JOC Article

Simple Thiazocine-2-acetic Acid Derivatives via Ring-Closing Metathesis

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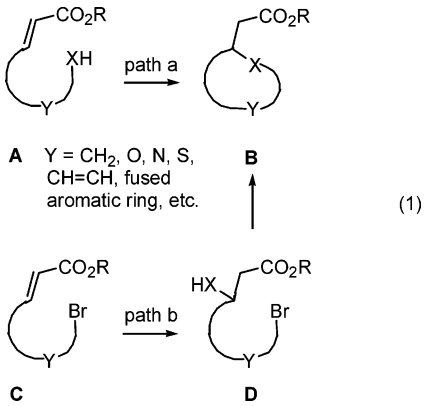
A new protocol for synthesis of 2-heterocylylacetic acid derivatives involving conjugate addition of allyl mercaptan to an acrylate containing a tethered olefinic site followed by RCM (ring-closing metathesis) is described. In this series, sulfanyl derivatives were unreactive, while sulfoxide and sulfone analogues provided the corresponding thiazocines in fair to excellent yields. Use of the sulfoxide oxidation state as a protecting group for sulfides inert to RCM is demonstrated also. Thus, oxidation of sulfide **9** [*N*-allyl-*N*-[2-(allylthio)-4-(1*H*-indol-1-yl)-4-oxobutyl]-4-methylbenzenesulfonamide] followed by cyclization yielded the corresponding thiazocine sulfoxide **12**. Deprotection (deoxygenation) of **12** was accomplished using Lawesson's reagent, producing 1-[[4-[4-(methylphenyl)sulfonyl]-3,4,5,8-tetrahydro-2*H*-1,4-thiazocin-2-yl]acetyl]-1*H*-indole (**21**) in 67% unoptimized yield.

Introduction

Heterocylylacetic acid derivatives are a diverse and important group of compounds. In addition to examples of NSAIDS (Myalex/fenclozic acid)[1] (including COX-2 specific inhibitors)[2] and nonbenzodiazepine hypnotics (Ambien/zolpidem),[3] compounds acting as blood platelet aggregation inhibitors,[4] aldose reductase inhibitors,[5] antimicrobial agents,[6] TACE inhibitors,[7] and medicinal chelating agents[8] and many others exhibiting useful biological activity have been reported. Many synthetic efforts have concentrated on five-, six-, seven-, and eight-membered ring examples of **B** (Y = $(CH_2)_n$, X = O) because of their prominence as building blocks for synthesis of fused polyether marine toxins (e.g., ciguatoxin)[9] and other natural products.[10] Compounds **B** (X = S) have also been prepared, but examples are scarce. Of the synthetic approaches developed, most target a specific member and are not general. Common general protocols (typically applicable only to five-, six-, and seven-membered ring compounds) involve conjugate addition to an α,β-unsaturated ester. Specifically, Michael addition of N-, O-, or S-centered nucleophiles to tethered acrylates[11] (**A**, eq 1, path a) or Michael addition of a protected nucleophile to an acrylate (for example, **C**) followed by deprotection and cyclization[12] (eq 1, path b)[13] have been used extensively.



Here we describe a new protocol for assembling compounds of type **B** making use of conjugate addition followed by ring-closing metathesis (RCM) (eq 2). This approach is illustrated by preparation of 2-thiazocinyl-

