4.58–4.52 (2 H, m), 3.91 (1 H, s), 3.56–3.50 (1 H, m), 2.27–1.18 (6 H, m).

30: oil; silica gel, 30% EtOAc/hexane, R_f 0.15; m/e, exact mass calcd for $C_{10}H_{12}O_2S$ 196.0555, found 196.0558, error = 1.5 ppm; IR (CCl_4, cm^{-1}) 1735 (C=O); 270-MHz NMR ($CDCl_3$, ppm) 6.62 (1 H, dd, J = 8.5, 6.6 Hz), 6.08 (1 H, d, J = 8.5 Hz), 4.47 (2 H, dd, J = 7.2, 5.3 Hz), 3.75 (1 H, d, J = 2.2 Hz),3.54–3.47 (1 H, m), 2.40–1.31 (6 H, m).

Desulfurization with Deactivated Raney Nickel. General Procedures. Raney Nickel Deactivation. Raney nickel was deactivated as follows: 6 mL of a well-shaken suspension of Raney nickel in absolute ethanol (containing ca. 600 mg of nickel/mL) was placed in a 10-mL round-bottom flask. After the nickel had settled, the ethanol was removed via pipet and replaced with 6 mL of acetone, and the resulting suspension was stirred at room temperature for 2 h (nickel clings to the stir bar). The acetone was removed via pipet and replaced with 6 mL of fresh acetone. One milliliter of a well-shaken (i.e., homogeneous) suspension of deactivated Raney nickel in acetone thus prepared was appropriate for the desulfurization of 0.05 mmol of a given substrate.

Desulfurizations. The substrate in 1 mL of acetone was added to an appropriate amount (1 mL/0.05 mmol of substrate) of the freshly prepared deactivated Raney nickel suspension in acetone. The mixture was stirred at room temperature and monitored by TLC, which usually indicated complete reaction within 1 h. After the disappearance of starting material, the mixture was diluted with ether (1:1) and filtered (Celite) with ether to rinse the residue.

Desulfurization of 25. The bicyclic ketone **25** (20 mg, 0.12 mmol) was desulfurized according to the general procedure. Purification of the crude product by HPLC (12% EtOAc/hexane) gave three eluates: **37** (1.4–2.0 column volumes, 2.9 mg, 17%, 20% based on recovered **25**), **38** (2.0–2.5 column volumes, 4.2 mg, 26%, 30% based on recovered **25**), and **25** (2.5–3.0 column volumes, 2.6 mg).

37: oil; silica gel, 15% EtOAc/hexane, R_f 0.28; m/e, exact mass calcd for $C_9H_{14}O$ 138.1041, found 138.1045, error = 3 ppm; IR (CCl_4, cm^{-1}) 1705 (C=O); 270-MHz NMR ($CDCl_3$, ppm) 5.52–5.21 (2 H, m), 2.90–2.75 (1 H, m), 2.57–1.45 (8 H, m), 1.61 (3 H, dd, J = 6.8, 1.6 Hz).

38: oil; silica gel, 15% EtOAc/hexane, R_f 0.14; m/e, exact mass calcd for $C_9H_{12}O$ 136.0885, found 136.0888, error = 2.2 ppm; IR (CCl_4, cm^{-1}) 1685 (C=O); 270-MHz NMR ($CDCl_3$, ppm) 5.38 (1 H, ddd, J = 16.9, 9.9, 8.1 Hz), 5.15 (1 H, dd, J = 16.9, 1.5 Hz), 4.99 (1 H, dd, J = 9.9, 1.5 Hz), 2.36–1.63 (9 H, m).

General Procedure for Sulfonium Salt Formation and Reduction with Zinc/Acetic Acid. The substrate was dissolved in dimethoxyethane (1 mL/8 mg of substrate) and stirred at room temperature under static nitrogen. Trimethyloxonium tetrafluoroborate (Aldrich, 3 equiv) was added, and the reaction was monitored by TLC; in each case, the substrate had disappeared within 1 h and had been replaced by a baseline spot. Dimethyl sulfide (Aldrich, 1 drop/3 mg of substrate) was added via pipet (quickly removing and replacing the septum/nitrogen inlet), and the mixture was stirred for 5 min. Acetic acid (2 drops/mg of substrate) was added, followed by zinc dust (Fisher, 35 mg/mg of substrate), and the septum was replaced with a caplug. The reaction was monitored by TLC; in each case, the baseline spot disappeared and was replaced by more mobile material(s) within 1 h. The mixture was poured into 50 mL of saturated aqueous $NaHCO_3$/25 mL of saturated aqueous NaCl/25 mL of CH_2Cl_2 and stirred for 10 min. The aqueous layer was extracted with 2 × 20 mL of CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$. Filtration through a 4 × 2 cm plug of silica gel, rotary evaporation, and evacuation gave crude product, which was purified by HPLC (Magnum 9 column, 4:1:1 hexane/CH_2Cl_2/ether).

Sulfide 31. The bicyclic ketone **25** (25 mg, 0.15 mmol) was alkylated and reduced according to the general procedure (vide supra). HPLC purification gave the sulfide **31** (16.5 mg, 60%) eluting at 1.8–2.1 column volumes. **31**: oil; silica gel, 7:1:2 hexane/CH_2Cl_2/ether; m/e, base = 136 amu, exact mass calcd for $C_{10}H_{16}OS$ 184.0918, found 184.0929, error = 6 ppm; IR (CCl_4, cm^{-1}) 1710 (C=O); 270-MHz NMR ($CDCl_3$, ppm) 5.49–5.37 (2 H, m), 3.12 (2 H, d, J = 6.5 Hz), 2.86–2.74 (1 H, m), 2.40–2.01 (4 H, m), 2.05 (3 H, s), 1.85–1.40 (4 H, m).

Sulfides 33a,b and 34. The tricycles **29** + **30** (16 mg, 82 μmol) were alkylated and reduced according to the general procedure. HPLC purification gave two eluates: **33a** (2.0 mg, 12%, 1.5–1.8 column volumes) and an inseparable mixture of **33b** and **34** (8.9 mg, 51% combined yield, 1.8–2.1 column volumes). **33a**: oil; silica gel, 7:1:2 hexane/CH_2Cl_2/ether, R_f 0.35; m/e, base = 107 amu, exact mass calcd for $C_{11}H_{16}O_2S$ 212.0867, found 212.0878, error = 5.2 ppm; IR (CCl_4 cm^{-1}) 1735 (C=O); 270-MHz NMR ($CDCl_3$, ppm) 5.83 (1 H, dt, J = 9.9, 3.7 Hz), 5.59 (1 H, br d, J = 9.9 Hz), 4.62–4.37 (2 H, m), 3.16 (1 H, d, J = 1.2 Hz), 2.25 (3 H, s), 2.14–1.94 (4 H, m), 2.87–1.61 (4 H, m).

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Synthesis of Azocine Derivatives from Thioaldehyde Diels–Alder Adducts

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Nitrogen-containing phenacyl sulfides **1** or **2** can be readily cleaved to thioaldehydes that are trapped by electron-rich dienes to give the adducts **4**, **5**, **11**, or **17**. The adducts have electrophilic character α to sulfur and can be converted into structures having new C–N bonds at the α-carbon. Thus, **4** leads to lactam **6** by S to N acyl transfer. A similar reaction occurs from **15** to the eight-membered **16**. Internal addition of amine nitrogen to Danishefsky diene adducts **11**, **17**, or **26** affords bicyclic aminals which are converted into azocine derivatives upon desulfurization. Stable structures such as **24**, **25**, and **31** are prepared in this way. The unusual enaminone **20** is not stable and rearranges upon attempted purification to **21**.

Previous reports from this laboratory have detailed the synthesis of 6–13-membered sulfur rings and their conversion into medium ring lactones (eq 1) by acyl transfer.[1,2]

The most difficult rings to prepare in this study were the eight-membered lactones (eq 1, 2). While other ring sizes were readily accessible by S to O acyl transfer (hydroxyalkyl thiolactone to mercaptoalkyl lactone), the two different approaches to eight-membered lactones (Figure 1) resulted in an equilibrium between product and starting material. The least favorable case (eq 1) was further complicated by the competing formation of diolides.[1]

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0022-3263/88/1953-2226$01.50/0

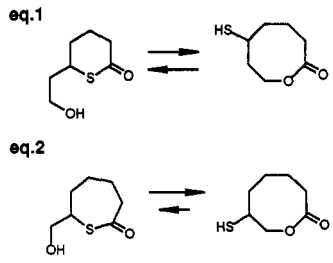

Figure 1.

