Asymmetric Lewis Acid-Catalyzed Addition of a Ketene Dithioacetal to a Chiral Bicyclic Lactam. Formation of Cyclobutanopyrrolidinones. A New Class of GABA Derivatives

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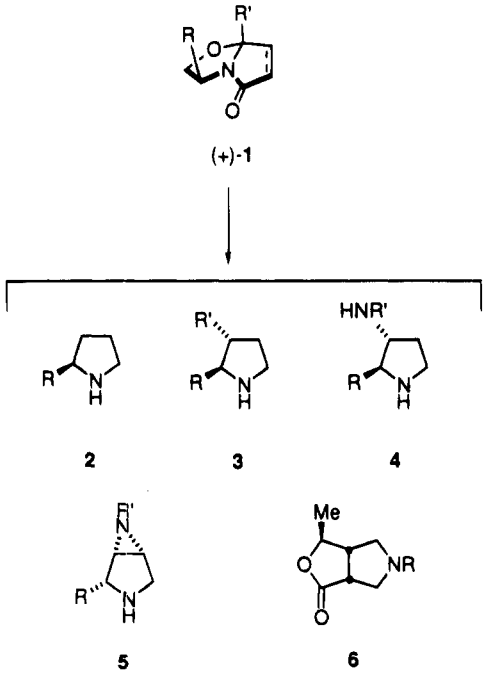
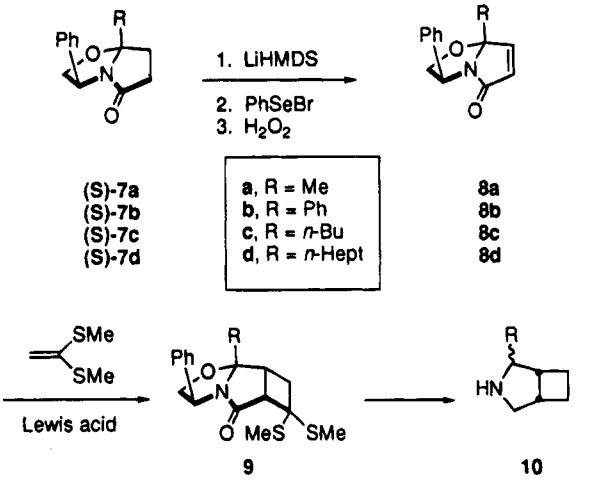
Additions to unsaturated chiral lactams **8** using methylenedithiolane, gave very high *endo*-selectivity of the cyclobutane adducts (2 + 2 addition) **13**, **16**. Removal of the phenylglycinol auxiliary by reductive cleavage produced the title compound (+)-**20** in very high (>99%) enantiomeric excess. Absolute stereochemistry of the cyclobutanopyrrolidinone, containing three contiguous stereocenters, was confirmed by X-ray crystallography.

Previous studies from our laboratory on the versatile nature of chiral nonracemic bicyclic lactams, e.g. **1**, have demonstrated that they are efficient precursors to a host of chiral products.[1] More recently we have shown[2] that a variety of chiral pyrrolidines **2**–**5** may also be reached in high enantiomeric purity by a few synthetic steps emanating from **1** or its slightly modified derivatives. The high selectivities observed by conjugate addition to **1** resulted in the generation of a new stereogenic center which was then retained in the final pyrrolidine products. Also observed[2c] were highly stereoselective (3 + 2) cycloadditions of azomethine ylides, affording, after some simple manipulations, the pyrrolidine lactones **6** containing three contiguous stereocenters.



We now wish to describe further studies on **1** which extend its synthetic prowess to cyclobutane fused pyrrolidinones (+)-**20** in high enantiomeric purity. Our initial goal was to simply utilize the known[3] ethylene dithioketal addition to enones using a Lewis acid to introduce the cyclobutane framework. Thus, we intended to utilize the readily accessible chiral lactams **7a**–**d** derived from (*S*)-



phenylglycinol and various γ-keto acids.[4] The unsaturation in **7** was introduced using lithium bis(trimethylsilyl)amide to generate the enolate which was treated with phenylselenenyl bromide followed by oxidation to afford the products **8** in good overall yields.[5]

The plan was to utilize an ethylene dithioketal to cycloadd to **8** affording **9** which then would be transformed after two to three steps to the cyclobutanopyrrolidine **10**, containing three contiguous stereocenters in high enantiomeric purity. We prepared the ethylene dithiomethyl ketal[6] and made numerous attempts to effect cycloaddition to **8a** using a variety of Lewis acids previously known[3b] to mediate this process (see Scheme 1). In some instances yields of cyclobutane adducts **13**

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(4) (a) Reference 1 above. (b) Burgess, L. E.; Tschantz, M. A.; Meyers, A. I. Org. Synth. **1995**, *74*, in press.