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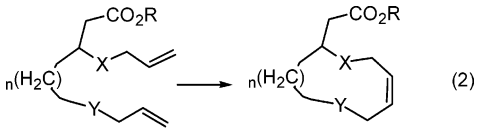
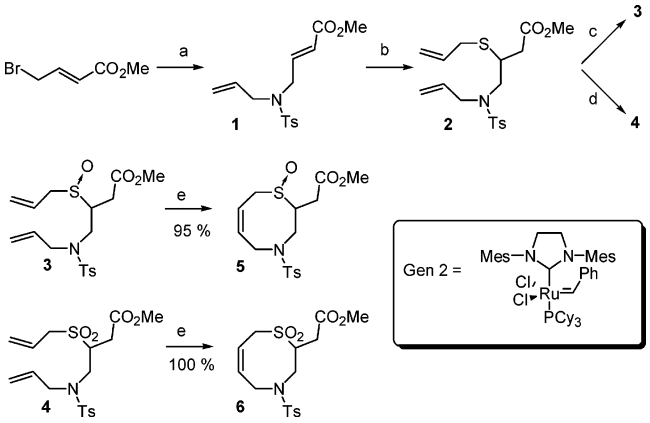
acetic acid derivatives and should be readily adaptable to other analogues as well. The specific target compounds were chosen because RCM has been shown to be an excellent methodology for N- and O-containing medium-sized ring synthesis[14] and eight-membered rings are the smallest simple *S*- and *N*,*S*-cycloalkanes for which conventional synthetic approaches fail.[15]



E X = S (no RCM), SO, SO_2 Y = N-Ts n = 1 **F**

Although olefin metathesis has experienced explosive growth, reports of applications of RCM to sulfur-containing compounds are comparatively rare. Initial work found the Grubbs first generation catalyst inferior to Mo- and W-based catalysts with respect to sulfur(II) tolerance.[16,17] Although Mo-based catalysts are quite tolerant of sulfur(II) sites in the substrate, the highly active N-heterocyclic carbene catalysts such as Grubbs' second generation catalyst (Gen 2; see Scheme 1) are more widely used as a result of their improved tolerance for sulfur(II) and their air and moisture stability. Numerous examples of additional successful RCM reactions of sulfides, disulfides, and dithioacetals using Ru/carbene complexes have been reported.[18] The literature suggests the sulfonyl oxidation state (sulfones,[19] sulfonamides,[20] etc.[21]) is better tolerated in RCM substrates than lower oxidation states of sulfur. Deactivation via Ru-sulfonyl oxygen coordination does not occur (even though Ru-sulfonyl ligation to assist ring closure has been suggested).[22] In contrast to the body of work available for sulfides and sulfones,

SCHEME 1 [a]



[a] Reagents: (a) *N*-tosylallylamine, NaOH, TBAH, DCM, rt, 100%; (b) allyl mercaptan, NaOMe, MeOH, reflux, 68%; (c) $NaIO_4$, acetone/water, 22 h, rt, 35%; (d) Oxone (3 equiv), MeOH/water, 3 d, rt, 58%; (e) 5 mol % Gen 2, DCM, reflux (6 h for **5**, 8 h for **6**).

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(16) For examples of RCM failures with Grubbs' Gen 1 catalyst on sulfur-containing compounds, see: (a) Fuerstner, A.; Seidel, G.; Kindler, N. *Tetrahedron* **1999**, *55*, 8215−8230. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (c) Bujard, M.; Gouverneur, V.; Mioskowski, C. *J. Org. Chem*. **1999**, *64*, 2119−2123. (d) Mascarenas, J. L.; Rumbo, A.; Castedo, L. *J. Org. Chem*. **1997**, *62*, 8620−8621.

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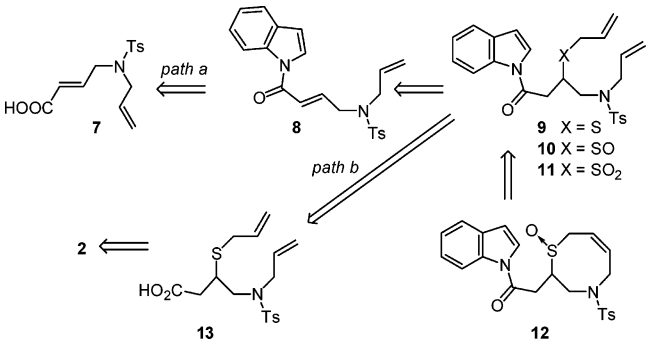
sulfoxides have been studied very little. DMSO treatment has been proposed[23] as a means of removing Ru-containing contaminants from RCM reaction mixtures, presumably due to coordination Ru. Only two reports of RCM chemistry applied to sulfoxides have been reported. One was successful[24] and the other was not.[19a] Therefore, sulfur-containing substrates for this study were prepared not only in the sulfanyl and sulfonyl oxidation states but also in the sulfinyl state as well.