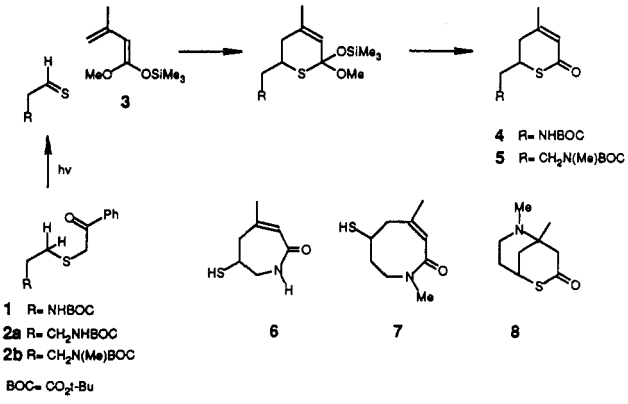

Figure 2.

The initial aim of the present study was to demonstrate that the nitrogen analogue of the acyl transfer process would be better suited for the synthesis of the most demanding eight-membered ring system. This effort has been extended to other methods of nitrogen incorporation which take advantage of 6-membered sulfides, readily obtained via thioaldehyde cycloaddition techniques.[3]

The thioaldehyde Diels–Alder approach provided rapid access to unsaturated thiolactones as shown in Figure 2. Photochemical thioaldehyde generation from 1 in the presence of ketene acetal **3** gave an unstable ortho lactone, and chromatography produced the thiolactone **4**. Similarly, the homologue **5** was obtained from **2a** (50–55% yield). Upon treatment with iodotrimethylsilane to cleave the *N*-BOC group, **4** was converted into the seven-membered lactam **6** (56% isolated). However, the same sequence starting from **5** did not result in the eight-membered lactam **7**. Instead, this produced the bicyclic thiolactone **8** derived from internal Michael addition to the conjugated double bond. The Michael product was isolated after conversion to the acetamide (56% isolated).

Attempts to influence the result in the reaction of **5** failed. So did the obvious alternative of reducing the unsaturated thiolactone to a saturated analogue that would be incapable of the undesired side reaction. However, it was still of interest to establish whether or not the key acyl transfer step would occur. For this reason, a longer route was developed to a saturated thiolactone (Figure 3).

Once again, a thioaldehyde-based route was employed, but the trapping agent was the dienyl sulfide **9**. This diene did not trap the photochemically generated thioaldehyde BOC-NH$(CH_2)_2$CH=S in practical yield. However, the thioaldehyde–cyclopentadiene adduct **10** was easily obtained (93%) from photochemical generation.[3] As described in other publications from our laboratory and elsewhere,[4] thermolysis of cyclopentadiene adducts can be

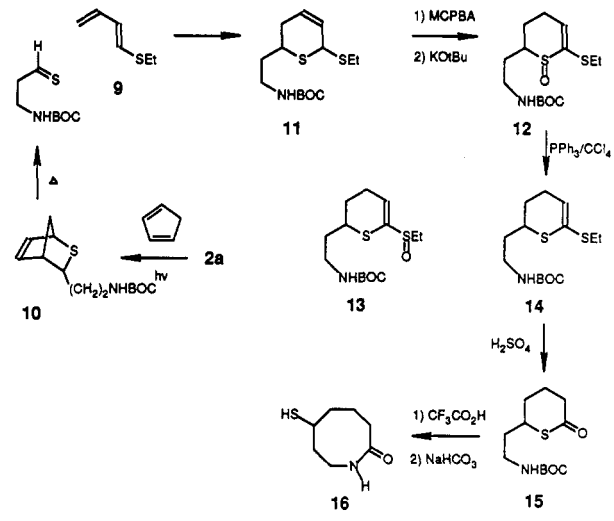

Figure 3.

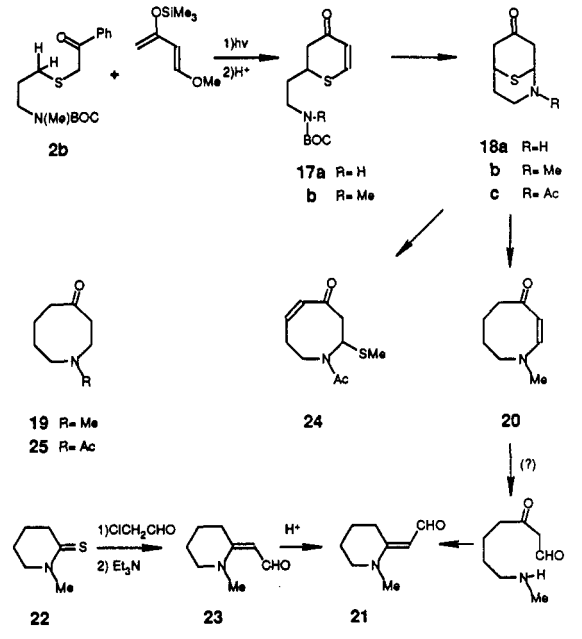

Figure 4.

a practical alternative source of thioaldehydes when the desired diene trapping agent is photochemically sensitive, or when it is relatively unreactive. In the present example, heating **9** with **10** at 140 °C afforded the adduct **11** in an exceptional yield of 99%.

Oxidation of **11** to sulfoxides followed by base-induced isomerization to the more stable ketene thioacetal monooxides **12** + **13** and, finally, sulfoxide reduction (PPh_3/CCl_4) produced the ketene thioacetal **14** in ca. 50% overall yield. Treatment of **14** with sulfuric acid then gave a mixture of hydrolysis products including the desired thiolactone **15** (22%) as well as ring cleavage products. No attempt was made to optimize this transformation.

With the saturated thiolactone **15** finally in hand, S to N acyl transfer was readily demonstrated. Cleavage of the BOC group with trifluoroacetic acid (TFA) and neutralization of amine salts with bicarbonate resulted in spontaneous formation of mercapto lactam **16** (92%). To establish the structure, we converted **16** into the parent

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(4) Vedejs, E.; Stults, J. S.; Wilde, R. G. *J. Am. Chem. Soc.*, submitted. Bladon, C. M.; Ferguson, I. E. G.; Kirby, G. W.; Lochead, A. W.; McDougal, D. C. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1541.

lactam by desulfurization with Ra-Ni. As expected from the much greater stability of an amide relative to the isomeric thiol ester in acyclic examples,[5] there was no sign of an equilibrium concentration of six-membered thiolactone in the acyl transfer experiment. This is in contrast to the analogous S to O acyl transfer process where there is no clear advantage for either the six-membered thiolactone or the eight-membered lactone (eq 1).[1]

The facile Michael addition encountered in Figure 2 suggested alternative approaches to azocine derivatives from thioaldehyde Diels–Alder adducts (Figure 4). Adducts **17** of the Danishefsky diene are easy to prepare from the photochemically generated phenacyl sulfide **2**, and it was expected that deprotection would afford internal Michael adducts **18** which could be easily desulfurized. No problems were encountered in this strategy, but the desulfurization experiments proved more subtle than expected.

Deprotection of **17b** afforded **18b** in 95% yield. However, the attempted desulfurization with Ra-Ni did not produce the expected **19** in observable quantity. Instead, this experiment formed an unstable, sulfur-free product containing an unusual double bond (^{1}H NMR: doublets at 6.51 and 4.58 ppm, J = 9.4 Hz) in high yield. The spectral data are consistent with the enaminone structure **20**, but attempts to isolate the pure substance or to convert it by hydrogenation into **19** failed. Upon exposure to silica gel, **20** rearranged to a stable isomer **21**. The enaminal structure was readily assigned from the spectral data (doublets at 9.57 and 5.09 ppm, J = 8.5 Hz), but our confidence was temporarily shaken when the Eschenmoser sulfur extrusion synthesis[6] from thiolactam **22** + $ClCH_2$-CHO (eq 3) gave a different substance. This material proved to be the less stable isomer **23** (65%), and treatment of **23** with toluenesulfonic acid resulted in conversion to **21** (87%). A recent paper reports the isolation of enaminone **20** and related compounds from an unusual transformation of N-methyl lactams.[7,8] However, the published spectral data[7] are in better agreement with our data for the more stable enaminal **21**.

