 EtOAc/hexanes) to yield the product as a mixture of diastereomers that formed a yellow oil (8.5043 g, 68%). This product epimerizes slowly at room temperature and spectral data is provided for the major diastereomer: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.45 (s, 4H), 7.41−7.27 (m, 9H), 7.25−7.19 (m, 6H), 7.19−7.05 (m, 9H), 6.95 (s, 3H), 6.74 (s, 1H), 6.60 (s, 1H), 5.68 (s, 1H), 5.33 (s, 1H), 5.23 (dd, $J$ = 6.6, 14.8, 3H), 4.68 (s, 1H), 4.24 (s, 1H), 3.68 (d, $J$ = 18.0, 1H), 3.60 (d, $J$ = 14.6, 1H), 3.50−3.38 (m, 3H), 2.74 (d, $J$ = 17.6, 1H), 2.57 (d, $J$ = 18.0, 1H), 2.34 (s, 3H), 2.29 (d, $J$ = 12.1, 3H); $^{13}$C NMR (101 MHz, CDCl3) $\delta$ 173.8, 173.2, 172.3, 170.6, 140.3, 139.6, 135.5, 135.4, 135.0, 134.5, 134.1, 133.2, 130.5, 130.4, 129.7, 129.6, 129.4, 129.1, 129.0, 128.9, 128.9, 128.8, 128.7, 128.6, 128.0, 127.9, 126.3, 105.0, 69.4, 68.9, 60.8, 59.6, 44.9, 44.8, 40.5, 38.1, 34.9, 21.4, 21.4; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{25}H_{24}N_2O_2S$ $(M + H)^+$ 417.1631, found 417.1628; IR (thin film) 1700, 1671, 1650 cm$^{-1}$.

**4CR Lactam Nitrile 30.** Amide **29** (0.289 g, 0.694 mmol) was dissolved in benzene (5 mL) and cooled to 0 °C. To this was added $POCl_3$ (0.32 mL, 3.470 mmol), and the mixture was heated to reflux under a reflux condenser for 12 h, turning a dark red color. After being cooled to 0 °C, the reaction was quenched and neutralized carefully using water saturated with $K_2CO_3$. At pH = 7, the mixture was partitioned between water and DCM (15 mL). The layers were separated, and the aqueous layer was extracted with 2 × 20 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 0.231 g of an inseparable mixture of diastereomers that was purified by flash chromatography (EtOAc/hexanes) to yield a clear oil (0.1999 g, 72%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.50−7.44 (m, 4H), 7.44−7.40 (m, 3H), 7.39−7.34 (m, 5H), 7.32−7.27 (m, 4H), 7.26−7.21 (m, 5H), 7.16 (d, $J$ = 7.9, 2H), 7.12−7.04 (m, 6H), 6.81 (s, 1H), 5.33 (d, $J$ = 14.5, 1H), 5.25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(d, $J$ = 14.7, 1H), 4.84 (s, 1H), 4.34 (s, 1H), 3.64 (d, $J$ = 14.7, 1H), 3.47 (d, $J$ = 14.5, 1H), 3.23 (dd, $J$ = 0.9, 17.5, 1H), 3.05 (dd, $J$ = 0.9, 17.2, 1H), 2.92−2.86 (m, 1H), 2.81−2.75 (m, 1H), 2.37 (s, 2H), 2.35 (s, 3H); $^{13}$C NMR (101 MHz, CDCl3) $\delta$ 170.2, 169.3, 141.7, 141.4, 137.1, 136.9, 135.2, 134.8, 134.2, 132.1, 130.6, 130.6, 130.3, 129.9, 129.7, 129.4, 129.2, 129.1, 129.1, 128. 6, 128.4, 128.4, 125.2, 125.0, 120.6, 118.1, 68.3, 66.8, 47.8, 47.3, 45.3, 45.0, 43.4, 40.7, 21.6; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{25}H_{22}N_2OS$ $(M + H)^+$ 399.1526, found 399.1521; IR (thin film) 2233, 1701 cm$^{-1}$.

**Allylated Lactam Nitrile 31.** Nitrile **30** was dissolved in dry toluene (10 mL), to which was added allyl tributyl tin and heated to 80 °C. AIBN was then added, and the reaction was heated to reflux for 3 h. After 3 h, more allyl tributyl tin and AIBN were added, and the reaction remained at reflux for 3 additional hours. The reaction was then cooled to 23 °C, quenched with saturated sodium thiosulfate solution, and partitioned between water and DCM. The layers were separated, and the aqueous layer was extracted with 2 × 15 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 0.1134 g as a yellow oil. The oil was purified by flash chromatography (hexanes to flush out the excess tin, followed by 20:80 EtOAc/hexanes) to yield the product as a clear oil (0.0737 g, 99%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.49−7.40 (m, 3H), 7.36−7.28 (m, 3H), 7.21−7.14 (m, 2H), 7.13−7.05 (m, 2H), 5.82−5.65 (m, 1H), 5.22 (d, $J$ = 14.4, 1H), 5.17 (d, $J$ = 10.2, 1H), 4.78 (dd, $J$ = 17.0, 1.2, 1H), 4.26 (s, 1H), 3.47 (d, $J$ = 14.3, 1H), 3.10 (dd, $J$ = 17.0, 0.8, 1H), 2.61 (d, $J$ = 17.0, 1H), 2.40 (dd, $J$ = 13.7, 6.3, 1H), 2.28 (dd, $J$ = 13.8, 8.4, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 170.4, 135.5, 134.9, 130.7, 129.8, 129.6, 129.1, 129.0, 128.4, 122.3, 119.7, 66.1, 45.1, 42.5, 42.4, 40.45, 28.1, 27.1, 17.8, 13.8; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{21}H_{20}N_2O$ $(M + H)^+$ 317.1649, found 317.1650; IR (thin film) 2245, 1702, 1362 cm$^{-1}$; TLC (20:80 EtOAc/hexanes) $R_f$ = 0.18.

**4CR Ester 33.** *para*-Methoxy-thiophenol (0.31 mL, 3.00 mmol), melaic anhydride (0.294 g, 3.00 mmol), benzaldehyde (0.31 mL, 3.00 mmol), and benzylamine (0.33 mL, 3.00 mmol) were mixed in toluene (10 mL). The mixture was stirred for 16 h at reflux under a Dean−Stark trap and then cooled to 23 °C. Toluene was removed in vacuo to yield a yellow crude mixture. This was dissolved in acetone (15 mL) and $K_2CO_3$ (0.830 g, 6.00 mmol), and iodomethane (0.89 mL 12.00 mmol) was added. After stirring at 23 °C for 24 h, the resulting mixture was partitioned between water (25 mL) and DCM (20 mL). The layers were separated, and the aqueous layer was extracted with 2 × 25 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 1.254 g as a yellow oil. The oil was purified by flash chromatography (20:80 EtOAc/hexanes) to yield the product as a yellow oil (0.342 g, 25%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.48−7.41 (m, 3H), 7.30−7.22 (m, 6H), 7.11−7.06 (m, 2H), 7.03−6.96 (m, 2H), 6.77−6.72 (m, 2H), 5.17 (d, $J$ = 17.4, 1H), 4.92 (s, $J$ = 7.0, 1H), 3.75 (s, 3H), 3.53 (s, 3H), 3.48 (d, $J$ = 17.4, 1H), 3.19 (d, $J$ = 15.7, 1H), 2.85 (s, $J$ = 15.5, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 172.1, 171.9, 161.2, 138.1, 135.9, 134.2, 129.4, 128.8, 128.3, 127.9, 120.4, 114.7, 67.0, 59.0, 59.0, 55.5, 53.1, 44.8, 40.9; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{26}H_{25}NO_4S$ $(M + H)^+$ 448.1577, found 448.1576; IR (thin film) 1731, 1698 cm$^{-1}$; TLC (50% EtOAc/hexanes) $R_f$ = 0.68.