Results and Discussion

Reaction of methyl 4-bromocrotonate with *N*-tosylallylamine[25] under phase transfer conditions followed by conjugate addition of allyl mercaptan provided the key intermediate **2** in 68% overall yield (Scheme 1). Oxidation of **2** to sulfoxide **3** (obtained as a 1:1 mixture of diastereomers) and sulfone **4** was readily accomplished by conventional means. Although **2** failed to undergo RCM[26] (Gen 2 catalyst),[27] both sulfone **4** *and sulfoxide* ***3*** cyclized [to thiazocines **6** and **5** (obtained as a 2:3 mixture of diastereomers), respectively] in excellent yield.

SCHEME 2. Alternative Pathways to Thiazocine 12



With this success in hand we applied the methodology to preparation of acyl indole **12** (Scheme 2), a system useful for SES/ring opening studies.[28] Preparation of this target demonstrates some of the potential obstacles in syntheses of RCM substrates of the type shown in eq 2. Thus, sulfide **9** was prepared in three steps from **1** in 19% overall yield, realizing path a in Scheme 2. The low yield is due to poor conversion of the acid chloride of **7** to the acylindole. The problem stems from the lability of the initially formed acylindole to nucleophilic attack; no acylation procedure attempted involving a strong nucleophile (OH^-) or nucleophilic solvent (H_2O) gave satisfactory yields of **8**. Alternative acylation conditions were not thoroughly explored because an alternative process forming the labile acylindole later in the sequence was developed. Reversing the order of the reactions leading to **9** (forward synthesis version of path b, Scheme 2) did not improve overall yield because ester hydrolysis of **2** to **13** proceeded in poor yield as a result of unavoidable (in our hands) retro-Michael addition of allyl mercaptan.

These difficulties were overcome using the well-known[29] stability of indoline amides relative to their indole amide counterpart and the ease of conversion of the former to the latter.[30] Execution of this strategy led to **9** in 44% yield (from **1**, path a in Scheme 3). Reversing the sequence of Michael addition and indoline oxidation (path b, Scheme 3) was not effective. Although Michael addition of allyl mercaptan to **14** proceeded very cleanly, subsequent reaction of **15** with DDQ gave not only oxidation of the indoline but also retro-Michael addition providing mainly compound **8**.

Oxidation[31] of indole **9** with 1 or 2 equiv of *m*-CPBA gave the corresponding sulfoxide (**10**, 72%, 2:3 inseparable mixture of diastereomers) or sulfone (**11**, 99%). Treatment of these compounds with Gen 2 (10 mol % for the sulfoxide and 5 mol % for the sulfone) produced the corresponding thiazocinyl acetamide derivatives **12** and **16** in 48% and 89%, respectively (Scheme 4). Compound **12** was isolated as a 2:3 mixture of diastereomers.

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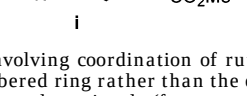
(26) Starting material (**2**) was recovered unchanged quantitatively. The lack of reactivity is probably not due to Ru coordination with the ester [no reaction was observed when $Ti(OiPr)_4$ was added to the RCM reaction according to Fuerstner's protocol (Fuerstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130−9136) and both S-oxidized counterparts to the sulfide (**3** and **4**) readily undergo RCM]. The problem is more likely due to inactivation of the catalyst by coordination of the Ru to S(II). Coordination/inactivation could occur intermolecularly prior to interaction of the Ru with the olefinic sites or intramolecularly, perhaps as shown in structure **i**.