The unusual conversion from **18b** to **20** can be attributed to residual strong base in the Raney nickel. It is surprising that **20** could not be hydrogenated to the saturated ketone **19** and somewhat unusual that **20** is so sensitive. Enaminones are normally stabilized by vinylogous amide delocaliation, but this would require four sp^2 centers in a planar geometry that the eight-membered ring environment cannot easily tolerate. Apparently, **20** more closely resembles an enamine than a vinylogous amide. Conversion to **21** probably involves the facile hydrolysis to a β-keto aldehyde intermediate and rapid reclosure (Figure 4).

A viable route to stable derivatives of the azocine ring system was realized by starting from the Danishefsky diene–thioaldehyde adduct **17a**. Deprotection gave an unstable bicyclic aminal **18a**, but treatment with acetic anhydride afforded the N-acyl analogue **18c** in 85% yield. With nitrogen protected, it was possible to demonstrate a stepwise cleavage of carbon–sulfur bonds in a way that preserves functionality. Thus, treatment of **18c** with methyl triflate followed by collidine produced the enone **24** (40%). Complete desulfurization as well as double-bond reduction occurred upon Ra-Ni treatment of **24** and gave the saturated ketone **25** (70%).

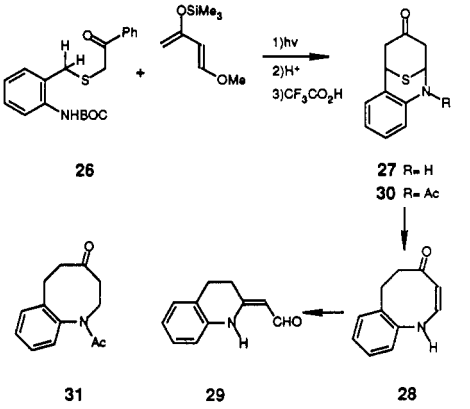

Figure 5.

An analogous series of experiments was performed by using an ortho-substituted thiobenzaldehyde adduct **26** (Danishefsky diene trapping) (Figure 5). Deprotection gave a mixture in which the intermediate amine could be detected, but prolonged treatment resulted in the bicyclic **27**. In contrast to the aliphatic series, **27** was stable enough to isolate, but in other respects the two series proved similar. Treatment with Ra-Ni gave the enaminal **29** (50%), presumably via an unstable enaminone **28**. Acylation of **27** afforded **30**, which could be desulfurized with Ra-Ni to the saturated benzazocine derivative **31** (43%).

In conclusion, several routes from thioaldehyde Diels–Alder adducts to eight-membered nitrogen-containing rings have been demonstrated. Applications of these methods to more complex synthetic problems will be described in future publications.

Experimental Section

Sequence to Phenyl Sulfide 1. *N*-(*tert*-Butoxycarbonyl)-2-bromoethylamine. 2-[(*tert*-Butoxycarbonyl)-amino]-1-ethanol (3.1 g, 21 mmol)[9] and triphenylphosphine (Aldrich, 7.3 g, 28 mmol) were dissolved in THF (75 mL). Carbon tetrabromide (Aldrich, 9.25 g, 28 mmol) in acetonitrile (30 mL) was added at such a rate that the reaction temperature was only slightly above ambient. The reaction mixture was stirred for 6 h, and the solvent was removed at reduced pressure. The residue was purified by column chromatography on silica gel (150 g, 20% ethyl acetate/hexane) to give the title compound, 3.0 g (70%): oil; silica gel 60, 20% ethyl acetate/hexane, R_f 0.1; m/e, no peak match, parent, (M – ^{79}Br), 223.0209, calcd 223.0209, error 0.00 ppm, formula $C_7H_{14}O_2BrN$; IR (neat, cm^{-1}) 3352 (NH), 1710 (CO); 200-MHz NMR ($CDCl_3$, ppm) 5.0 (1 H, br s), 3.50–3.30 (4 H, m), 1.42 (9 H, s).

***N*-(*tert*-Butoxycarbonyl)-2-(acetylthio)ethylamine.** N,N-Diisopropylethylamine (Aldrich, 3.7 mL, 21.2 mmol) was added to thiolacetic acid (Aldrich, 1.5 mL, 21.0 mmol) in acetonitrile (30 mL) followed by the bromide from above (3.0 g, 13.5 mmol). The reaction mixture was heated at 53 °C overnight and cooled to room temperature and the solvent removed under reduced pressure to give a red oil. The residue was purified by column chromatography on silica gel (100 g, 25% ether/hexane) to give 2.6 g (88%) of the thiolacetate: oil; silica gel 60, ether, R_f 0.60; m/e, base = 57 amu; exact mass calcd for $C_9H_{17}O_3NS$ 219.0925, found 219.0929, error = 1.8 ppm; IR (neat, cm^{-1}) 1690 (CO), 3360 (NH); 200-MHz NMR ($CDCl_3$, ppm) 4.88 (1 H, br s), 3.24 (2 H, dt, J = 6.5, 6.4 Hz), 2.96 (2 H, t, J = 6.5 Hz), 2.29 (3 H, s), 1.39 (9 H, s).

Phenacyl Sulfide 1. The thiol ester from above (0.88 g, 4.0 mmol) was dissolved in methanol (10 mL), and a solution of sodium methoxide (223 mg, 4.0 mmol) in methanol (3 mL) was

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(6) Roth, M.; Dubs, P.; Gotschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710. Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539.
(7) Suzuki, K.; Ohkuma, T.; Tsuchihashi, G. *J. Org. Chem.* **1987**, *52*, 2929.
(8) We thank a referee for bringing this work (ref 7) to our attention.
(9) Stults, J. S. Ph.D. Dissertation, University of Wisconsin, 1986.

added. The reaction mixture was stirred for 15 min, and then a solution of phenacyl chloride (Aldrich, 530 mg, 4.0 mmol) in THF (10 mL) was added. After an additional 3 h, the solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel (40 g, 1:1 ethyl acetate/hexane) to give **1**, 1.0 g (85%): oil; silica gel 60, 50% ethyl acetate/hexane, R_f 0.2; *m/e*, base = 105 amu, exact mass calcd for $C_{15}H_{21}O_3NS$ 295.1237, found 295.1241, error = 1.3 ppm; IR ($CDCl_3$, cm^{-1}) 3360 (NH), 1700 (CO), 1670 (CO); 200-MHz NMR ($CDCl_3$, ppm) 8.00–7.90 (2 H, m), 7.60–7.40 (3 H, m), 5.02 (1 H, br s), 3.82 (2 H, s), 3.38 (2 H, dt, J = 7.5, 5.7 Hz), 2.67 (2 H, t, J = 7.5 Hz), 1.42 (9 H, s).

Sequence to Phenacyl Sulfides 2. *N*-(*tert*-Butoxycarbonyl)-3-(acetylthio)propylamine. Thiolacetic acid (Aldrich, 2.3 mL, 32 mmol) was dissolved in acetonitrile (75 mL) at 0 °C, and Hunig's base (Aldrich, 6.1 mL, 35 mmol) was added dropwise. The salt was stirred for 5 min, and then a solution of 1-[(*tert*-butoxycarbonyl)amino]-3-bromopropane[9] (6.0 g, 27 mmol) in acetonitrile (50 mL) was added dropwise at 0 °C. After addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for an additional $1^1/_2$ h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (250 g, 33% ether/hexane) to give an oil, which solidified in the freezer and which was used without further purification, 5.87 g (100%): IR (neat, cm^{-1}) 3350 (NH), 1700 (CO), 1680 (COS); 200-MHz NMR ($CDCl_3$, ppm) 4.83 (1 H, br s), 3.09 (2 H, dt, J = 6.5, 6.5 Hz), 2.84 (2 H, t, J = 7.0 Hz), 2.26 (3 H, s), 1.69 (2 H, tt, J = 7.0, 6.5 Hz), 1.37 (9 H, s).