**Sulfoxide 34.** To a cooled (−78 °C) solution of **28** (0.990 g, 1.869 mmol) in 10 mL of THF was added *m*-CPBA (0.419 g, 1.869 mmol, 77%). The mixture was stirred for 3 h and then allowed to warm to 23 °C, and a saturated solution of $Na_2S_2O_3$ in water (5 mL) was added. The resulting mixture was partitioned between water (10 mL) and DCM (15 mL). The layers were separated, and the aqueous layer was extracted with 2 × 20 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 0.1059 g of clear oil. The oil was purified by flash chromatography (20:80 EtOAc/hexanes to 30:70 EtOAc/hexanes) to yield the product as white solid (0.4990 g, 49%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.04 (d, $J$ = 15.8, 1H), 7.65−7.58 (m, 1H), 7.51−7.42 (m, 2H), 7.30−7.20 (m, 9H), 6.93 (dd, $J$ = 2.9, 6.5, 2H), 6.28 (d, $J$ = 15.8, 1H), 5.50 (s, 1H), 5.03 (d, $J$ = 14.4, 1H), 4.32−4.18 (m, 2H), 3.68 (s, 3H), 3.42 (d, $J$ = 14.5, 1H), 2.83 (s, 2H), 2.38 (s, 3H), 1.33 (t, $J$ = 7.1, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 169.9, 167.1, 166.4, 143.4, 142.3, 137.4, 136.6, 134.9, 132.3, 130.0, 129.9, 129.0, 128.6, 128.2, 128.2, 127.3, 125.4, 122.7, 72.4, 61.3, 60.6, 45.2, 34.7, 21.8, 14.6; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{31}H_{31}NO_6S$ $(M + H)^+$ 546.1945, found 546.1947; IR (thin film) 1728, 1704, 1685 cm$^{-1}$; TLC (50% EtOAc/hexanes) $R_f$ = 0.21.

**4CR Sulfoxide 35.** To a cooled (−78 °C) solution of **32** (0.2483 g, 0.555 mmol) in 10 mL of THF was added *m*-CPBA (0.1243 g, 0.555 mmol, 77%). The mixture was stirred for 3 h and then allowed to warm to 25 °C, and a saturated solution of $Na_2S_2O_3$ in water (10 mL) was added. The resulting mixture was partitioned between water and 15 mL of DCM. The layers were separated, and the aqueous layer was extracted with 2 × 15 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 0.2438 g of a purple oil. This was purified by flash chromatography (20:80 EtOAc/hexanes) to yield the product as a clear oil (0.1234 g, 48% yield): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.52−7.45 (m, 3H), 7.42−7.35 (m, 1H), 7.31−7.30 (m, 1H), 7.29−7.25 (m, 4H), 7.04−6.99 (m, 2H), 6.96−6.91 (m, 2H), 5.28 (s, 1H), 5.11 (d, $J$ = 14.7, 1H), 3.82 (s, 3H), 3.58 (s, 3H), 3.53 (d, $J$ = 14.7, 1H), 2.74 (dd, $J$ = 16.4, 0.8, 1H), 2.68 (d, $J$ = 16.4, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 170.5, 166.9, 163.1, 135.4, 133.0, 130.2, 129.8, 129.4, 128.9, 128.4, 128.1, 127.1, 114.7, 77.6, 77.3, 77.0, 73.0, 65.6, 55.7, 53.4, 45.0, 34.3; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{26}H_{25}NO_5S$ $(M + H)^+$ 464.1526, found 464.1524; IR (thin film) 1724, 1698, 1592 cm$^{-1}$; TLC (50% EtOAc/hexanes) $R_f$ = 0.19.

**2-Pyrrolin-5-one Ester 37.** Isolated at the same time as **34** to yield the product as a purple oil (0.1236 g, 55% yield): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.58 (d, $J$ = 7.5, 1H), 7.41 (t, $J$ = 7.7, 1H), 7.31 (t, $J$ = 7.5, 1H), 7.23 (d, $J$ = 15.9, 1H), 7.10−7.01 (m, 3H), 6.98 (d, $J$ = 7.6, 1H), 6.69 (d, $J$ = 6.0, 2H), 6.14 (d, $J$ = 15.9, 1H), 4.42 (d, $J$ = 15.2, 1H), 4.36 (d, $J$ = 15.2, 1H), 4.17 (q, $J$ = 7.1, 2H), 3.63 (d, $J$ = 24.3, 1H), 3.55 (d, $J$ = 24.4, 1H), 3.47 (s, 3H), 1.27 (t, $J$ = 7.1, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 175.9, 166.4, 163.3, 153.2, 140.3, 136.5, 133.7, 130.6, 130.3, 129.8, 129.7, 128.5, 128.3, 127.8, 127.8, 126.3, 120.5, 106.9, 77.7, 77.4, 77.1, 60.7, 51.4, 44.5, 37.2, 14.5; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{24}H_{23}NO_5$ $(M + H)^+$ 406.1649, found 406.1649; IR (thin film) 1701, 1636, 1594 cm$^{-1}$; TLC (50% EtOAc/hexanes) $R_f$ = 0.40.

**4CR Ester Sulfoxide 39.** To a cooled (−78 °C) solution of **16** (1.3823 g, 3.2 mmol) in 7 mL of THF was added *m*-CPBA (0.7179 g, 3.2 mmol, 77%). The mixture was stirred for 3 h and then allowed to warm to 25 °C, and a saturated solution of $Na_2S_2O_3$ in water (10 mL) was added. The resulting mixture was partitioned between water and 15 mL of DCM. The layers were separated, and the aqueous layer was extracted with 2 × 15 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 1.5126 g of a yellow oil. The oil was purified by flash chromatography (10:90 to 20:80 EtOAc/hexanes) to yield the product as a yellow oil (0.401 g, 29%). This was recrystallized from DCM to yield a crystalline solid: mp 92−95 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.48 (m, 3H), 7.43−7.33 (m, 1H), 7.31−7.22 (m, 8H), 7.01 (m, 2H), 5.27 (s, 1H), 5.12 (d, $J$ = 14.7, 1H), 3.56 (s, 3H), 3.53 (d, $J$ = 14.9, 1H), 2.78 (d, $J$ = 16.4, 1H), 2.70 (d, $J$ = 16.3, 1H), 2.39 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 170.4, 166.8, 143.2, 136.3, 135.4, 133.0, 129.9, 129.9, 129.4, 128.9, 128.4, 128.1, 125.2, 72.8, 65.6, 53.4, 45.0, 34.2, 21.8; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{26}H_{25}NO_4S$ $(M + H)^+$ 448.1572, found 448.1576; IR (thin film) 1723, 1699, 1686, 698 cm$^{-1}$; TLC (50% EtOAc/hexanes) $R_f$ = 0.33.