i

The latter process (involving coordination of ruthenium to hydroxyl oxygen via a six-membered ring rather than the eight-membered ring as in **i**) has been suggested previously (for example, Washburn, D. G.; Heidebrecht, R. W.; Martin, S. F. *Org. Lett.* **2003**, 5, 3523−3525) to explain Grubbs' catalyst inactivation. This process seems less likely in the present context because of the size of the ring involved and the necessity to invoke selective reaction of the *N*-allylic olefinic site, even though the *S*-allylic olefinic site is sterically and electronically similar.

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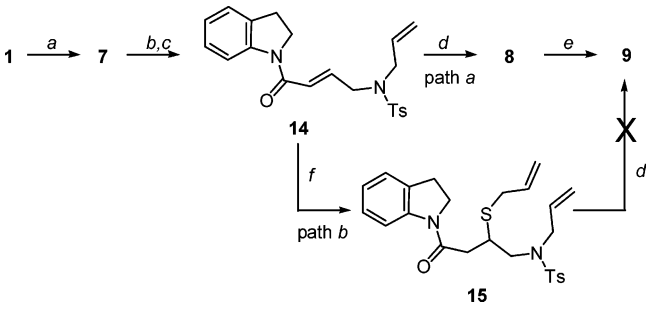
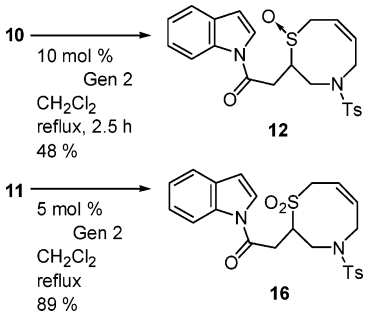
SCHEME 3. Acylindole 9 via Oxidation of Indoline Amide 8[a]

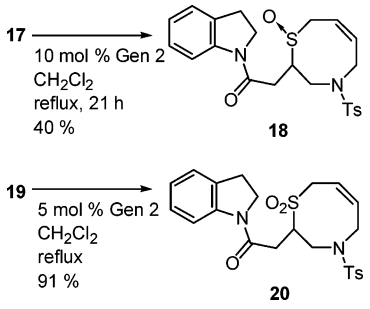


[a] Reagents: (a) LiOH, THF/H_2O, 0 °C, 95%; (b) oxalyl chloride, THF, 24 h, 0 °C; (c) indoline, pyridine, DMAP, 64%; (d) DDQ, dioxane, 70 °C, 3 d, 89%; (e) allyl mercaptan, Et_3N, CH_2Cl_2, 80%; (f) allyl mercaptan, NaOMe, MeOH/THF, 15 min, 0 °C, 95%.

SCHEME 4. RCM of Acylindoles 10 and 11

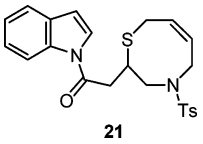


SCHEME 5. RCM of Indoline Amides 17 and 19



This pattern of reactivity was duplicated in the corresponding indoline analogues. Thus, treatment of **15** with either 1 or 2 equiv of *m*-CPBA gave the corresponding sulfoxide **17** (as an inseparable 2:3 ratio of diastereomers) or sulfone (**19**). Treatment of these compounds with Gen 2 (10 mol % for the sulfoxide and 5 mol % for the sulfone) produced the corresponding thiazocines **18** and **20** in 40% and 91%, respectively (Scheme 5). Compound **18** was isolated as a 3:4 mixture of diastereomers.

In view of the mixed history of success with S(II) substrates in RCM processes, our current results on successful RCM on sulfoxides where the corresponding sulfides fail, the abundance of simple oxidation procedures for the sulfide to sulfoxide transformation,[32] and the ease of the reverse deoxygenation process[32] suggest sulfoxides may be useful protecting groups for thioethers undergoing RCM.[33] As a demonstration of the concept, the most labile sulfoxide in the series (compound **12**) was treated with Lawesson's reagent[34] to produce sulfide **21** in 67% yield.