Phenacyl Sulfide 2a. Thiol ester from the preceding experiment (5.60 g, 25.6 mmol) was dissolved in ether (100 mL) at 0 °C. A solution of sodium hydroxide (2.48 g, 61.4 mmol) and tetrabutylammonium hydroxide (Aldrich, 0.1 mL) was added, and the solution was vigorously stirred for 18 h. The reaction was quenched by the addition of 1 N sulfuric acid (32 mL). The aqueous phase was extracted with ether (2 × 100 mL), and the combined extracts were dried (magnesium sulfate). The solvent was removed under reduced pressure and replaced by THF (30 mL). Hunig's base (Aldrich, 7.1 g, 55 mmol) and phenacyl chloride (Aldrich, 3.98 g, 25.7 mmol) were added. The reaction mixture was stirred for 2 h at room temperature, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (150 g, 25% ether/hexane to remove phenacyl chloride followed by 50% ether/hexane) to give **2a**, 7.5 g (94%); solid, mp 43–44 °C (crystallized from ether/hexane); *m/e*, base = 105 amu, exact mass calcd for $C_{16}H_{23}O_3NS$ 309.1393, found 309.1398, error = 1.6 ppm; IR (neat, cm^{-1}) 1710 (CO), 3390 (NH), 1680 (CO); 200-MHz NMR ($CDCl_3$, ppm) 8.00–7.36 (5 H, m), 4.66 (1 H, br s), 3.77 (2 H, s), 3.17 (2 H, dt, J = 6.4, 6.4 Hz), 2.56 (2 H, t, J = 7.2 Hz), 1.76 (2 H, tt, J = 7.2, 6.4 Hz), 1.40 (9 H, s).

Sequence to 2b. *N*-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsiloxy)propylamine. 3-[(*tert*-Butoxycarbonyl)-amino]-1-propanol[9] (20.0 g, 124 mmol) was dissolved in DMF (50 mL), and *tert*-butyldimethylchlorosilane (Petrarch, 24.4 g, 162 mmol) followed by imidazole (Aldrich, 21.1 g, 300 mmol) was added. The solution was stirred overnight, poured into water (500 mL), and extracted with ether/pentane (1:1) (3 × 300 mL). The combined organic extracts were dried, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (500 g, 20% ethyl acetate/hexane) to give the silyl ether, 29.5 g (86%): oil; silica gel 60, 20% ethyl acetate/hexane, R_f 0.1; IR (neat, cm^{-1}) 1700 (CO); 100-MHz NMR ($CDCl_3$, ppm) 5.1 (1 H, br s), 3.64 (2 H, t, J = 6.0 Hz), 3.16 (2 H, t, J = 6.5 Hz), 1.80–1.60 (2 H, m), 1.44 (9 H, s), 0.92 (9 H, s), 0.04 (6 H, s).

***N*-(*tert*-Butoxycarbonyl)-*N*-methyl-3-(*tert*-butyldimethylsiloxy)propylamine.** Sodium hydride (Alfa, 5.6 g, 122 mmol) was washed with ether (3 × 10 mL) and covered with THF (250 mL). A solution of the silyl ether from above (26.9 g, 97.2 mmol) in THF (250 mL) was added dropwise. The solution was stirred for 30 min, methyl iodide (Aldrich, 20.0 mL, 320 mmol) was added, and the reaction mixture was stirred overnight. The reaction was carefully quenched by addition of citric acid (1 M, 100 mL in water) followed by aqueous sodium thiosulfate (saturated, 100 mL). The aqueous phase was extracted with ether (3 × 200 mL), and the ether layer was dried (magnesium sulfate) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (400 g, 1:1 ether/hexane) to give the *N*-methyl product, 12.4 g (67%): oil; silica gel 60, 50% ether/hexane, *Rf* 0.68; IR (CCl_4, cm^{-1}) 1700 (CO); 100-MHz NMR ($CDCl_3$, ppm) 3.58 (2 H, t, J = 7.0 Hz), 3.22 (2 H, t, J = 7.0 Hz), 2.88 (3 H, s), 1.90–1.60 (2 H, m), 1.48 (9 H, s), 0.90 (9 H, s), 0.02 (6 H, s).

***N*-(*tert*-Butoxycarbonyl)-*N*-methyl-3-hydroxypropylamine.** The N-methylated silyl ether from above (1.93 g, 6.65 mmol) was dissolved in THF (5 mL), tetrabutylammonium fluoride (Aldrich, 25 mmol, 1 M in THF) was added, and the reaction mixture was stirred for 30 min. The reaction mixture was poured into aqueous citric acid (1 M, 25 mL) and extracted with ether (3 × 25 mL). The combined organic extracts were dried (magnesium sulfate) and evaporated (aspirator), and the residue was purified by column chromatography on silica gel (40 g, ether) to give the alcohol, 1.22 g (96.8%), sufficiently pure for the next step.

***N*-(*tert*-Butoxycarbonyl)-*N*-methyl-3-chloropropylamine.** The alcohol from the previous experiment (1.3 g, 6.9 mmol) was dissolved in carbon tetrachloride (10 mL), and tributylphosphine (Aldrich, 5.1 g, 25 mmol) was added dropwise. After 15 min, the reaction mixture was poured directly on silica gel (30 g, eluted with 50% ether/hexane). The liquid was further purified by distillation to give the chloride, 1.37 g (96%): bp 80–115 °C at 0.3 mm, Kugelrohr; *m/e*, base = 57 amu, exact mass calcd for $C_9H_{18}O_2ClN$ 207.1022, found 207.1027, error = 2.5 ppm; IR (CCl_4, cm^{-1}) 1700 (CO); 200-MHz NMR ($CDCl_3$, ppm) 3.48 (2 H, t, J = 6.6 Hz), 3.30 (2 H, t, J = 6.7 Hz), 2.81 (3 H, s), 1.93 (2 H, tt, J = 6.7, 6.6 Hz), 1.40 (9 H, s).

***N*-(*tert*-Butoxycarbonyl)-*N*-methyl-3-(acetylthio)-propylamine.** Thiolacetic acid (Aldrich, 7.2 g, 93 mmol) was dissolved in acetonitrile (125 mL). Triethylamine (9.6 g, 96 mmol) was carefully added followed by a solution of the chloride from above (8.7 g, 42 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature for 30 min and then heated at 40 °C overnight. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (120 g, 1:1 ether/hexane) to give the thiolacetate, 9.75 g (94%): oil; silica gel 60, 50% ether/hexane, R_f 0.37; *m/e*, base = 57 amu, exact mass calcd for $C_{11}H_{21}O_3NS$ 247.1237, found 247.1241, error = 1.7 ppm; IR (neat, cm^{-1}) 1700 (CO), 1680 (COS); 200-MHz NMR ($CDCl_3$, ppm) 3.14 (2 H, t, J = 7.0 Hz), 2.82 (3 H, s), 2.81 (2 H, t, J = 6.9 Hz), 2.30 (3 H, s), 1.77 (2 H, tt, J = 7.0, 6.9 Hz), 1.44 (9 H, s).

Phenacyl Sulfide 2b. The thiol ester from the previous experiment (1.8 g, 7.3 mmol) was dissolved in methanol (30 mL), and potassium carbonate (Aldrich, 2.0 g, 14 mmol) was quickly added. The suspension was stirred for 30 min, and phenacyl chloride (Aldrich, 1.13 g, 7.3 mmol) was added. The reaction mixture was stirred for an additional 30 min, the solvent was removed under reduced pressure, and the organic residue was purified by HPLC (10% ethyl acetate/hexane, 1.2 column volumes) to give **2b**, 2.05 g (87%), oil: *m/e*, base = 57 amu, exact mass calcd for $C_{17}H_{25}O_3NS$ 323.155, found 323.1555, error = 1.7 ppm; IR (neat, cm^{-1}) 1698 (CO), 1670 (CO); 200-MHz NMR ($CDCl_3$, ppm) 8.00–7.40 (5 H, m), 3.78 (2 H, s), 3.25 (2 H, q, J = 6.8 Hz), 2.80 (3 H, s), 2.54 (2 H, t, J = 7.4 Hz), 1.79 (2 H, tt, J = 7.4, 6.8 Hz), 1.42 (9 H, s).