**Pyrrolidine Ester 40.** Acid **27** (2.1526 g, 3.86 mmol) was dissolved in THF (25 mL) and cooled to 0 °C. To this was added $BH_3$·DMS (3.8616 mL, 7.72 mmol) as a 2 M solution in THF. The solution was immediately heated to reflux and stirred for 2.5 h and then cooled to 0 °C and quenched with MeOH. The mixture was then partitioned between water (50 mL) and DCM (50 mL). The layers were separated, and the aqueous layer was extracted with 2 × 50 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 2.1135 g of a white oil. The oil was purified by flash chromatography (5:95 EtOAc/hexanes) to yield the product as a clear oil (1.6973 g, 81%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.96 (dd, $J$ = 1.7, 7.9, 1H), 7.86 (dd, $J$ = 1.2, 7.9, 1H), 7.44 (m, 1H), 7.24 (m, 5H), 7.15 (m, 2H), 7.02 (m, 3H), 4.57 (s, 1H), 3.71 (m, 4H),


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3.28 (d, $J$ = 13.2, 1H), 3.13 (m, 1H), 2.62−2.56 (m, 1H), 2.42 (m, 1H), 2.30−2.24 (m, 4H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 173.4, 140.4, 139.7, 139.3, 139.1, 136.0, 132.6, 130.2, 129.7, 128.9, 128.8, 128.4, 128.3, 127.7, 127.2, 102.8, 77.7, 64.3, 57.9, 53.0, 51.5, 37.2, 21.5; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{26}H_{26}INO_2S$ $(M + H)^+$ 544.0802, found 544.0791; IR (thin film) 1705, 698 $cm^{-1}$; TLC (20% EtOAc/hexanes) $R_f$ = 0.65.

**Pyrrolidine Ester 41.** To a flame-dried flask were added palladium acetate (0.075 g, 0.333 mmol) and iodide **40** (1.70 g, 3.12 mmol) as a solution in DMF (20 mL). Next were added ethyl acrylate (1.41 mL, 13.33 mmol) and triethylamine (0.93 mL, 6.66 mmol). The mixture was heated to 100 °C under argon and a reflux condenser for 24 h and then cooled to 23 °C. The resulting mixture was partitioned between DCM (30 mL) and water (40 mL). The layers were separated, and the water layer was extracted with 2 × 30 mL DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 1.62 g of a bright red oil. The oil was purified by flash chromatography (10:90 EtOAc/hexanes) to yield the product as a red oil (0.7572 g, 47%) containing approximately 5% of the minor diastereomer carried from the 4CR to make the lactam: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.40 (d, $J$ = 15.7, 1H), 8.16 (d, $J$ = 7.8, 1H), 7.60 (d, $J$ = 7.4, 1H), 7.51 (t, $J$ = 7.5, 1H), 7.38 (d, $J$ = 6.8, 1H), 7.29−7.18 (m, 5H), 7.06 (s, 2H), 7.00 (d, $J$ = 8.3, 2H), 6.37 (d, $J$ = 15.7, 1H), 4.58 (s, 1H), 4.30 (q, $J$ = 7.1, 2H), 3.75−3.66 (m, 4H), 3.20 (d, $J$ = 13.0, 1H), 3.08 (d, $J$ = 6.2, 1H), 2.63 (d, $J$ = 8.2, 1H), 2.32−2.21 (m, 5H), 1.37 (t, $J$ = 7.1, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 173.4, 167.3, 143.2, 139.5, 138.8, 138.1, 136.5, 136.1, 135.6, 131.4, 129.6, 129.4, 128.9, 128.4, 128.4, 128.1, 127.2, 126.5, 120.1, 69.3, 64.6, 60.7, 58.1, 52.8, 51.6, 37.9, 21.4, 14.6; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{31}H_{33}NO_4S$ $(M + H)^+$ 516.2203, found 516.2192; IR (thin film) 1713, 1637, 1599 $cm^{-1}$; TLC (10% EtOAc/hexanes) $R_f$ = 0.40.

**Pyrrolidine Sulfoxide 42.** To a cooled (−78 °C) solution of **41** (0.734 g, 1.42 mmol) in 10 mL of THF was added $m$-CPBA (0.328 g, 1.42 mmol, 75%). The mixture was stirred for 3 h and then allowed to warm to 23 °C, and a saturated solution of $Na_2S_2O_3$ in water (10 mL) was added. The resulting mixture was partitioned between water and 15 mL of DCM. The layers were separated, and the aqueous layer was extracted with 2 × 15 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 0.823 g of a yellow oil. This was purified by flash chromatography (15:85 EtOAc/hexanes) to yield the product as a clear oil (0.3932 g, 52% yield) containing approximately 5% of the minor diastereomer carried from the 4CR to make the lactam: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.55 (d, $J$ = 15.8, 1H), 8.19 (d, $J$ = 7.8, 1H), 7.64 (d, $J$ = 7.6, 1H), 7.53 (s, 1H), 7.39 (d, $J$ = 7.4, 1H), 7.35 (d, $J$ = 8.2, 2H), 7.26 (m, 2H), 7.21 (m, 5H), 6.40 (d, $J$ = 15.7, 1H), 4.76 (s, 1H), 4.29 (q, $J$ = 7.1, 2H), 3.86 (s, 3H), 3.73 (d, $J$ = 13.0, 1H), 3.22 (d, $J$ = 13.0, 1H), 3.09−3.02 (m, 1H), 2.36 (s, 3H), 2.30−2.22 (m, 1H), 2.02 (s, 2H), 1.36 (t, $J$ = 7.1, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 168.7, 167.4, 143.7, 142.5, 138.4, 137.7, 136.9, 136.6, 130.6, 129.7, 129.5, 128.9, 128.8, 128.5, 127.3, 127.1, 126.2, 120.4, 77.7, 67.7, 60.6, 57.5, 53.1, 50.9, 31.5, 21.7, 14.7; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{31}H_{33}NO_5S$ $(M + H)^+$ 532.2152, found 532.2140; IR (thin film) 1707, 1635, 1596 $cm^{-1}$; TLC (20% EtOAc/hexanes) $R_f$ = 0.34.

**Pyrroline Ester 43.** Isolated at the same time as **42** as a purple oil (0.2645 g, 47%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.38 (d, $J$ = 15.8, 1H), 7.48 (dd, $J$ = 3.5, 7.6, 2H), 7.34 (d, $J$ = 7.6, 1H), 7.27−7.12 (m, 7H), 6.90 (d, $J$ = 2.1, 1H), 6.26 (d, $J$ = 15.8, 1H), 5.16 (s, 1H), 4.24 (t, $J$ = 7.1, 2H), 4.01−3.91 (m, 1H), 3.58 (d, $J$ = 5.3, 1H), 3.54 (s, 3H), 3.52−3.43 (m, 1H), 1.33 (t, $J$ = 7.1, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 167.3, 163.7, 143.4, 140.9, 140.3, 139.0, 137.0, 134.9, 130.3, 129.7, 128.6, 128.4, 127.9, 127.2, 127.0, 119.6, 70.3, 60.6, 58.5, 57.1, 51.6, 14.6; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{24}H_{25}NO_4$ $(M + H)^+$ 392.1857, found 392.1852; IR (thin film) 1704, 1633, 1600 $cm^{-1}$; TLC (20% EtOAc/hexanes) $R_f$ = 0.49.