In conclusion, sulfone and sulfoxide derivatives of compound **E** (Y = *N*-Ts, eq 2) undergo RCM in good to excellent yield with Grubbs second generation catalyst, providing a new route to (1,4-thiazocinyl)-2-acetic acid derivatives. Sulfide derivatives in the series do not undergo RCM with Grubbs' second generation catalyst, but such compounds are available through a protection/deprotection sequence involving the corresponding sulfoxide. Application of the methodology to other 2-heterocyclyl acetic acid derivatives is underway.

Experimental Section

Methyl (2*E*)-4-[Allyl[(4-methylphenyl)sulfonyl]amino]-but-2-enoate (1). To a well-stirred mixture of *N*-allyl-4-methylbenzensulfonamide (0.42 g, 2 mmol), powdered NaOH (2.0 equiv, 0.16 g, 4 mmol), and tetrabutylammonium hydrogen sulfate (0.06 equiv, 0.04 g) in CH_2Cl_2 (15 mL) was added dropwise a solution of methyl γ-bromocrotonate (1.5 eq, 0.537 g, 3 mmol) in CH_2Cl_2 (5 mL) in an ice−water bath. The resulting mixture was stirred at 0 °C for 5 min and at room temperature for 2 h. After filtering, the filtrate was washed with distilled water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Column chromatography on silica gel (EtOAc/hexane, 1:4) gave 0.62 g (100%) of **1** as a white solid: mp 58−60 °C; IR 1724 cm^{-1}; ^1H NMR δ 7.65 (d, 2H, J = 8.0 Hz), 7.27 (d, 2H, J = 8.0 Hz), 6.68 (dt, 1H, J = 15.6, 6.0 Hz), 5.87 (d, 1H, J = 15.6 Hz), 5.55 (m, 1H), 5.13−5.07 (m, 2H), 3.87 (d, 2H, J = 6.0 Hz), 3.75 (d, 2H, J = 6.4 Hz), 3.68 (s, 3H), 2.38 (s, 3H); ^{13}C NMR δ 166.0, 143.6, 142.6, 136.7, 132.1, 129.8, 127.1, 123.4, 119.7, 51.6, 50.4, 47.2, 21.4; MS [*m*/*z*] 278 (M^+). Anal. Calcd for $C_{15}H_{19}O_4NS$: C, 58.23; H, 6.19; N, 4.53. Found: C, 58.36; H, 6.32; N, 4.53.

Methyl 4-[Allyl[(4-methylphenyl)sulfonyl]amino]-3-(allylthio)butanoate (2). To a well-stirred solution of allyl mercaptan (5.0 equiv, 0.20 mL, 2.5 mmol) and MeONa (1.1 equiv, 0.03 g, 0.6 mmol) in methanol (7 mL) was added a solution of **1** (0.16 g, 0.5 mmol) in MeOH (4 mL) at room temperature. The resulting mixture was refluxed for 3 h, cooled, poured into ice water, and extracted with EtOAc. The combined organic layers were washed with distilled water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Column chromatography on silica gel (EtOAc/hexane, 1:4) gave 0.13 g (68%) of **2** as an oily liquid: IR 1739 cm^{-1}; ^1H NMR δ 7.65 (d, 2H, J = 8.0 Hz), 7.27 (d, 2H, J = 8.0 Hz), 5.74 (m, 1H), 5.48 (m, 1H), 5.16−5.03 (m, 4H), 3.80−3.76 (m, 2H), 3.67 (s, 3H), 3.37 (dd, 1H, J = 14.0, 10.0 Hz), 3.22 (m, 1H), 3.14 (d, 2H, J = 6.8 Hz), 3.09 (dd, 1H, J = 14.0, 4.8 Hz), 2.87 (dd, 1H, J = 16.4, 4.8 Hz), 2.49 (dd, 1H, J = 16.4, 8.4 Hz), 2.39 (s, 3H); ^{13}C NMR δ 171.9, 143.5, 136.4, 134.4, 132.4, 129.7, 127.2, 119.7, 117.4, 51.7, 51.6, 51.5, 39.1, 37.4, 34.8, 21.4; MS [*m*/*z* (rel intensity)] 228 (78), 224 (79), 155 (100).