Thiolactone 4. Sulfide **1** (1.0 g, 3.3 mmol) and diene **3** (8.1 equiv) were dissolved in benzene (250 mL) and irradiated for 14.5 h by using the sun-lamp apparatus as previously described.[3] The solvent was removed under reduced pressure and excess diene recovered by distillation [bulb-to-bulb, 30 °C (0.3 Torr)]. The residue was purified by column chromatography on silica gel (50 g, 20% ethyl acetate/hexane) to give **4**, 0.39 g (45%): oil; silica gel 60, 50% ether/hexane, R_f 0.20; *m/e*, IR (neat, cm^{-1}) 3260 (NH), 1715 (CO), 1650 (COS), 200-MHz NMR ($CDCl_3$, ppm) 5.96 (1 H, q, J = 1.6 Hz), 4.92 (1 H, br s), 3.7–3.2 (3 H, m), 2.65 (1 H, dd, J = 17.7, 4.7 Hz), 2.44 (1 H, dd, J = 17.7, 7.2 Hz), 1.98 (3 H, d, J = 1.6 Hz), 1.41 (9 H, s).

Thiolactone 5. Sulfide **2b** (400 mg, 1.23 mmol) and 1-methoxy-1-(trimethylsiloxy)-3-methylbutadiene[10] (2.0 g, 10.7 mmol)

(10) Casey, C. P.; Jones, C. R.; Tukada, H. *J. Org. Chem.* **1981**, *46*, 2089.

were dissolved in benzene (100 mL), and the reaction mixture was photolyzed for 7 h as before. The benzene was removed under reduced pressure, and excess diene was recovered by distillation [bulb-to-bulb, 30 °C (0.01 torr)]. The residue was purified by column chromatography on silica gel (10 g, 1:1 ether/hexane) to give **5**, 195 mg (55%).

4-Methyl-6-mercapto-2,5,6,7-tetrahydro-2-oxo-1*H*-azepine (6). Thiolactone **4** (20 mg, 0.08 mmol) was dissolved in acetonitrile (0.3 mL). Trimethylsilyl iodide (Aldrich, 0.086 mmol, 12.3 μL) was added. After 15 min, methanol (0.1 mL) was added and the solution stirred in the dark overnight. The solvents were removed under reduced pressure, and the residue was purified by PTLC (10% methanol/chloroform) to give **6**, 6.9 mg (56%): oil; silica gel 60, 10% methanol/chloroform, R_f 0.32; IR ($CDCl_3$, cm^{-1}) 3410 (NH), 1654 (CON); 200-MHz NMR ($CDCl_3$, ppm) 6.36 (1 H, br s), 5.79 (1 H, br s), 3.60–3.20 (3 H, m), 2.81 (1 H, dd, J = 15.7, 6.4 Hz), 2.41 (1 H, dd, J = 15.7, 6.4 Hz), 1.96 (3 H, d, J = 1.2 Hz), 1.69 (1 H, d, J = 7.8 Hz).

Bicyclic Thiolactone 8. Thiolactone **5** (5.3 mg, 0.019 mmol) was dissolved in methylene chloride (0.1 mL), and trifluoroacetic acid (0.1 mL) was added. The reaction mixture was stirred for 5 min, and then the solvents were removed under reduced pressure. THF (5 mL) and triethylamine (0.1 mL) were added, and the suspension was stirred for 6 h. Acetic anhydride (0.1 mL) and triethylamine (0.1 mL) were added, and the solution was stirred overnight. The solvents were removed under reduced pressure to give a residue, which was purified by column chromatography on silica gel (pipet, ethyl acetate) to give **8**, 2.1 mg (56%): oil; R_f 0.37; m/e, exact mass calcd for $C_{10}H_{15}O_2NS$ 213.082, found 213.0824, error = 1.9 ppm; IR ($CDCl_3$, cm^{-1}) 1660 (CO); 200-MHz NMR ($CDCl_3$, ppm) 4.12 (1 H, dd, J = 17.7, 2.0 Hz), 3.76 (1 H, dt, J = 4.6, 3.5 Hz), 3.60–3.30 (2 H, m), 2.28–2.16 (4 H, m), 2.09 (3 H, s), 2.01 (1 H, dd, J = 14.3, 3.5 Hz), 1.57 (3 H, s).

Cyclopentadiene Adduct 10. Sulfide **2a** (1.41 g, 4.56 mmol) and cyclopentadiene (9.0 mL, 30 equiv) in benzene (150 mL) were divided into six flasks and photolyzed[3] in groups of three until the starting sulfide was completely consumed. The solvent and excess cyclopentadiene were evaporated under reduced pressure and the combined residues purified by column chromatography on silica gel (100 g, 20% ethyl acetate/hexane) to give **10** as a 4.4:1 mixture of endo/exo isomers, which was used without further purification, 1.09 g (93%): IR ($CDCl_3$, cm^{-1}) 3450 (NH), 1700 (CO); 200-MHz NMR (C_6D_6, ppm) endo (major) 6.13 (1 H, dd, J = 5.5, 2.9 Hz), 5.46 (1 H, dd, J = 5.5, 3.1 Hz), 4.07 (1 H, br s), 3.60–2.56 (1 H, m), 3.45 (1 H, ddd, J = 3.8, 3.5, 3.3 Hz), 3.02 (2 H, dt, J = 6.8, 6.6 Hz), 2.91–2.85 (1 H, m), 1.82–1.20 (4 H, m), 1.48 (9 H, s), exo (minor) 6.05 (1 H, dd, J = 5.5, 3.3 Hz), 5.59 (1 H, dd, J = 5.5, 3.2 Hz), 4.07 (1 H, br s), 3.66–3.62 (1 H, m), 3.22–3.00 (1 H, m), 3.02 (2 H, dt, J = 6.8, 6.6 Hz), 2.60–2.55 (1 H, m), 1.82–1.20 (4 H, m), 1.48 (9 H, s).

Dienyl Sulfide Adduct 11. Cyclopentadiene adduct **10** (110 mg, 0.43 mmol) and 1-(ethylthio)butadiene (0.56 g, 4.9 mmol) were dissolved in xylene (5 mL) and degassed at −78 °C. The reaction mixture was heated overnight at 140 °C. The solvent and excess diene were removed under reduced pressure, and the residue was purified by column chromatography on silica gel (10 g, 20% ethyl acetate/hexane) to give **11** as a 1.8:1 ratio of diastereomers, 130 mg (99%).

Sulfoxides 12 and 13. Sulfide **11** (500 mg, 1.65 mmol) was dissolved in methylene chloride (5 mL) and cooled to −78 °C. *m*-Chloroperoxybenzoic acid (*m*CPBA) (1.65 mmol, 3.77 mL in methylene chloride) was added all at once. The solution was stirred for 5 min, dimethyl sulfide (Aldrich, 0.1 mL) was added, and the solution was allowed to warm to room temperature. The methylene chloride was poured into an aqueous solution of sodium bicarbonate (10 mL, 10%), the aqueous phase was extracted with methlene chloride (3 × 15 mL), and the combined organic extracts were dried (magnesium sulfate) and evaporated under reduced pressure. Purification by rapid filtration chromatography on silica gel (7 g, ethyl acetate) gave a mixture of sulfoxides, 390 mg (75%), sufficiently pure for the double bond isomerization step. The sulfoxides (280 mg, 0.88 mmol) were dissolved in *tert*-butyl alcohol (4 mL), and potassium *tert*-butoxide (Alfa, 0.64 M in THF, 0.1 mL) was added. The solution was stirred overnight and diluted with water (5 mL), and the aqueous phase was extracted with methylene chloride (3 × 5 mL). The combined organic extracts were dried (magnesium sulfate) and evaporated (aspirator), and the residue was purified on silica gel (5 g, 10% methanol/chloroform) to give isomerized sulfoxides **12**, 32 mg (13%), and **13**, 128 mg (51%).