**Butyl Ester 44.** Melaic anhydride (1.177 g, 12.00 mmol) was dissolved in benzene (100 mL), and triethylamine (1 drop) was added. This was heated to 60 °C, and butane thiol (1.29 mL, 12.00 mmol) was added dropwise over 5 min. This was stirred for 30 min and cooled to room temperature, and the benzene and triethylamine were removed via rotary evaporation, producing a thiol-substituted anhydride. Concurrently, in a separate flask, $o$-iodobenzaldehyde (2.026 g, 8.720 mmol) was dissolved in DCM (20 mL), after which were added benzyl amine (0.95 mL, 8.720 mmol) and anhydrous $MgSO_4$ (2.89 g, 24 mmol). This was stirred for 14 h, after which the $MgSO_4$ was removed by filtration, and the DCM removed by rotary evaporation, producing an imine. After being dissolved in toluene, the thiol-substituted anhydride was added to the imine, and the mixture was heated to reflux for 6 h. Toluene was removed in vacuo to yield a yellow/brown crude mixture. This was dissolved in acetone (20 mL) and $K_2CO_3$ (2.4131 g, 17.45 mmol), and iodomethane (2.60 mL 34.92 mmol) was added. After stirring at 20 °C for 24 h, the resulting mixture was partitioned between water (25 mL) and DCM (20 mL). The layers were separated, and the aqueous layer was extracted with 2 × 20 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 5.1352 g of a brown oil. This was purified by flash chromatography (10:90 EtOAc/hexanes) to yield the product as a light yellow oil (2.6781 g, 59% yield): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.77 (d, $J$ = 7.9, 1H), 7.28 (t, $J$ = 7.5, 1H), 7.17 (t, $J$ = 7.6, 3H), 7.02 (d, $J$ = 7.8, 1H), 7.00−6.88 (m, 3H), 5.35 (s, 1H), 4.97 (d, $J$ = 14.6, 1H), 3.56 (d, $J$ = 3.8, 3H), 3.42 (d, $J$ = 16.9, 1H), 3.29 (d, $J$ = 14.6, 1H), 2.76 (d, $J$ = 16.9, 1H), 2.25 (t, $J$ = 7.3, 2H), 1.21−1.06 (m, 4H), 0.68 (t, $J$ = 7.2, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 171.8, 171.6, 140.4, 137.5, 135.5, 130.8, 128.8, 128.7, 128.7, 128.4, 128.0, 101.6, 70.6, 70.5, 55.4, 53.3, 45.2, 41.3, 31.0, 30.7, 22.1, 13.8; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{23}H_{26}INO_3S$ $(M + H)^+$ 524.0751, found 524.0743; IR (thin film) 1724, 1697 $cm^{-1}$; TLC (20% EtOAc/hexanes) $R_f$ = 0.18.

**Butyl Ester 45.** To a flame-dried flask were added palladium acetate (0.057 g, 0.252 mmol) and iodide **43** (1.32 g, 2.52 mmol) as a solution in DMF (10 mL). Next were added ethyl acrylate (1.07 mL, 10.08 mmol) and triethylamine (0.70 mL, 5.04 mmol). The mixture was heated to 105 °C under argon and a reflux condenser for 24 h and then cooled to 23 °C. The resulting mixture was partitioned between DCM (25 mL) and water (25 mL). The layers were separated and the water layer was extracted with 2 × 25 mL DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 1.6 g of a red oil. This was purified by flash chromatography (15:85 EtOAc/hexanes) to yield the product as a red oil (0.751 g, 60% yield): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.86 (d, $J$ = 15.7, 1H), 7.57−7.53 (m, 1H), 7.43−7.34 (m, 2H), 7.25−7.15 (m, 4H), 6.92 (dd, $J$ = 2.8, 6.6, 2H), 6.24 (d, $J$ = 15.7, 1H), 5.32 (s, 1H), 5.10 (d, $J$ = 14.6, 1H), 4.20 (dt, $J$ = 6.7, 13.5, 2H), 3.65 (s, 3H), 3.55 (d, $J$ = 17.0, 1H), 3.35 (d, $J$ = 14.0, 1H), 2.81 (d, $J$ = 17.0, 1H), 2.19 (qd, $J$ = 5.8, 11.4, 2H), 1.28 (t, $J$ = 7.1, 3H), 1.26−1.06 (m, 4H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 172.1, 171.9, 166.4, 141.5, 135.8, 135.4, 133.7, 130.1, 129.4, 128.9, 128.4, 128.1, 127.5, 121.7, 62.3, 62.3, 60.6, 55.2, 53.4, 45.1, 41.6, 30.9, 30.6, 22.1, 14.6, 13.7; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{28}H_{33}NO_5S$ $(M + H)^+$ 496.2152, found 496.2147; IR (thin film) 1717, 1688, 1628 $cm^{-1}$; TLC (20:80 EtOAc/hexanes) $R_f$ = 0.19.

**Sulfoxide 46.** To a cooled (−78 °C) solution of **45** (0.751 g, 1.52 mmol) in 10 mL of THF was added $m$-CPBA (0.340 g, 1.52 mmol, 77%). The mixture was stirred for 3 h and then allowed to warm to 23 °C, and a saturated solution of $Na_2S_2O_3$ in water (10 mL) was added. The resulting mixture was partitioned between water and 15 mL of DCM. The layers were separated, and the aqueous layer was extracted with 2 × 15 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 0.823 g of a purple oil. This was purified by flash chromatography (20:80 EtOAc/hexanes to 40:60 EtOAc/hexanes) to yield the product as a yellow oil (0.2409 g, 31%). Elimination product **37** was also isolated (0.4086 g, 67%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.93 (d, $J$ = 15.8, 1H), 7.60 (d, $J$ = 8.9, 1H), 7.50−7.39 (m, 2H), 7.31−7.23 (m, 3H), 7.15−7.08 (m, 1H), 6.97 (s, 2H), 6.25 (d, $J$ = 15.8, 1H), 5.57 (s, 1H), 5.07 (d, $J$ = 14.4, 1H), 4.28−4.12 (m, 2H), 3.80 (s, 3H), 3.39 (d, $J$ = 14.4, 1H), 3.18 (d, $J$ = 16.7, 1H), 2.54 (d, $J$ = 17.0, 2H), 2.33 (dd, $J$ = 9.9, 19.4, 1H), 1.62 (s, 1H), 1.53 (s, 1H), 1.30 (m, 5H), 0.85 (t, $J$ = 7.3, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 169.5, 167.8, 166.3, 142.0, 137.0, 135.0, 132.1, 130.0, 129.9, 129.0, 128.6, 128.2, 128.2, 127.2, 122.5, 69.7, 61.3, 60.5, 54.1, 49.1, 45.2, 34.2, 25.5, 22.2, 14.6, 13.8; HRMS (FTMS + p ESI)

$m/z$ calcd for $C_{28}H_{33}NO_6S$ $(M + H)^+$ 512.2102, found 512.2100; IR (thin film) 1707, 1634, 1596 $cm^{-1}$; TLC (20% EtOAc/hexanes) $R_f$ = 0.20.