Methyl 4-[Allyl[(4-methylphenyl)sulfonyl]amino]-3-(allylsulfinyl)butanoate (3). To an ice-cooled solution of **2**

(32) For leading references see Jog, P. V.; Brown, R. E.; Bates, D. K. *J. Org. Chem.* **2003**, *68*, 8240−8243.

(33) Gladysz and co-workers have reported use of a cationic rhenium compound that serves both as a protecting group for S(II) and RCM catalyst for thioethers: Martin-Alvarez, J. M.; Hampel, F.; Arif, A. M.; Gladysz, J. A. *Organometallics* **1999**, *18*, 955−957.

(34) (a) Bartsch, H.; Erker, T. *Tetrahedron Lett.* **1992**, *33*, 199−200. (b) Tewari, N.; Kumar, Y.; Thaper, R. K.; Khanna, J. M. *Synth. Commun.* **1996**, *26*, 1169−1173.

(0.81 g, 2.12 mmol) in acetone (12 mL) was added a solution of sodium periodate (1.05 equiv, 0.48 g, 2.23 mmol) in H_2O (6 mL) at 0 °C. The resulting mixture was stirred at room temperature for 22 h and concentrated in vacuo. The residue was diluted with H_2O (40 mL) and extracted with $CHCl_3$. The combined organic layers were washed with distilled water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Column chromatography on silica gel (EtOAc) gave 0.30 g (35%) of **3** as a colorless sticky liquid (mixture of two diastereomers in a 1:1 ratio): IR 1725 cm^{-1}; ^1H NMR δ 7.66 (d, 2H, J = 7.6 Hz), 7.29 (d, 2H, J = 7.6 Hz), 5.85 (m, 1H), 5.55−5.39 (m, 3H), 5.19−5.11 (m, 2H), 3.82−3.75 (m, 2H), 3.70 (s, 3H), 3.69 (s, 3H), 3.60 (dd, 1H, J = 12.0, 6.8 Hz), 3.51 (m, 1H), 3.41 (dd, 2H, J = 13.6, 7.6 Hz), 3.27 (dd, 1H, J = 14.8, 7.6 Hz), 2.96 (dd, 1H, J = 18.0, 5.2 Hz), 2.89 (dd, 1H, J = 18.0, 5.6 Hz), 2.79 (dd, 1H, J = 18.0, 8.0 Hz), 2.52 (dd, 1H, J = 18.0, 6.4 Hz), 2.40 (s, 3H); ^{13}C NMR δ 171.9, 171.4, 143.9, 135.6, 135.5, 132.1, 132.0, 129.9, 129.8, 127.4, 127.3, 125.9, 125.8, 123.9, 123.8, 120.5, 120.4, 54.6, 53.9, 53.4, 52.4, 52.3, 52.2, 52.1, 52.0, 47.4, 44.6, 32.0, 28.3, 21.5; MS [*m*/*z* (rel intensity)] 224 (47), 155 (66).