12: diastereomer mixture; oil, silica gel 60, 10% methanol/chloroform, R_f 0.25; m/e, base = 246 amu, exact mass calcd for $C_{14}H_{25}O_3NS_2$ 319.127, found 319.1274, error = 1.2 ppm; IR ($CDCl_3$, cm^{-1}) 1060 (SO); 200-MHz NMR ($CDCl_3$, ppm) 6.52 (0.5 H, dd, J = 4.3, 4.3 Hz), 6.41 (0.5 H, dd, J = 4.4, 4.4 Hz), 4.92 (0.5 H, br s), 4.70 (0.5 H, br s), 3.34–3.18 (3 H, m), 3.02–2.68 (3 H, m), 2.46–2.32 (2 H, m), 1.94–1.70 (3 H, m), 1.41 (9 H, s), 1.0–0.8 (3 H, m).

13: oil; silica gel 60, ethyl acetate, R_f 0.02; m/e, base = 246 amu, exact mass calcd for $C_{14}H_{25}O_3NS_2$ 319.127, found 319.1274, error = 1.2 ppm; IR ($CDCl_3$, cm^{-1}) 1710 (CO), 3450 (NH), 1050 (SO); 200-MHz NMR ($CDCl_3$, ppm) 6.42 (1 H, dd, J = 4.4, 4.2 Hz), 5.63 (1 H, br s), 3.38–3.18 (3 H, m), 2.98–2.72 (3 H, m), 2.46–2.38 (2 H, m), 2.28–2.12 (1 H, m), 1.98–1.72 (2 H, m), 1.42 (9 H, s), 1.20 (3 H, t, J = 7.2 Hz).

Reduction of Sulfoxides. Conversion to 14. Sulfoxides **12** and **13** (84.7 mg, 0.266 mmol) were dissolved in carbon tetrachloride (10 mL). Triphenylphosphine (209 mg, 0.80 mmol) was added, and the solution was refluxed for 4 h. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel (10% ethyl acetate/hexane) to give **14**, 60 mg (75%): oil; silica gel 60, 25% ethyl acetate/hexane, R_f 0.29; m/e, exact mass calcd for $C_{14}H_{25}O_2NS_2$ 303.1321, found 303.1334, error = 4.2 ppm; IR ($CDCl_3$, cm^{-1}) 1695 (CO); 270-MHz NMR ($CDCl_3$, ppm) 6.04 (1 H, dd, J = 4.4, 4.2 Hz), 4.59 (1 H, br s), 3.30–3.08 (3 H, m), 2.73 (2 H, qd, J = 7.4, 1.5 Hz), 2.30–2.23 (2 H, m), 1.87–1.66 (4 H, m), 1.42 (9 H, s), 1.22 (3 H, t, J = 7.4 Hz).

Hydrolysis to Thiolactone 15. Ketene thioacetal **14** (26.5 mg, 0.087 mmol) was dissolved in THF (3 mL), and sulfuric acid (1 N, 23 drops) was added. After 4 h, starting material remained and an additional amount of sulfuric acid (1 N, 23 drops) was added. After the reaction mixture was stirred for an additional 4 h, the solution was adjusted to pH 7 with 10% aqueous sodium bicarbonate, the aqueous phase was extracted with methylene chloride (3 × 10 mL), the combined extracts were dried (magnesium sulfate), and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (25% ethyl acetate/hexane) and gave two fractions. The less polar (R_f 0.5, 6.9 mg) was not identified while the next fraction (5 mg; 22%) proved to be thiolactone **15**: oil; silica gel 60, 25% ethyl acetate/hexane, R_f 0.16; m/e, base = 116 amu, exact mass calcd for $C_{12}H_{22}O_3NS$ 260.1315, found 260.1301, error = 5.4 ppm; IR ($CDCl_3$, cm^{-1}) 3440 (NH), 1710 (CO), 1670 (COS), 200-MHz NMR ($CDCl_3$, ppm) 4.46 (1 H, br s), 3.50–3.38 (1 H, m), 3.18–3.01 (2 H, m), 2.61–2.30 (2 H, m), 2.20–1.50 (7 H, m), 1.33 (9 H, s). Further elution of the column with 10% methanol/chloroform gave a fraction (8.8 mg) containing carboxylic acids from ring cleavage.

Mercapto Lactam 16. Thiolactone **15** (2.1 mg, 0.008 mmol) was dissolved in methylene chloride (0.3 mL). Trifluoroacetic acid (1.0 mL) was added and the solution stirred for 5 min. The solvents were removed under reduced pressure, and methylene chloride (5 mL) and water (2 mL) were added. The pH was adjusted to 7 (sodium bicarbonate), and the solution was allowed to stand for 1 h and then was extracted with methylene chloride (2 × 2 mL). The combined extracts were dried (magnesium sulfate) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (10% methanol/chloroform) to give **16**, 1.2 mg (92%): oil; silica gel 60, 10% methanol/chloroform, R_f 0.37; m/e, exact mass calcd for $C_7H_{13}ONS$ 159.0715, found 159.0716, error = 0.6 ppm; IR ($CDCl_3$, cm^{-1}) 1660 (CON); 270-MHz ($CDCl_3$, ppm) 5.56 (1 H, br s), 3.54–3.40 (0.5 H, m), 3.36–3.24 (2 H, m), 3.11–2.99 (0.5 H, m), 2.48–2.36 (2 H, m), 2.12–1.70 (6 H, m), 1.71 (1 H, d, J = 6.0 Hz).

2-[2-[(*tert*-Butoxycarbonyl)amino]ethyl]-3,4-dihydro-2*H*-thiopyran-4-one (17a). Sulfide **2a** (300 mg, 0.97 mmol) and Danishefsky's diene (1.33 g, 7.7 mmol, Aldrich) were dissolved in benzene (80 mL), and the solution was irradiated for 5 h. The benzene was removed under reduced pressure and the excess diene recovered (bulb-to-bulb distillation). The residue was purified by column chromatography on silica gel (30 g, 1:1 ether/hexane)

to give **17a**, 165 mg (66%). An increase to 13.5 equiv of diene gave an 83% yield of cycloadduct.

17a: oil, silica gel 60, 50% ether/hexane, R_f 0.21; m/e, base = 57 amu, exact mass calcd for $C_{12}H_{19}O_3NS$ 257.1081, found 257.1084, error = 1.2 ppm; IR ($CDCl_3$, cm^{-1}) 3440, (NH), 1700 (CO), 1640 (CO); 200-MHz NMR ($CDCl_3$, ppm) 7.38 (1 H, J = 10.0 Hz), 6.19 (1 H, d, J = 10.0 Hz), 4.58 (1 H, br s), 3.60–3.40 (1 H, m), 3.25 (2 H, dt, J = 7.6, 6.4 Hz), 2.83 (1 h, dd, J = 6.3, 3.9 Hz), 2.59 (1 H, dd, J = 16.3, 10.6 Hz), 2.00–1.80 (2 H, m), 1.42 (9 H, s).

2-[2-[(*tert*-Butoxycarbonyl)methylamino]ethyl]-3,4-dihydro-2*H*-thiopyran-4-one (17b). Sulfide **2b** (1.8 g, 5.5 mmol) and Danishefsky's diene (17.1 mL, 15.1 g, 87.8 mmol) were dissolved in benzene (150 mL). The reaction mixture was divided into thirds, and each was photolyzed separately until TLC showed no starting sulfide. The solvents were removed under reduced pressure, and the excess diene was recovered (bulb-to-bulb distillation). The combined residues were purified by column chromatography on silica gel (90 g, 1:1 ether/hexane) to give two fractions: A, eliminated product, **17b**, 590 mg (42%), and B, 670 mg (42%), a 1:1 mixture of diastereomers of methoxy-containing adducts.

17b: oil; silica gel 60, 50% ether/hexane, R_f 0.30; m/e, base = 57 amu, exact mass calcd for $C_{13}H_{21}O_3NS$ 271.1237, found 271.1243, error = 2.3 ppm; IR (neat, cm^{-1}) 1686 (CO), 1618 (C=C); 200-MHz NMR ($CDCl_3$, ppm) 7.34 (1 H, d, J = 10.3 Hz), 6.13 (1 H, d, J = 10.3 Hz), 3.60–3.40 (1 H, m), 3.30 (2 H, t, J = 6.8 Hz), 2.82 (1 H, dd, J = 16.1, 3.7 Hz), 2.80 (3 H, s), 2.27 (1 H, dd, J = 16.1, 10.4 Hz), 2.00–1.80 (2 H, m), 1.41 (9 H, s).