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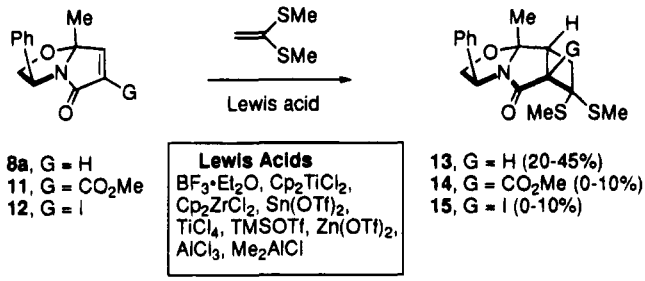
Scheme 1



8a, G = H
11, G = CO_2Me
12, G = I

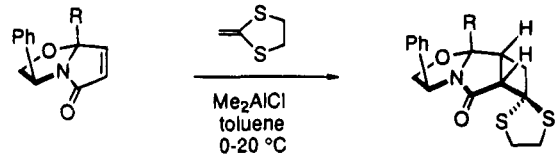
Lewis Acids
BF_3•Et_2O, Cp_2TiCl_2, Cp_2ZrCl_2, $Sn(OTf)_2$, $TiCl_4$, TMSOTf, $Zn(OTf)_2$, $AlCl_3$, Me_2AlCl

13, G = H (20-45%)
14, G = CO_2Me (0-10%)
15, G = I (0-10%)

as high as 45% were reached using dimethylaluminum chloride,[3b] whereas little or no product was observed with all the other mentioned Lewis acids. Large amounts of decomposition products, starting material recovery, and long reaction times (~72 h) made these results far from satisfactory. Solvents of various polarity were also examined (i.e. THF, ether, hydrocarbon) as well as stoichiometry and reaction temperatures, all to no avail. Overall, dimethylaluminum chloride (1.1 equiv) in toluene at room temperature, after 7 days, gave our best results (~45% of **13**). These were clearly not the results hoped for, and further attempts were made to enhance the addition of the thioketal to the unsaturated lactam by increasing the electrophilicity. In this regard the α-carbomethoxy group was inserted to give **11** which we had previously employed in some diastereoselective cuprate additions.[2b] Examination of the ethylene dithiomethyl ketal under all conditions stated above gave virtually no cycloadduct **14**. Similar results were obtained when the iodo-substituted lactam **12**[7] was scrutinized under these conditions.

It was noticed during this investigation that in many instances, the Lewis acids were decomposing the ethylene dithiomethyl ketals but affecting the chiral lactams to a minimal degree. Therefore, a more sturdy dithioketal might be required to withstand the undesired side reactions mediated by the Lewis acid.

As it turned out, the methylenedithiolane[8] proved to be an excellent cycloaddition partner for the reaction with chiral lactams **8**. Treatment of the latter lactams **8a–d** with 1.0 equiv of dimethylaluminum chloride and 4.0 equiv of the dithiolane, in toluene at 0 °C for 8–12 h, gave excellent yields of the cyclobutane adducts **16a-d** as single diastereomers following chromatography.[9] The