Methyl 4-[Allyl[(4-methylphenyl)sulfonyl]amino]-3-(allylsulfonyl)butanoate (4). To an ice-cooled solution of **2** (0.73 g, 1.91 mmol) in MeOH (15 mL) was added a solution of Oxone (3.0 equiv, 3.52 g, 5.73 mmol) in H_2O (15 mL) at 0 °C. The resulting cloudy slurry was stirred at room temperature for 3 d. After filtering, the filtrate was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Column chromatography on silica gel (EtOAc/hexane, 2:3) gave 0.46 g (58%) of **4** as a colorless sticky liquid: IR 1739 cm^{-1}; ^1H NMR δ 7.67 (d, 2H, J = 8.0 Hz), 7.31 (d, 2H, J = 8.0 Hz), 5.89 (m, 1H), 5.54−5.40 (m, 3H), 5.19−5.12 (m, 2H), 4.07 (m, 1H), 3.85−3.76 (m, 4H), 3.73 (s, 3H), 3.45−3.42 (m, 2H), 2.99 (dd, 1H, J = 18.0, 6.4 Hz), 2.84 (dd, 1H, J = 18.0, 5.6 Hz), 2.42 (s, 3H); ^{13}C NMR δ 171.0, 144.2, 135.3, 131.7, 131.0, 127.5, 125.5, 123.9, 120.8, 58.3, 56.1, 52.5, 52.4, 46.1, 30.9, 21.5; MS [*m*/*z* (rel intensity)] 260 (5), 224 (1), 155 (8).

Methyl [4-(4-Methylphenylsulfonyl]-1-oxido-3,4,5,8-tetrahydro-2H-1,4-thiazocin-2-yl]acetate (5). To a solution of **3** (0.26 g, 0.65 mmol) in CH_2Cl_2 (10 mL) was added a solution of commercial Gen 2 catalyst (5% mol, 0.028 g) in CH_2Cl_2 (4 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 6 h. The mixture was cooled to room temperature and concentrated in vacuo. Column chromatography of the residue on silica gel (EtOAc) gave 0.23 g (95%) of **5** separable mixture of two diastereomers in a 2:3 ratio both of which were viscous, tacky semiliquids. Minor diastereomer (higher R_f): IR 1733 cm^{-1}; ^1H NMR δ 7.65 (d, 2H, J = 8.0 Hz), 7.31 (d, 2H, J = 8.0 Hz), 5.84 (dd, 1H, J = 11.2, 4.0 Hz), 5.57 (m, 1H), 4.14 (d, 2H, J = 8.8 Hz), 4.00−3.76 (m, 3H), 3.70 (s, 3H), 3.48 (m, 1H), 3.04 (d, 1H, J = 14.8 Hz), 2.83 (dd, 1H, J = 16.4, 6.4 Hz), 2.44 (dd, 1H, J = 16.4, 8.0 Hz), 2.40 (s, 3H); ^{13}C NMR δ 170.6, 144.2, 133.5, 133.1, 130.0, 127.4, 119.0, 53.1, 52.2, 49.2, 45.5, 44.2, 33.3, 21.5; MS [*m*/*z* (rel intensity)] 371 (M^+, 9), 216 (8), 155 (68). Major diastereomer (lower R_f): IR 1736 cm^{-1}; ^1H NMR δ 7.59 (d, 2H, J = 8.4 Hz), 7.30 (d, 2H, J = 7.6 Hz), 5.87−5.74 (m, 2H), 4.30 (dd, 1H, J = 14.0, 8.0 Hz), 4.21 (d, 1H, J = 18.0 Hz), 3.92 (dd, 1H, J = 14.0, 8.0 Hz), 3.65 (s, 3H), 3.60−3.50 (m, 3H), 3.14−3.07 (m, 2H), 2.60 (dd, 1H, J = 17.2, 9.2 Hz), 2.40 (s, 3H); ^{13}C NMR δ 171.0, 144.2, 134.1, 132.2, 130.0, 127.1, 118.8, 55.6, 52.2, 49.7 48.6, 47.9, 31.8, 21.5; MS [*m*/*z* (rel intensity)] 371 (M^+, 15), 216 (11), 155 (56).