Bicyclic Ketone 18b. Sulfide **17b** (15 mg, 0.055 mmol) was dissolved in methylene chloride (1 mL). Trifluoroacetic acid (3 mL) was added and the solution stirred for 1 h. The solvents were removed under reduced pressure, the residue was dissolved in methanol (20 mL), and potassium carbonate (30 mg) was added. The suspension was stirred overnight, and methanol was then removed under reduced pressure to give a dark residue. After treatment with hydrochloric acid (12 drops, 10% aqueous hydrogen chloride in 5 mL of water), the residue was extracted with ether (5 mL). The aqueous phase was made basic (potassium carbonate), extracted with methylene chloride (3 × 10 mL), dried (magnesium sulfate), and evaporated under reduced pressure to give **18b**, which was isolated by chromatography, 9.0 mg. **18b**: oil; silica gel 60, 10% methanol/chloroform, R_f 0.3; m/e, base = 171 amu, exact mass calcd for $C_8H_{13}NOS$ 171.0715, found 171.0718, error = 1.7 ppm; IR ($CDCl_3$, cm^{-1}) 1708 (CO); 200-MHz NMR ($CDCl_3$, ppm) 4.23–4.17 (1 H, m), 3.34–3.30 (1 H, m), 3.20–2.70 (5 H, m), 2.58 (3 H, s), 2.52–2.32 (1 H, m), 1.54–1.36 (1 H, m), 1.36–1.24 (1 H, m).

***N*-Acetyl Bicyclic Ketone 18c.** Thioaldehyde adduct **17a** (110 mg, 0.38 mmol) was dissolved in methylene chloride (1 mL). Trifluoroacetic acid (1 mL) was added, the solution was stirred for 20 min, and the acid was removed under reduced pressure. Methanol (1 mL) and potassium carbonate (100 mg) were added, and the reaction mixture was stirred for 4 h. Solvent was removed, and the residue was extracted by methylene chloride (5 mL). Acetic anhydride (0.4 mL) and pyridine (0.4 mL) were then added, and the solution was stirred overnight. After solvent removal, the residue was dissolved in methylene chloride (3 mL) and washed with water (1 mL). Back-extraction of the aqueous layer with methylene chloride (2 × 2 mL), drying ($MgSO_4$), and solvent removal under reduced pressure gave a gum. The residue was purified by column chromatography on silica gel (50% ethyl acetate/hexane; then ethyl acetate) to give **18c**, 70 mg (85%): oil; silica gel 60, ethyl acetate, R_f 0.34; m/e, base = 199 amu, exact mass calcd for $C_9H_{13}O_2NS$ 199.0664, found 199.0663, error = 0.5 ppm; IR ($CDCl_3$, cm^{-1}) 1710 (CO), 1650 (CON); 200-MHz NMR ($CDCl_3$, ppm) *N*-acetyl *E*, *Z* isomers 6.20 (1 H, dd, J = 3.1, 2.4 Hz), 4.75 (0.33 H, dd, J = 14.3, 4.6 Hz), 3.82 (0.67 H, dd, J = 16.1, 4.1 Hz), 3.58–3.51 (1 H, m), 3.50–3.28 (0.67 H, m), 3.13–2.69 (4.33 H, m), 2.38–2.20 (1 H, m), 2.17 (1 H, s), 2.09 (2 H, s), 1.97–1.85 (1 H, m).

Enaminone 20 and Enaminal 21. Bicyclic ketone **18b** (4.0 mg, 0.023 mmol) was dissolved in ethanol (0.1 mL), and W-2 Raney nickel was added. The solution was stirred for 2 min and then filtered through Celite to give **20** (3.2 mg, 100%), which rearranged upon attempted purification on silica gel, upon treatment with acid, or upon stirring over silica gel to give **21**, 3.1 mg (97%).

20: IR ($CDCl_3$, cm^{-1}) 1630 (NC=CCO), 1589 (NC=CCO), 1403 (NC=CCO); 200-MHz NMR ($CDCl_3$, ppm) 6.51 (1 H, d, J = 9.4 Hz), 4.58 (1 H, d, J = 9.4 Hz), 3.33–3.23 (2 H, m), 2.99 (3 H, s), 2.59–2.47 (2 H, m), 1.88–1.73 (4 H, m).

21: oil; silica gel F254, 10% methanol/chloroform, R_f 0.2; m/e, base = 122 amu, exact mass calcd for $C_8H_{13}ON$ 139.0994, found 139.00996, error = 1.4 ppm; IR ($CDCl_3$, cm^{-1}) 1602 (NC=CCHO), 1565 (NC=CCHO); 200-MHz NMR ($CDCl_3$, ppm) 9.52 (1 H, d, J = 8.5 Hz), 5.09 (1 H, d, J = 8.5 Hz), 3.31 (2 H, t, J = 6.0 Hz), 2.94–2.88 (2 H, m), 2.90 (3 H, s), 1.90–1.61 (4 H, m).

Independent Synthesis of 21 via 23. Thioamide **22** (50 mg, 0.39 mmol) was dissolved in acetonitrile (3 mL). Chloroacetaldehyde (53 mg, 0.43 mmol, dried by toluene/chloroform azeotropic removal of water) and sodium iodide (1 mg) were added, and the solution was heated at reflux for 5 min. After cooling to room temperature, triethylamine (0.1 mL) and triphenylphosphine (110 mg, 0.42 mmol) were added. The solution was refluxed for 1 h, solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (10% methanol/chloroform) to give **23**, 35 mg (65%): oil; silica gel F254, 10% methanol/chloroform, R_f 0.20; m/e, exact mass calcd for $C_8H_{13}ON$ 139.0994, found 139.1002, error = 5.8 ppm; IR ($CDCl_3$, cm^{-1}) 1605 (NC=CCHO), 1565 (NC=CCHO); 200-MHz NMR ($CDCl_3$, ppm) 9.27 (1 H, d, J = 9.1 Hz), 5.05 (1 H, d, J = 9.1 Hz), 3.30 (2 H, t, J = 6.3 Hz), 2.87 (3 H, s), 2.83 (2 H, t, J = 6.5 Hz), 1.81–1.57 (4 H, m).

Conversion of 23 to 21. Vinylogous amide **23** (15 mg, 0.11 mmol) was dissolved in methylene chloride (1.0 mL), and *p*-toluenesulfonic acid (1 mg) was added. After the mixture was stirred overnight, the solvent was removed under pressure and the residue purified by PTLC (10% methanol/chloroform) to give **21**, 13 mg (87%), identical with the Raney nickel product.

Unsaturated Aminal 24. Amide **18c** (6.90 mg, 0.03 mmol) was dissolved in deuterioacetonitrile (0.3 mL). Methyl triflate (6 μL, 0.05 mmol) was added and the reaction mixture stirred for 90 min. Next 2,6-lutidine (10.7 mg, 0.10 mmol) was added and the solution was refluxed for 20 min. The solvent was removed under reduced pressure, and the residue was purified by PTLC to give **24**, 2.6 mg (40%): oil; silica gel 60, ethyl acetate, R_f 0.50; m/e, exact mass calcd for $C_{10}H_{15}O_2NS$ 213.082, found 213.0799, error = 9.9 ppm; IR ($CDCl_3$, cm^{-1}) 1640 (CON); 200-MHz NMR ($CDCl_3$, ppm) 7.03–6.96 (1 H, m), 5.13 (1 H, d, J = 9.8 Hz), 4.36–4.26 (1 H, m), 3.12 (2 H, br t, J = 12.4 Hz), 2.88 (1 H, dd, J = 17.5, 1.5 Hz), 2.70 (1 H, dd, J = 17.5, 11.6 Hz), 2.40–2.22 (2 H, m), 2.09 (3 H, s).