**Pyrrolidine Ester 47.** Iodide **44** (0.2096 g, 0.400 mmol) was dissolved in THF (15 mL) and cooled to 0 °C. To this was added $BH_3$·DMS (0.40 mL, 0.801 mmol) as a 2 M solution in THF. The solution was immediately heated to reflux and stirred for 2 h and then cooled to 0 °C and quenched with MeOH (2 mL). The mixture was then partitioned between water (20 mL) and DCM (10 mL). The layers were separated, and the aqueous layer was extracted 2 × 30 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 0.2040 g of a yellow oil. This was purified by flash chromatography (5:95 EtOAc/hexanes) to yield the product as a light yellow oil (0.196 g, 96% yield): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.90 (d, $J$ = 7.9, 1H), 7.82 (d, $J$ = 7.9, 1H), 7.40 (t, $J$ = 7.5, 1H), 7.27−7.20 (m, 5H), 7.00 (t, $J$ = 6.7, 1H), 4.55 (s, 1H), 3.82 (s, 3H), 3.69 (d, $J$ = 13.2, 1H), 3.23 (d, $J$ = 13.2, 1H), 3.08 (d, $J$ = 8.4, 1H), 2.80 (dd, $J$ = 6.2, 12.7, 1H), 2.45−2.37 (m, 1H), 2.32−2.25 (m, 1H), 2.18−2.09 (m, 1H), 1.99 (d, $J$ = 11.5, 1H), 1.29−1.16 (m, 4H), 0.78 (t, $J$ = 7.1, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 173.9, 140.9, 139.4, 139.1, 132.9, 129.9, 128.8, 128.8, 128.4, 127.6, 127.1, 102.5, 77.8, 61.3, 57.8, 51.6, 38.2, 31.1, 30.5, 22.3, 13.8; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{23}H_{28}INO_2S$ $(M + H)^+$ 510.0958, found 510.0952; IR (thin film) 1720 $cm^{-1}$; TLC (20% EtOAc/hexanes) $R_f$ = 0.68.

**Pyrrolidine Ester 48.** To a flame-dried flask were added palladium acetate (0.042 g, 0.188 mmol) and iodide **47** (0.959 g, 1.88 mmol) as a solution in DMF (15 mL). Next were added ethyl acrylate (0.80 mL, 7.54 mmol) and triethylamine (0.52 mL, 3.77 mmol). The mixture was heated to 105 °C under argon and a reflux condenser for 24 h and then cooled to 23 °C. The resulting mixture was partitioned between DCM (30 mL) and a saturated LiCl solution in water (40 mL). The layers were separated, and the aqueous layer was extracted with 2 × 30 mL DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 1.1043 g of a red oil. This was purified by flash chromatography (5:95 EtOAc/hexanes) to yield the product as a light yellow oil (0.5372 g, 60% yield) containing approximately 5% of the minor diastereomer carried from the 4CR to make the lactam: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.42 (d, $J$ = 15.7, 1H), 8.10 (d, $J$ = 7.9, 1H), 7.56 (d, $J$ = 7.0, 1H), 7.45 (t, $J$ = 7.6, 1H), 7.33 (d, $J$ = 6.6, 1H), 7.24 (dt, $J$ = 7.0, 15.6, 5H), 6.37 (d, $J$ = 15.7, 1H), 4.53 (s, 1H), 4.28 (t, $J$ = 7.1, 2H), 3.81 (s, 3H), 3.69 (d, $J$ = 13.1, 1H), 3.16−3.09 (m, 1H), 3.10−3.04 (m, 1H), 2.87 (dd, $J$ = 5.2, 12.6, 1H), 2.28 (s, 1H), 2.13 (dd, $J$ = 7.7, 19.6, 2H), 1.88 (s, 1H), 1.35 (t, $J$ = 7.1, 3H), 1.28−1.09 (m, 4H), 0.75 (t, $J$ = 7.1, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 173.8, 167.3, 143.2, 138.8, 138.0, 135.3, 131.6, 129.4, 128.8, 128.4, 128.3, 127.2, 126.3, 120.0, 69.2, 61.1, 60.6, 57.9, 53.0, 51.6, 38.1, 31.0, 30.3, 22.3, 14.6, 13.8; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{28}H_{35}NO_4S$ $(M + H)^+$ 482.2360, found 482.2353; IR (thin film) 1705, 1635 $cm^{-1}$; TLC (20% EtOAc/hexanes) $R_f$ = 0.58.

**Sulfoxide 49a.** To a cooled (−78 °C) solution of **48** (0.0358 g, 0.074 mmol) in 5 mL of THF was added *m*-CPBA (0.017 g, 0.074 mmol, 77%). The mixture was stirred for 4 h and then allowed to warm to 23 °C, and a saturated solution of $Na_2S_2O_3$ in water (10 mL) was added. The resulting mixture was partitioned between water and 10 mL of DCM. The layers were separated, and the aqueous layer was extracted with 2 × 10 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 0.0390 g of a yellow oil. The data listed below is for the first compound off the column. Afforded a clear oil. This was purified by flash chromatography (20:80 EtOAc/hexanes) to yield the product as a clear oil (0.0167 g, 45% yield): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.16 (dd, $J$ = 7.1, 8.4, 2H), 7.63 (dd, $J$ = 1.1, 7.8, 1H), 7.53−7.46 (m, 1H), 7.40−7.34 (m, 1H), 7.30−7.27 (m, 1H), 7.23 (t, $J$ = 7.9, 4H), 6.40 (d, $J$ = 15.7, 1H), 4.35 (s, 1H), 4.29 (m, 2H), 3.76 (s, 3H), 3.70 (d, $J$ = 13.2, 1H), 3.23 (t, $J$ = 7.7, 1H), 3.04 (d, $J$ = 13.2, 1H), 2.77 (dd, $J$ = 1.7, 7.8, 1H), 2.49−2.37 (m, 2H), 2.28 (ddd, $J$ = 5.0, 9.4, 12.3, 1H), 2.07−1.92 (m, 1H), 1.68−1.53 (m, 1H), 1.46 (d, $J$ = 6.2, 1H), 1.35 (t, $J$ = 7.1, 3H), 1.30−1.20 (m, 2H), 0.81 (t, $J$ = 7.3, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 170.4, 167.1, 142.3, 138.2, 135.4, 135.3, 131.8, 130.2, 128.9, 128.8, 128.5, 127.3, 126.9, 120.3, 75.3, 70.7, 60.8, 57.4, 53.1, 51.8, 48.4, 25.3, 24.1, 22.1, 14.6, 13.8; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{28}H_{35}NO_5S$ $(M + H)^+$ 498.2309, found 498.2297; IR (thin film) 1708, 1632, 1453 $cm^{-1}$; TLC (50% EtOAc/hexanes) $R_f$ = 0.60.