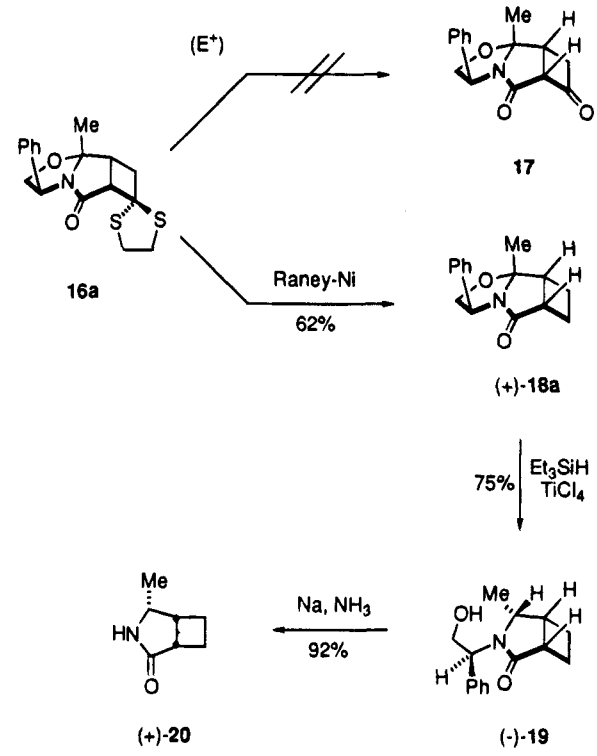


8a, R = Me
8b, R = Ph
8c, R = *n*-Bu
8d, R = *n*-Hept

16a, R = Me (92%)
16b, R = Ph (89%)
16c, R = *n*-Bu (88%)
16d, R = *n*-Hept (86%)

stereochemistry of the addition was readily shown to be the result of *endo*-addition of the dithiolane as written for **16**. The stereochemical assignment was based on NOE studies in which the angular methyl group in **16a** (R = Me) was irradiated and produced a 4.3% enhancement of the adjacent proton signal. This mode of addition to the unsaturated lactams is consistent with previous studies wherein other cycloadditions or nucleophiles proceeded from the *endo* face when the angular substituent R in **8** was other than hydrogen.[1,2] As seen from the equations, four different angularly substituted lactams **16a-d** were efficiently prepared in this manner.

It now remained to transform the cyclobutano lactam to the desired pyrrolidine or pyrrolidinone and retain the stereochemical integrity of the angular substituent. This has been an area of concern not only for oxazolidines but for dioxolanes as well.[10] First, it was necessary to determine whether the dithio group in **16a** could be transformed to the carbonyl group **17**, but all attempts (NBS, $AgNO_3$, $HgCl_2$, Et_3OBF_4) led to decomposed products. It was, therefore, decided to reductively remove the sulfur by Raney nickel treatment, and this provided the cyclobutano lactam **18a** in 60–65% yield. The removal of the dithiolane moiety in **16a** was necessary since the next step (Et_3SiH•$TiCl_4$) would be completely incompatible with the sulfur group. Treatment of (+)-**18a** with



the reducing agent gave a clean, single product **19** in 75% yield after purification. However, the stereochemistry of the methyl group was still an open question. By analogy, we initially assigned the methyl to the β-face (opposite to that shown in **19**) since this was consistently seen in related systems studied earlier.[1,2,10] However, NMR assignments could not be made with certainty, and **19** was an oily substance which could not be induced to crystallize for suitable X-ray determination. Therefore, the phenylglycinol moiety was removed and this was accomplished using sodium in liquid ammonia and afforded the cyclobutano pyrrolidinone **20** in 92% yield. HPLC analysis of the crude material indicated a 94:6 ratio of diastereomers indicating that the silane reduction proceeded with almost complete, but yet uncertain, stereoselectivity. Chromatography gave pure, crystalline **20** in 92% yield. The latter exhibited suitable crystals

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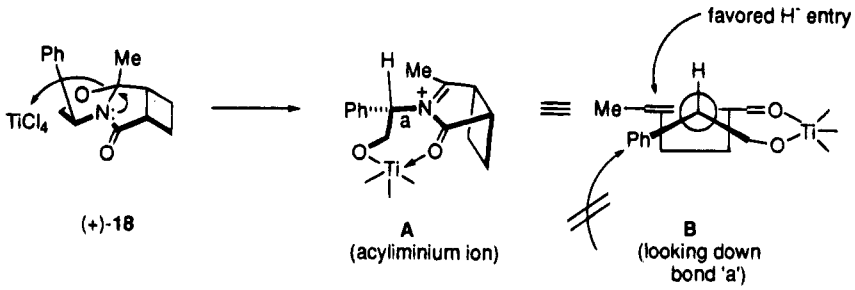

Figure 1.

for an X-ray determination to establish whether the methyl group in **19** and **20** was the result of a retention or inversion step during the $Et_3SiH-TiCl_4$ step. It was clearly shown[11] that the methyl group in **20** inverted during the reduction step, and the structure drawn for **19** is correct. Rationalization of the stereochemical outcome in the reduction of **18** to **19** may be reasonably presented by the structures given in Figure 1. If one assumes, as was previously discussed,[10] that the acyliminium ion **A** is readily generated[12] by the $TiCl_4$ complex with **18**, then the intermediate **A** is accessible from only one face (β). The configuration of the phenylglycine moiety, the complexation of the oxophilic titanium salt, and the presence of the *endo*-fused cyclobutane ring (in **A** or **B**) all appear to block the α-side to nucleophilic hydride entry. Thus, the β-entry of hydride provides the inverted position taken by the methyl group, in accordance with the X-ray data.