Methyl [4-(4-Methylphenylsulfonyl]-1,1-dioxido-3,4,5,8-tetrahydro-2*H*-1,4-thiazocin-2-yl]acetate (6). To a solution of **4** (0.40 g, 0.96 mmol) in CH_2Cl_2 (10 mL) was added a solution of commercial Gen 2 catalyst (5% mol, 0.041 g) in CH_2Cl_2 (5 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 8 h. The mixture was cooled to room temperature and concentrated in vacuo. Column chromatography of the residue on silica gel (EtOAc/hexane, 2:3) gave 0.38 g (100%) of **6** as a white solid: mp 155−7 °C; IR 1740 cm^{-1}; ^1H NMR δ 7.63 (d, 2H, J = 8.0 Hz), 7.29 (d, 2H, J = 8.0 Hz), 5.77−5.66 (m, 2H), 4.39 (m, 1H), 4.12−3.94 (m, 3H), 3.77−3.69 (m, 2H), 3.66 (s, 3H), 3.22 (dd, 1H, J = 14.4, 2.8 Hz), 3.03 (dd, 1H, J = 16.8, 3.6 Hz), 2.41−2.35 (m, 4H); ^{13}C NMR δ 170.2, 144.3, 134.4, 132.7, 130.0, 127.3, 118.7, 55.6, 52.8, 52.1, 49.4, 49.0, 29.0, 21.3; MS [*m*/*z* (rel intensity)] 232 (14), 155 (32). Anal. Calcd for $C_{16}H_{21}O_6NS_2$: C, 49.60; H, 5.46; N, 3.62. Found: C, 49.54; H, 5.56; N, 3.64.

1-[[4-[4-(Methylphenyl)sulfonyl]-3,4,5,8-tetrahydro-2*H*-1,4-thiazocin-2-yl]acetyl]-1*H*-indole (21). To a solution of **12** (see Supporting Information for preparation; 30.8 mg, 0.0675 mmol) in CH_2Cl_2 (5 mL) was added portionwise a freshly solution of Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide, 27.3 mg, 0.0654 mmol] in CH_2Cl_2 (3 mL). The mixture was stirred at room temperature until TLC indicated the reaction was complete (15 min), at which time solvent was evaporated in vacuo. One milliliter of methanol was added, and the mixture was stirred (1 min) during which time the product was obtained as a white solid (20.0 mg, 67%): mp 177−178.5 °C; ^1H NMR δ 8.39 (d, 1H, J = 7.9 Hz), 7.61 (d, 2H, J = 8.2 Hz), 7.55 (d, 1H, J = 7.3 Hz), 7.40 (d, 1H, J = 3.6 Hz), 7.34−7.26 (m, 4H), 6.65 (d, 1H, J = 3.6 Hz), 5.79 (ddd, 1H, J = 11.3, 7.6, 2.7 Hz), 5.66 (ddd, 11.3, 4.0, 3.7 Hz), 4.37 (dd, 1H, J = 13.1, 8.6 Hz), 4.25 (dd, 1H, J = 17.7, 3.7 Hz), 3.99−3.94 (m, 1H), 3.77 (dd, 1H, J = 13.1, 9.2 Hz), 3.55 (dd, 1H, J = 17.7, 4.0 Hz), 3.36 (dd, 1H, J = 13.1, 2.7 Hz), 3.23−3.17 (m, 2H), 3.04 (dd, 1H, J = 16.4, 8.2 Hz), 2.38 (s, 3H); ^{13}C NMR δ 168.3, 143.9, 135.8, 135.0, 130.6, 130.1, 128.1, 127.3, 125.6, 125.5, 124.5, 124.2, 121.2, 116.7, 110.1, 58.1, 49.4, 38.3, 37.0, 27.2, 21.7; MS [*m*/*z*, rel int)]: 440 (6), 117 (100).

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Supporting Information Available: Full experimental details for preparation of compounds **7**−**12** and **14**−**20** and selective spectroscopic and analytical data for these compounds and copies of ^1H and ^{13}C NMR spectra for compounds **1**−**12** and **14**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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