**Sulfoxide 49b.** Isolated at the same time as **49a**. The data listed below is for the second compound off the column. This was purified by flash chromatography (20:80 EtOAc/hexanes) to yield the product as a clear oil (0.0072 g, 20% yield): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.43 (d, $J$ = 15.7, 1H), 8.06 (d, $J$ = 7.9, 1H), 7.61 (d, $J$ = 7.6, 1H), 7.48 (t, $J$ = 7.6, 1H), 7.37 (t, $J$ = 7.6, 1H), 7.29 (m, 1H), 7.21 (m, 4H), 6.37 (d, $J$ = 15.7, 1H), 4.75 (s, 1H), 4.27 (q, $J$ = 7.1, 2H), 3.93 (s, 3H), 3.72 (d, $J$ = 13.0, 1H), 3.19 (d, $J$ = 13.0, 1H), 3.11−3.06 (m, 1H), 2.50 (m, 2H), 2.35 (m, 1H), 1.74 (m, 1H), 1.63 (m, 1H), 1.55 (m, 1H), 1.35 (m, 6H), 0.87 (t, $J$ = 7.3, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 169.5, 167.4, 143.5, 138.4, 136.4, 136.3, 130.6, 129.7, 128.8, 128.8, 128.5, 127.4, 127.0, 120.1, 75.1, 67.7, 60.6, 57.4, 53.6, 51.0, 48.3, 31.0, 25.8, 22.3, 14.6, 13.9; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{28}H_{35}NO_5S$ $(M + H)^+$ 498.2309, found 498.2300; IR (thin film) 1707, 1634, 1455 $cm^{-1}$; TLC (50% EtOAc/hexanes) $R_f$ = 0.45.

**Tricyclic Lactam 50.** To a flame-dried flask was added **33** (0.154 g, 0.283 mmol) dissolved in dry THF and cooled to −78 °C. To this was added *i*-PrMgCl (0.353 mL, 0.565 mmol) as a 1.6 M solution in $Et_2O$. This was stirred at −78 °C for 2 h and then allowed to warm to 23 °C. After quenching with MeOH, the mixture was quickly partitioned between water (10 mL) and DCM (10 mL). The layers were separated, and the aqueous layer was extracted with 2 × 10 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 0.1001 g of yellow oil. The oil was purified by flash chromatography (50% $Et_2O$/toluene) to yield the product as a clear oil (0.0880 g, 77%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.26 (m, 8H), 7.16 (d, $J$ = 7.4, 1H), 5.30 (d, $J$ = 15.1, 1H), 4.92 (s, 1H), 4.27−4.11 (m, 4H), 3.67 (s, 3H), 2.98 (d, $J$ = 16.8, 1H), 2.89 (dd, $J$ = 6.4, 16.3, 1H), 2.59 (dd, $J$ = 8.6, 16.3, 1H), 2.44 (d, $J$ = 16.8, 1H), 1.28 (t, $J$ = 7.2, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 174.3, 172.7, 171.9, 142.9, 138.9, 135.9, 129.5, 129.0, 128.5, 128.4, 128.1, 124.9, 124.3, 68.8, 68.8, 61.2, 57.6, 53.0, 52.9, 46.0, 44.5, 35.8, 35.1, 14.4; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{24}H_{25}NO_5$ $(M + H)^+$ 408.1806, found 408.1801; IR (thin film) 1731, 1693 $cm^{-1}$; TLC (33:67 MeOH/DCM) $R_f$ = 0.49.

**Bis-*p*-bromobenzylamide 51.** To a flame-dried flask was added *para*-bromobenzylamine (0.152 g, 0.822 mmol), which was dissolved in $CDCl_3$ (5 mL) under argon. This was cooled to 0 °C, and trimethylaluminum (0.411 mL, 0.8220 mmol, 2.0 M) was added, and then the mixture stirred and allowed to return to 23 °C. Diester **50** dissolved in dry DCM (5 mL) was added slowly via syringe. This mixture was allowed to stir at 23 °C for 8 h. After careful quenching with MeOH, the mixture was partitioned between water (10 mL) and DCM (10 mL). The layers were separated, and the aqueous layer was extracted with 2 × 15 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 0.0321 g of clear oil. The oil was purified by flash chromatography (10:90 EtOAc/hexanes to 60:40 EtOAc/hexanes) to yield the product as a clear oil (0.0113 g, 20%) that was approximately 90% pure. Recrystallization from 50:50 EtOAc/hexanes yielded a small number of crystals that were used for crystallography: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.15 (t, $J$ = 5.8, 1H), 7.48−7.45 (m, 3H), 7.41 (d, $J$ = 8.3, 2H), 7.36−7.30 (m, 3H), 7.28 (d, $J$ = 9.1, 2H), 7.22 (dd, $J$ = 6.4, 13.5, 4H), 7.15 (d, $J$ = 8.3, 2H), 7.11 (d, $J$ = 8.3, 2H), 6.66 (t, $J$ = 5.7, 1H), 5.46 (s, 1H), 5.02 (d, $J$ = 15.4, 1H), 4.51−4.45 (m, 1H), 4.31 (dd, $J$ = 5.5, 18.6, 3H), 4.17 (d, $J$ = 7.9, 1H), 3.86 (d, $J$ = 15.3, 1H), 2.78 (d, $J$ = 17.6, 2H), 2.62 (d, $J$ = 17.5, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 174.5, 172.5, 171.5, 145.0, 138.4, 137.7, 136.9, 135.7, 132.1, 131.9, 131.8, 129.7, 129.7, 129.5, 129.2, 129.1, 128.0, 128.0, 127.9, 126.2, 125.0, 121.9, 121.3, 105.4, 67.9, 56.0, 47.0, 44.2, 43.6, 43.4, 39.8, 38.5, 21.4; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{35}H_{31}Br_2N_3O_3$ $(M + H)^+$ 700.0805, found 700.0825; IR (thin film) 1638, 1545 $cm^{-1}$.

**Tetracyclic Ketone 53.** Isolated concurrently with **50** after quenching with MeOH (5 mL) and stirring at room temperature for 3 h (0.043 g, 33%) as a white solid: mp 166 °C; $^1$H NMR (300 MHz,


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$CDCl_3$) $\delta$ 7.42−7.29 (m, 9H), 5.26 (d, $J$ = 15.6, 1H), 5.18 (s, 1H), 4.31 (dd, $J$ = 4.8, 10.7, 1H), 4.01 (d, $J$ = 15.6, 1H), 3.87 (s, 1H), 3.75 (s, 3H), 3.15 (dd, $J$ = 10.7, 18.1, 1H), 2.63 (dd, $J$ = 4.8, 18.1, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 207.2, 173.4, 165.3, 144.9, 138.8, 135.1, 130.5, 129.3, 128.3, 128.1, 125.8, 125.7, 67.6, 60.0, 59.7, 53.5, 47.6, 46.2, 45.1; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{22}H_{19}NO_4$ $(M + H)^+$ 362.1387, found 362.1389; IR (thin film) 1733, 1677, 1603 $cm^{-1}$.