Although only one cyclobutane adduct **18a** has been taken on to the cyclobutano pyrrolidinone **20**, there is no reason to believe that the other derivatives would not also proceed in this manner. It is noteworthy that (+)-**20** represents a rigid analog of γ-aminobutyric acid (GABA) derivatives which have been shown to be important inhibitory neurotransmitters in the mammalian brain.[13] Furthermore, several GABA analogs have been implicated as useful therapeutics in the treatment of neurological and psychiatric disorders.[14]

Experimental Section

α,β-Unsaturated Bicyclic Lactam 8a (General Procedure). Phenylselenenyl bromide was prepared by the slow addition of 0.79 mL (15.2 mmol) of bromine to a vigorously stirred solution of 5.49 g (17.6 mmol) of diphenyl diselenide in dry THF (10 mL) at 0 °C. The resulting reddish-brown solution was allowed to warm to rt.

A 500 mL round bottomed flask fitted with a magnetic stir bar was charged with 5.00 g (23.4 mmol) of bicyclic lactam **7a**[2b,15] and THF (150 mL) under an argon atmosphere. The solution was stirred and cooled to −78 °C where 51.6 mL (51.6 mmol, 1.0 *M* in hexanes) of lithium hexamethyldisilazide (LiHMDS) was added slowly *via* syringe over 30 min. The solution was allowed to stir an additional 30 min at −78 °C followed by the dropwise addition of the previously prepared phenylselenenyl bromide solution. After 2 h, the reaction was quenched with aqueous ammonium chloride (75 mL) and warmed to rt. Water (100 mL) was added, and the phases were separated. The aqueous portion was extracted with diethyl ether (3 × 50 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford crude α-phenylselenenyl lactams. This crude mixture was taken up in dichloromethane (100 mL) and cooled to 0 °C. To this solution was added 7.97 mL (70.3 mmol, 30% by weight) of hydrogen peroxide and the mixture stirred for 12 h. The mixture was concentrated *in vacuo* and the residue taken up in ethyl ether (50 mL), washed with 1 N HCl (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (4:1 hexanes/ethyl acetate) afforded 4.23 g (84%) unsaturated lactam **8a** as a pale yellow solid: mp 76−78 °C; $[\alpha]_D$ = +119 (*c* 1.10, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.10−7.36 (m, 5H), 7.11 (d, 1H, *J* = 5.8 Hz), 6.08 (d, 1H, *J* = 5.8 Hz), 5.07 (app t, 1H, *J* = 6.8 Hz), 4.66 (app t, 1H, *J* = 8.0 Hz), 4.29 (dd, 1H, *J* = 6.5, 8.9 Hz), 1.53 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 177.8, 150.9, 139.6, 128.6, 127.9, 127.4, 125.7, 100.9, 75.8, 58.3, 21.7. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09. Found: C, 72.65; H, 6.03.

Unsaturated Lactam 8b. Prepared according to General Procedure with 4.00 g (14.3 mmol) of lactam **7b**. The reaction provided 2.73 g (70%) of unsaturated lactam **8b** following flash column chromatography (4:1 hexanes/ethyl acetate): mp 122−123 °C; $[\alpha]_D$ = +301 (*c* = 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.53−7.56 (m, 2H), 7.32−7.38 (m, 3H), 7.11−7.24 (m, 5H), 7.07 (d, 1H, *J* = 5.7 Hz), 6.06 (d, 1H, *J* = 5.7 Hz), 5.03 (app t, 1H, *J* = 8.2 Hz), 4.81 (app t, 1H, *J* = 8.4 Hz), 4.10 (app t, 1H, *J* = 8.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.7, 151.2, 138.6, 136.6, 128.8, 128.7, 128.4, 127.4, 126.7, 126.5, 126.0, 103.6, 76.9, 59.6. Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45. Found: C, 77.86; H, 5.47.