Saturated Amine 25. Aminal **24**[9] (2.68 mg, 0.12 mmol) was dissolved in acetone (0.1 mL). 1,3-Cyclohexadiene (0.1 mL) and W-2 Raney nickel were added, and the solution was refluxed for 1 h. The resulting suspension was filtered through Celite, the solvent removed under reduced pressure, and the residue purified by PTLC to give **25**, 1.6 mg (70%): oil; silica gel 60, ethyl acetate, R_f 0.40; m/e, base = 99 amu, exact mass calcd for $C_9H_{15}O_2N$ 169.1099, found 169.1088, error = 6.5 ppm; IR ($CDCl_3$, cm^{-1}) 1630 (CNO); 200-MHz NMR ($CDCl_3$, ppm) 3.75 (0.8 H, dd, J = 5.9, 5.5 Hz), 3.60 (1.2 H, dd, J = 6.0, 5.7 Hz), 3.47–3.22 (2 H, m), 2.64 (1 H, dd, J = 6.0, 5.7 Hz), 2.45–2.37 (1 H, m), 2.13 (1.8 H, s), 2.09 (1.2 H, s), 1.96–1.64 (6 H, m).

Bicyclic Ketone 27. Phenacyl sulfide **26**[9] (106 mg, 0.3 mmol) was dissolved in deoxygenated benzene (10 mL) with the Danishefsky diene (800 mg, 4 mmol). Photolysis as usual[3] for 1 h followed by solvent evaporation (aspirator) and excess diene removal (0.01 Torr, 30 °C) gave an oil. Elution on silica gel with 3:1 hexane/ethyl acetate gave a major fraction of adduct stereoisomers (69 mg, 69%, R_f 0.23).

The thioaldehyde adduct (69.0 mg, 0.21 mmol) was dissolved in methylene chloride (0.2 mL), and trifluoroacetic acid (Aldrich, 2.0 mL) was added. After the reaction mixture was stirred for 30 min, solvents were removed at reduced pressure and more methylene chloride (5 mL) was added. Potassium carbonate (100 mg) was then added to neutralize residual acid. After the reaction mixture was stirred for 30 min, the suspension was filtered, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (2 g, 50% ethyl acetate/hexane) to give **27**: oil; silica gel 60, 50% ethyl acetate/hexane, R_f 0.42; m/e, exact mass calcd for $C_{11}H_{11}ONS$

205.0559, found 205.0562, error = 1.4 ppm; IR ($CDCl_3$, cm^{-1}) 3400 (NH), 1700 (C=O); 200-MHz NMR ($CDCl_3$, ppm) 7.95-7.10 (2 H, m), 6.72 (1 H, dd, J = 7.3, 1.0 Hz), 6.57 (1 H, dd, J = 8.2, 1.1 Hz), 5.19-5.11 (1 H, m), 4.66 (1 H, br s), 4.54 (1 H, dd, J = 6.9, 3.5 Hz), 3.00-2.86 (4 H, m).

Enaminal 29. Bicyclic ketone **27** (12.4 mg, 0.06 mmol) was dissolved in acetone (0.1 mL), Raney nickel (30 mg in ethanol) was added, and the suspension was refluxed overnight. After filtration through Celite with ethanol, the solvent was removed under reduced pressure, and the residue was purified by PTLC to give **29**, 5.2 mg (50%): oil; silica gel F254, 50% ethyl acetate/hexane, R_f 0.50; m/e, base = 172 amu, exact mass calcd for $C_{11}H_{11}ON$ 173.0838, found 173.0842, error = 2.3 ppm; IR ($CDCl_3$, cm^{-1}) 1570 (NH-=CHO); 200-MHz NMR ($CDCl_3$, ppm) 11.3 (1 H, br s), 9.12 (1 H, dd, J = 2.4, 0.3 Hz), 7.24-6.82 (4 H, m), 5.12 (1 H, d, J = 2.4 Hz), 2.85-2.56 (4 H, m).

***N*-Acetyl Bicyclic Ketone 30.** A solution of **27** (16.3 mg, 0.08 mmol) in methylene chloride (0.3 mL) and pyridine (0.4 mL) was treated with acetyl chloride (distilled; 0.1 mL) for 1 h. The solvent was removed under reduced pressure (15-0.01 Torr), and the residue was purified by PTLC to give **30**, 14.1 mg (71%): oil; silica gel 60, 50% ethyl acetate/hexane, R_f 0.26; m/e, exact mass calcd for $C_{13}H_{13}O_2NS$ 247.0664, found 247.0659, error = 1.9 ppm; IR ($CDCl_3$, cm^{-1}) 1715 (C=O), 1670 (NC=O); 200-MHz NMR ($CDCl_3$, ppm) 7.26-7.10 (4 H, m), 6.60 (1 H, ddd, J = 7.1, 2.2, 2.2 Hz), 4.45-4.42 (1 H, m), 3.13-2.76 (4 H, m), 2.24 (3 H, s).

Ra-Ni Desulfurization of 30 to 31. W-2 Raney nickel was deactivated by refluxing in acetone for 3 h. Amide **30** (10.7 mg, 0.043 mmol) was added and the solution refluxed for an additional 3 h. After cooling to room temperature, the suspension was filtered through Celite and the Celite washed with ethanol. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (300 mg, ethyl acetate) to give **31**, 4.0 mg (43%): oil; silica gel 60, ethyl acetate, R_f 0.29; m/e, base = 132 amu, exact mass calcd for $C_{13}H_{15}O_2N$ 217.1099, found 217.1105, error = 2.7 ppm; IR ($CDCl_3$, cm^{-1}) 1652 (NC=O), 1703 (C=O); 270-MHz NMR ($CDCl_3$, ppm) 7.40-7.20 (4 H, m), 4.95-4.86 (1 H, m), 3.33-3.09 (2 H, m), 2.93-2.80 (3 H, m), 2.67-2.51 (1 H, m), 2.35-2.28 (1 H, m), 1.81 (1.5 H, s), 1.61 (1.5 H, s).

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Site Selectivity in the Reactions of Various 1,3-Dipoles with (Phenylsulfonyl)-1,2-propadiene

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The cycloaddition reactions of (phenylsulfonyl)-1,2-propadiene (1) with various 1,3-dipoles have been investigated. MNDO calculations suggest that the reaction of the activated allene will proceed in a highly regioselective fashion and undergo cycloaddition across the more activated π-bond. This proved to be the case in the reactions of diazomethane and diazopropane with 1. The formation of 4-[(phenylsulfonyl)methyl]pyrazole (8) was rationalized in terms of a 1,3-allylic sulfonyl shift from the expected 1,3-dipolar cycloadduct. Related allylic sulfonyl shifts were also proposed to occur in the cycloaddition of 1 with benzonitrile oxide and the silyl nitronate of *aci*-nitrophenylmethane. The isolation of 1,3-diphenyl-5-[(phenylsulfonyl)methyl]pyrazole (16) as the major product from the reaction of 1 with 1-(α-chlorobenzylidene)-2-phenylhydrazine is suggested to proceed via a stepwise Michael addition of the initially formed aza anion onto the central allene carbon. The strongly activated allene promotes conjugate addition as a consequence of its markedly lowered LUMO level.

Allenes are an interesting group of substrates since they contain two positions for attack.[1] (Phenylsulfonyl)-1,2-propadiene (1) represents one of the more reactive allenes known. This material has been shown to undergo the Diels-Alder reaction exclusively across the activated C_1-C_2 double bond.[2] Recently, we reported that (phenylsulfonyl)-1,2-propadiene (1) is also a useful dipolarophile in nitrone cycloaddition chemistry due to its enhanced reactivity.[3] As part of our ongoing interest in the synthetic applications of 1,3-dipolar cycloaddition chemistry,[4] we have further investigated the reactivity of (phenylsulfonyl)allene with other 1,3-dipoles.[5] The phenylsulfonyl group can be readily removed by various methods[6] after the cycloaddition, and thus the dipolar cycloadducts formed should be of some use in organic synthesis.

MNDO calculations of (methylsulfonyl)-1,2-propadiene indicate that the introduction of a sulfonyl group causes a significant lowering of the LUMO energy level compared with allene (ΔE = 1.3 eV) and the largest LUMO coefficient resides on the central carbon and the next on the position bearing the sulfonyl group. This suggests that the reaction of 1 with various type I dipoles[7] will proceed in a highly regioselective fashion and undergo cycloaddition across the activated C_1-C_2 π-bond.

Results and Discussion

The cycloadditions of simple diazoalkanes are generally HO(1,3-dipole)-LU(dipolarophile) controlled.[7,8] This proved to be the case in the reaction of diazopropane (or diazomethane) with (phenylsulfonyl)-1,2-propadiene (1). Stirring a solution of diazopropane and 1 in ether at 25

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