**Pyrrolidine Amide 54.** To a solution of *para*-thiocresol (3.89 mL, 3.89 mmol, 1 M) in toluene were added melaic anhydride (0.381 g, 3.89 mmol), *o*-iodobenzaldehyde (0.902 g, 3.89 mmol), and benzylamine (0.42 mL, 3.89 mmol). The mixture was stirred for 14 h at reflux under a Dean−Stark trap and then cooled to 23 °C. The toluene was removed by rotary evaporation to yield a crude oil. This crude oil was split, and 0.704 g (1.296 mmol) was dissolved in DMF. Next were added HATU (0.542 g, 1.425 mmol) and pyrrolidine (0.32 mL, 3.887 mmol), and this was heated to 50 °C under a reflux condenser for 14 h and cooled to 23 °C. The resulting mixture was partitioned between water (25 mL) and DCM (15 mL). The layers were separated, and the aqueous layer was extracted with 2 × 20 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 0.6821 g of a brown oil. The oil was purified by flash chromatography (20:80 to 50:50 EtOAc/hexanes) to yield the product as a pale yellow oil (0.422 g, 57%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.76 (d, $J$ = 7.9, 1H), 7.32 (t, $J$ = 7.5, 1H), 7.26 (d, $J$ = 6.3, 1H), 7.19−7.13 (m, 3H), 7.04−6.96 (m, 3H), 6.92 (d, $J$ = 8.0, 2H), 6.79 (d, $J$ = 8.1, 2H), 5.71 (s, 1H), 4.89 (d, $J$ = 14.9, 1H), 3.65−3.36 (m, 6H), 2.91 (d, $J$ = 17.2, 1H), 2.21 (s, 3H), 1.72 (d, $J$ = 43.8, 5H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 172.1, 167.2, 140.3, 139.1, 138.0, 135.6, 133.9, 130.8, 130.7, 130.0, 128.7, 128.7, 128.4, 127.7, 127.3, 102.9, 71.8, 58.7, 45.5, 42.3, 21.4; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{29}H_{29}IN_2O_2S$ $(M + H)^+$ 597.1067, found 597.1064; IR (thin film) 1701 $cm^{-1}$.

**Pyrrolidine Amide 55.** To a flame-dried flask were added palladium acetate (0.0060 g, 0.027 mmol) and iodide **54** (0.157 g, 0.266 mmol) as a solution in DMF (8 mL). Next were added ethyl acrylate (0.11 mL, 1.06 mmol) and triethylamine (0.074 mL, 0.532 mmol). The mixture was heated to 100 °C under argon and a reflux condenser for 24 h and then cooled to 23 °C. The resulting mixture was partitioned between DCM (20 mL) and water (30 mL). The layers were separated, and the water layer was extracted with 2 × 20 mL DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 0.1723 g of a red oil. This was purified by flash chromatography (20:80 EtOAc/hexanes to 50:50 EtOAc/hexanes) to yield the product as a red oil (0.0567 g, 37% yield): $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.54 (d, $J$ = 15.7, 1H), 7.48 (d, $J$ = 7.7, 1H), 7.45 (d, $J$ = 7.5, 1H), 7.43−7.39 (m, 1H), 7.36 (d, $J$ = 7.7, 1H), 7.29−7.24 (m, 3H), 7.00 (dd, $J$ = 10.3, 13.9, 2H), 6.92 (t, $J$ = 11.0, 2H), 6.84−6.77 (m, 2H), 6.17 (d, $J$ = 15.7, 1H), 5.29 (s, 1H), 5.12 (d, $J$ = 14.7, 1H), 4.24−4.16 (q, $J$ = 7.1, 2H), 3.58 (d, $J$ = 16.6, 1H), 3.50−3.22 (m, 5H), 2.92 (d, $J$ = 16.6, 1H), 2.24 (s, 3H), 1.72 (s, 4H), 1.31 (t, $J$ = 7.1, 3H); $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 172.5, 167.1, 166.2, 142.1, 139.3, 136.3, 135.8, 134.3, 130.0, 129.8, 129.4, 129.0, 128.8, 128.6, 128.0, 127.9, 122.1, 61.7, 60.7, 59.2, 48.9, 45.1, 42.9, 31.8, 22.8, 21.3, 14.5, 14.3; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{34}H_{36}N_2O_4S$ $(M + H)^+$ 569.2469, found 569.2470; IR (thin film) 1697, 1624 $cm^{-1}$; TLC (50:50 EtOAc/hexanes) $R_f$ = 0.31.

**Pyrroline 56.** To a cooled (−78 °C) solution of **53** (0.670 g, 1.18 mmol) in 10 mL of THF was added *m*-CPBA (0.0.2642 g, 1.18 mmol, 77%). The mixture was stirred for 3 h and then allowed to warm to 23 °C, and a saturated solution of $Na_2S_2O_3$ in water (5 mL) was added. The resulting mixture was partitioned between water and 15 mL of DCM. The layers were separated, and the aqueous layer was extracted with 2 × 15 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 0.8538 g of a purple oil. This was purified by flash chromatography (10:90 EtOAc/hexanes to 50:50 EtOAc/hexanes) to yield the product as a purple oil (0.1888 g, 36% yield). Multiple rotomers complicated NMR characterization at room temperature. For high temperature experiments, please see the Supporting Information: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.60 (d, $J$ = 7.3, 1H), 7.44 (d, $J$ = 15.8, 1H), 7.39 (s, 1H), 7.32−7.27 (m, $J$ = 8.6, 2H), 7.08 (d, $J$ = 7.0, 3H), 6.72 (d, $J$ = 7.9, 2H), 6.26 (d, $J$ = 15.9, 1H), 4.59 (d, $J$ = 15.3, 1H), 4.35 (d, $J$ = 15.3, 1H), 4.22 (q, $J$ = 7.1, 2H), 3.68 (s, 2H), 3.25 (m, 4H), 1.69 (m, 4H), 1.32 (t, $J$ = 7.1, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 176.0, 166.4, 163.6, 145.1, 140.8, 136.7, 133.6, 130.9, 130.6, 130.3, 130.1, 128.9, 128.7, 128.5, 127.7, 127.6, 126.6, 120.5, 112.7, 60.8, 44.6, 38.9, 14.5; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{27}H_{28}N_2O_4$ $(M + H)^+$ 445.2122, found 445.2121; IR (thin film) 1706, 1630, 1622 $cm^{-1}$.

**4CR Lactam Amide 58.** To a solution of *para*-thiocresol (4.66 mL, 4.66 mmol, 1 M) in toluene were added melaic anhydride (0.457 g, 4.66 mmol), *o*-iodobenzaldehyde (1.082 g, 4.66 mmol), and benzylamine (0.51 mL, 4.66 mmol). The mixture was stirred for 14 h at reflux under a Dean−Stark trap and then cooled to 23 °C. The toluene was removed in vacuo to yield a crude oil. This crude oil was redissolved in benzene and cooled to 0 °C. Next was added $SOCl_2$, (0.68 mL 9.32 mmol) and this was heated to 80 °C under a reflux condenser for 14 h and cooled to 23 °C. The benzene and excess $SOCl_2$ were removed in vacuo, and this crude mixture was redissolved in DCM (10 mL) and cooled to 0 °C. Ammonium hydroxide (0.85 mL, 21.33 mmol) was added very slowly and then allowed to warm to 23 °C over 5 h. The resulting mixture was partitioned between water (25 mL) and DCM (15 mL). The layers were separated, and the aqueous layer was extracted with 2 × 20 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 2.8 g of a brown oil. The oil was purified by flash chromatography (20:80 to 40:60 EtOAc/hexanes) to yield the product as a pale yellow oil (1.675 g, 66%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.90 (d, $J$ = 6.9, 1H), 7.47 (t, $J$ = 7.1, 1H), 7.31−7.22 (m, 4H), 7.20−7.11 (m, 3H), 7.08−6.96 (m, 5H), 5.93 (s, 1H), 5.13 (d, $J$ = 14.6, 1H), 5.08 (s, 1H), 3.43 (d, $J$ = 14.7, 1H), 3.37 (d, $J$ = 16.8, 1H), 2.83 (d, $J$ = 16.8, 1H), 2.29 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 173.8, 172.8, 140.4, 139.8, 136.8, 135.1, 134.4, 131.2, 130.3, 129.2, 129.0, 129.0, 128.8, 128.0, 126.6, 101.7, 71.7, 58.8, 45.1, 41.3, 21.4; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{25}H_{23}IN_2O_2S$ $(M + H)^+$ 543.0598, found 543.0596; IR (thin film) 1710, 1678, 1587 $cm^{-1}$; TLC (50% EtOAc/hexanes) $R_f$ = 0.46.