Unsaturated Lactam 8c. Prepared according to General Procedure with 2.00 g (7.71 mmol) of saturated lactam **7c**. The reaction provided 1.51 g (76%) of unsaturated lactam **8c** as a yellow solid following flash column chromatography (4:1 hexanes/ethyl acetate): mp 64−65 °C $[\alpha]_D$ = +158.1 (*c* 2.10, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.20−7.41 (m, 5H), 7.12 (d, 1H, *J* = 5.8 Hz), 6.09 (d, 1H, *J* = 5.8 Hz), 5.05 (t, 1H, *J* = 7.2 Hz), 4.66 (t, 1H, *J* = 8.3 Hz), 4.30 (dd, 1H, *J* = 8.7, 6.6 Hz), 1.75 (m, 2H), 1.22 (m, 4H), 0.83 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.2, 150.1, 139.9, 128.6, 127.4, 125.6, 103.6, 75.7, 58.2, 33.9, 26.2, 22.7 13.8; IR (thin film) 3089, 3061, 3029, 2957, 2929, 2868, 1713, 1601, 1496, 1468, 1446, 1352, 1324, 1219, 1175, 1048, 816, 727, 699 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H 7.44. Found: C, 74.62; H, 7.39.

(11) The X-ray structure appears in the supporting information. All details have been deposited with the Cambridge Crystallographic Data File.

(12) Earlier evidence for the bicyclic lactam transformation to acyliminium ion was reported to account for some unexpected transformations: Meyers, A. I.; Bienz, S.; Busacca, C. *J. Am. Chem. Soc.* **1989**, *111*, 1905.

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(15) Experimental procedures for synthesis of bicyclic lactams **7a−d** although published partly in refs 2bd, may be found in supporting information accompanying this article.

Unsaturated Lactam 8d. Prepared according to General Procedure with 2.80 g (9.30 mmol) of saturated lactam **7d**. The reaction provided 2.01 g (72%) of unsaturated lactam **8d** as a yellow oil following flash column chromatography (4:1 hexanes/ethyl acetate). $[\alpha]_D$ = +128.8 (*c* 1.65, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 7.12 (d, 1H, *J* = 5.9 Hz), 6.09 (d, 1H, *J* = 5.9 Hz), 5.06 (t, 1H, *J* = 7.2 Hz), 4.67 (dd, 1H, *J* = 8.8, 7.9 Hz), 4.27 (dd, 1H, *J* = 8.8, 6.6 Hz), 1.77 (m, 2H), 1.22 (m, 10H), 0.84 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.2, 150.1, 139.9, 128.6, 127.4, 125.6, 103.6, 75.7, 58.2, 34.3, 31.6, 29.5, 28.9, 24.0, 22.5, 14.0; IR (thin film) 2951, 2923, 2852, 1717 cm^{-1}.

Lewis Acid-Catalyzed Addition of Methylenedithiolanes, 16a (General Procedure). An oven-dried 50 mL flask was charged with 200 mg (0.93 mmol) of lactam **8a** and dry toluene (20 mL). The solution was cooled to 0 °C, 0.93 mL (0.93 mmol, 1.0 *M* in hexanes, 1.0 equiv, Aldrich) of dimethylaluminum chloride was added dropwise, and the solution was allowed to stir for 15 min. To this solution was added 439 mg (3.72 mmol, 4.0 equiv) of methylenedithiolane in dry toluene (5 mL) and the reaction warmed to rt and allowed to stir for 8 h. The reaction mixture was recooled to 0 °C and quenched with 1 N HCl (10 mL). The layers were separated, and the aqueous portion was extracted with toluene (3 × 15 mL). The organic layers were combined, washed with water (10 mL) and brine (10 mL), and dried over Na_2SO_4. Column chromatography (CH_2Cl_2) provided 292.7 mg (94%) of **16a** as a light yellow solid: mp 164–166 °C; $[\alpha]_D$ = +119.5 (*c* 1.08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5H), 5.28 (t, 1H, *J* = 7.6 Hz), 4.79 (t, 1H, *J* = 8.5 Hz), 4.20 (dd, 1H, *J* = 8.6, 7.0 Hz), 3.69 (m, 1H), 3.30 (m, 4H), 2.96 (m, 2H), 2.77 (m, 1H), 1.35 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.0, 140.0, 128.7, 127.4, 125.6, 98.8, 74.5, 63.7, 60.9, 57.7, 40.1, 39.3, 38.0, 36.9, 25.6; IR (thin film) 2929, 1702 cm^{-1}. Anal. Calcd for $C_{17}H_{19}NO_2S_2$: C, 61.23; H, 5.74. Found: C, 61.10; H, 5.77.