**4CR Lactam Amide 59.** To a flame-dried flask were added palladium acetate (0.010 g, 0.045 mmol) and iodide **58** (0.241 g, 0.445 mmol) as a solution in DMF (8 mL). Next were added ethyl acrylate (0.19 mL, 1.78 mmol) and triethylamine (0.12 mL, 0.889 mmol). The mixture was heated to 105 °C under argon and a reflux condenser for 24 h and then cooled to 23 °C. The resulting mixture was partitioned between DCM (15 mL) and water (20 mL). The layers were separated, and the water layer was extracted with 2 × 20 mL DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 0.4123 g of a red/brown oil. The oil was purified by flash chromatography (33:67 EtOAc/hexanes) to yield the product as a red-orange solid (0.1503 g, 66%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.59−7.50 (m, 3H), 7.46 (t, $J$ = 7.5, 1H), 7.40 (d, $J$ = 7.7, 1H), 7.24 (dd, $J$ = 1.9, 5.0, 3H), 7.13 (d, $J$ = 8.2, 2H), 7.05 (d, $J$ = 8.1, 2H), 6.98−6.93 (m, 2H), 6.77 (s, 1H), 6.24 (d, $J$ = 15.6, 1H), 5.48 (s, 1H), 5.20 (d, $J$ = 14.7, 1H), 5.12 (s, 1H), 4.22 (q, $J$ = 7.1, 2H), 3.50 (d, $J$ = 14.6, 1H), 3.37 (d, $J$ = 17.0, 1H), 2.82 (d, $J$ = 17.0, 1H), 2.29 (s, 3H), 1.31 (t, $J$ = 7.1, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 174.2, 172.8, 166.4, 140.7, 139.6, 135.5, 135.0, 134.1, 133.1, 130.3, 130.1, 129.6, 128.9, 128.7, 128.5, 128.0, 127.6, 126.7, 122.3, 63.8, 60.9, 58.9, 45.2, 41.5, 21.3, 14.5; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{30}H_{30}N_2O_4S$ $(M + H)^+$ 515.1999, found 515.1996; IR (thin film) 1705, 1677, 1655, 1598 $cm^{-1}$; TLC (50% EtOAc/hexanes) $R_f$ = 0.23.

**4CR Nitrile 60.** Amide **59** (0.150 g, 0.292 mmol) was dissolved in benzene and cooled to 0 °C. $POCl_3$ (0.14 mL, 1.46 mmol) was added slowly via syringe, and the mixture was heated to reflux for 14 h and then cooled to 23 °C. The resulting mixture was partitioned between water (20 mL) and DCM (20 mL). The layers were separated, and the aqueous layer was extracted with 2 × 20 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 0.1523 g of a brown oil. The oil was purified by flash chromatography (20:80 EtOAc/hexanes) to yield the product as a white solid (0.1281 g, 88%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.57 (dd, $J$ = 9.0, 11.6, 2H), 7.51 (td, $J$ = 1.9, 4.3, 2H), 7.39−7.24 (m, 7H), 7.14 (d, $J$ = 8.3, 2H), 6.99 (d, $J$ = 2.7, 2H), 6.21 (d, $J$ = 15.6, 1H), 5.21

(d, $J$ = 14.5, 2H), 4.24 (q, $J$ = 7.1, 2H), 3.58 (d, $J$ = 14.5, 1H), 3.08 (d, $J$ = 17.4, 1H), 2.94 (d, $J$ = 17.4, 1H), 2.34 (s, 3H), 1.32 (t, $J$ = 7.1, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 170.1, 165.9, 141.6, 140.1, 136.8, 136.2, 134.2, 130.8, 130.6, 130.3, 129.9, 129.3, 128.7, 128.6, 128.4, 128.3, 124.7, 123.8, 120.3, 63.4, 60.9, 46.5, 45.6, 43.9, 21.5, 14.5; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{30}H_{28}N_2O_3S$ (M + H)$^+$ 497.1893, found 497.1892; IR (thin film) 2235, 1702, 1635 cm$^{-1}$; TLC (20% EtOAc/hexanes) $R_f$ = 0.09.

**Nitrile Sulfoxide 61.** To a cooled (−78 °C) solution of **60** (0.120 g, 0.242 mmol) in 5 mL of THF was added *m*-CPBA (0.0542 g, 0.242 mmol, 77%). The mixture was stirred for 3 h and then allowed to warm to 23 °C, and a saturated solution of $Na_2S_2O_3$ in water (5 mL) was added. The resulting mixture was partitioned between water (10 mL) and DCM (10 mL). The layers were separated, and the aqueous layer was extracted with 2 × 15 mL of DCM. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 0.1059 g of a purple oil. The oil was purified by flash chromatography (20:80 EtOAc/hexanes to 30:70 EtOAc/hexanes) to yield the product as a purple oil (0.0356 g, 30%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.71 (d, $J$ = 15.7, 1H), 7.59 (t, $J$ = 6.9, 3H), 7.51 (dt, $J$ = 3.7, 4.4, 2H), 7.35 (d, $J$ = 8.3, 2H), 7.33−7.27 (m, 3H), 7.21−7.15 (m, 1H), 7.01 (dd, $J$ = 2.8, 6.5, 2H), 6.21 (d, $J$ = 15.7, 1H), 5.23 (s, 1H), 5.11 (t, $J$ = 9.1, 1H), 4.28−4.18 (m, 2H), 3.54 (d, $J$ = 14.5, 1H), 2.91 (d, $J$ = 17.1, 1H), 2.43 (s, 3H), 2.37−2.31 (m, 1H), 1.32 (t, $J$ = 7.1, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 168.1, 165.9, 144.8, 140.7, 137.5, 135.6, 133.8, 130.8, 130.4, 130.2, 130.0, 129.3, 129.0, 128.7, 127.2, 125.9, 124.2, 116.1, 106.1, 64.1, 62.7, 60.8, 45.8, 36.5, 21.8, 14.5; HRMS (FTMS + p ESI) $m/z$ calcd for $C_{30}H_{28}N_2O_4S$ (M + H)$^+$ 513.1843, found 513.1846; IR (thin film) 2235, 1703, 1635 cm$^{-1}$; TLC (10% EtOAc/hexanes) $R_f$ = 0.39.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

General experimental methods, $^1$H and $^{13}$C NMR spectra for all new compounds, experimental details for computational studies of **38**, and X-ray crystallographic information for **39**, **51**, and **53**. This material is available free of charge via the Internet at http://pubs.acs.org/.

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