Cycloadduct 16b. Prepared according to General Procedure using 500 mg (1.80 mmol) of lactam **8b** in 25 mL of dry toluene. The reaction provided 632 mg (89%) of **16b** as a light yellow solid: mp 62–64 °C; $[\alpha]_D$ = +78.6 (*c* 1.22, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.00–7.40 (m, 10H), 5.25 (m, 1H), 4.81 (dd, 1H, *J* = 8.9, 8.0 Hz), 4.01 (t, 1H, *J* = 8.2 Hz), 3.74 (m, 1H), 3.33 (m, 4H), 2.98–3.16 (m, 2H), 2.78 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.9, 142.7, 138.3, 128.7, 128.3, 128.2, 127.5, 126.9, 124.9, 101.0, 75.1, 63.6, 60.6, 59.3, 40.5, 40.1, 39.1, 38.0; IR (thin film) 3060, 3025, 2980, 1703 cm^{-1}. Anal. Calcd for $C_{22}H_{21}NO_2S_2$: C, 66.80; H, 5.35. Found: C, 66.90; H, 5.40.

Cycloadduct 16c. Prepared according to General Procedure using 500 mg (1.94 mmol) of lactam **8c** in 25 mL dry toluene. The reaction provided 633 mg (87%) of **16c** as a light yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5H), 5.30 (t, 1H, *J* = 7.7 Hz), 4.78 (t, 1H, 8.5 Hz), 4.17 (dd, 1H, *J* = 8.6, 1.5 Hz), 3.61 (m, 1H), 3.30 (m, 4H), 3.05 (m, 1H), 2.90 (ddd, 1H, *J* = 13.5, 6.2, 0.9 Hz), 2.73 (m, 1H), 1.65 (m, 1H), 1.48 (m, 1H), 1.23 (m, 4H), 0.80 (app t, 3H, *J* = 7.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.2, 140.0, 128.5, 127.3, 125.4, 100.9, 74.1, 63.7, 60.9, 57.6, 40.0, 39.1, 37.0, 36.8, 35.6, 25.5, 22.5, 13.8; IR (thin film) 3062, 3032, 2951, 1704 cm^{-1}. FAB-LSIMS (glycerol): *m/z* (M + 1) 376.1391 (calcd for $C_{20}H_{26}NO_2S_2$ = 376.1405).

Cycloadduct 16d. Prepared according to General Procedure using 500 mg (1.67 mmol) of lactam **8d** in 25 mL of dry toluene. The reaction provided 596.4 mg (87%) of **16d** as a light yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.28 (t, 1H, *J* = 7.6 Hz), 4.77 (t, 1H, *J* = 8.5 Hz), 4.17 (dd, 1H, *J* = 8.6, 7.0 Hz), 3.61 (m, 1H), 3.30 (m, 4H), 3.05 (m, 1H), 2.92 (ddd, 1H, *J* = 13.5, 6.2, 0.9 Hz), 2.73 (m, 1H), 1.63 (m, 1H), 1.47 (m, 1H), 1.20 (m, 10H), 0.83 (app t, 3H, *J* = 6.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.3, 140.0, 128.6, 127.3, 125.5, 100.9, 74.2, 63.8, 60.9, 57.6, 40.0, 39.2, 37.2, 37.1, 35.6, 31.5, 29.4, 29.0, 23.4, 22.5, 14.0; IR (thin film) 3060, 2957, 1704 cm^{-1}; FAB-LSIMS (glycerol) *m/z* (M + 1) 418.1858 (calcd for $C_{23}H_{32}NO_2S_2$ = 418.1874).

Desulfurization of 16a. Formation of Cyclobutano Derivative 18a. A 25 mL flask was charged with 570 mg (1.71 mmol) of cycloadduct **16a** and absolute ethanol (10 mL). Approximately 4.00 g of Raney nickel (as a 50% slurry in water, Aldrich) was added, and the mixture was warmed to 40 °C for 4 h. The mixture was filtered over Celite and washed with dichloloromethane (5 × 25 mL). The combined organic layers were dried over $MgSO_4$. Column chromatography (7:1 hexanes/ethyl acetate) provided 257 mg (62%) of saturated tricyclic lactam **18a** as a white solid: mp 125–127 °C; $[\alpha]_D$ = +212.1 (*c* 1.42, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.18 (t, 1H, *J* = 7.7 Hz), 4.78 (t, 1H, *J* = 8.5 Hz), 4.21 (dd, 1H, *J* = 8.6, 7.4 Hz), 3.35 (m, 1H), 3.00 (m, 1H), 2.35 (m, 2H), 2.03 (m, 2H), 1.40 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.2, 139.8, 128.7, 127.4, 125.5, 99.2, 75.1, 57.1, 45.5, 43.0, 24.8, 22.4, 19.3; IR (thin film) 2977, 2947, 2884, 1700 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04. Found: C, 74.04; H, 7.08.

Triethylsilane Reduction of 18a. Formation of (−)-19. An oven-dried 25 mL flask was charged with 200 mg (0.822 mmol) of tricyclic lactam **18a** and dry dichloromethane (10 mL). The solution was cooled to −78 °C using an external dry ice–acetone bath. After stirring at −78 °C for 15 min, 0.25 mL (1.54 mmol, 1.8 equiv, Aldrich) of triethylsilane and 1.89 mL (1.89 mmol, 1.0 *M* in dichloromethane, 2.2 equiv, Aldrich) of titanium(IV) chloride were added consecutively, and the reaction mixture was allowed to gradually warm to rt over 10 h. The reaction was subsequently quenched by the slow addition of 5 mL of NH_4Cl (saturated). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (7:1 hexanes/ethyl acetate) provided 149 mg (75%) of (−)-**19** as a clear oil: $[\alpha]_D$ = −68.8 (*c* 1.11, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.65 (m, 1H), 4.22 (m, 1H), 4.08 (m, 1H), 3.79 (m, 1H), 3.43 (br s, 1H), 3.08 (m, 1H), 2.92 (m, 1H), 2.42 (m, 1H), 1.89–2.23 (m, 3H), 0.90 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.0, 138.1, 128.5, 127.4, 127.3, 64.4, 61.2, 58.7, 41.9, 36.7, 22.9, 19.8, 15.2; IR (thin film) 3509–3160, 2949, 2875, 1656 cm^{-1}.

5(*R*)-Methyl-3(*S*),4(*R*)-Cyclobutanopyrrolidinone, (+)-20. An oven-dried 50 mL three-necked flask fitted with a magnetic stir bar and cold finger was charged with 177 mg (0.721 mmol) of **19**, THF (3.0 mL), and absolute ethanol (1.0 mL). The solution was cooled to −78 °C using an external acetone/dry ice bath, and approximately 20 mL of ammonia was condensed into the reaction vessel. While stirring at −78 °C, 71.0 mg (3.09 mmol, 4.0 equiv) of sodium metal were added in small portions until a blue color persisted for 3 min. The reaction was then quenched by the careful addition of solid NH_4Cl, and the cold finger was removed. After all of the ammonia had evaporated, the residue was taken up in ethyl acetate (10 mL) and washed with water (1 × 5 mL). The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (ethyl acetate) provided 83.2 mg (92%) of (+)-**20** as a white solid: mp 90–92 °C; $[\alpha]_D$ = +36.8 (*c* 1.38, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) indicated >96% diastereomeric purity: δ 6.62 (br s, 1H), 3.80 (m, 1H), 2.93 (m, 2H), 2.29 (m, 2H), 1.94 (m, 2H), 1.11 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.8, 51.3, 42.1, 38.6, 22.5, 19.0, 15.3; IR (thin film) 3490, 2968, 2948, 2868, 1685, 1459, 1429, 1378, 1338, 1308, 1258, 1233, 1213, 1203, 1152, 1122, 1062, 1007, 941 cm^{-1}. Anal. Calcd for $C_7H_{11}NO$: C, 67.16; H, 8.86. Found: C, 67.05; H, 8.82.

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Supporting Information Available: Experimental details for **7a–d** and ^1H-NMR spectra for **8a–d**, **16a–d**, **18a**, **19**, and **20** and an ORTEP structure for **20** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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