Use of Ketene Dithioacetal as a Latent Carboxylic Acid in the Macrolactonization Applicable to the Synthesis of Dilactonic Pyrrolizidine Alkaloids

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Acid **5a** (or **5b**) bearing the ketene dithioacetal moiety functioned as an equivalent of a dicarboxylic acid. Use of the ketene dithioacetal in the formation of 11-membered dilactones is demonstrated. Compound **5a** (or **5b**) was converted to an acid imidazolide which reacted regioselectively with retronecine at the allylic position. Mild acidic hydrolysis of the ketene dithioacetal moiety led to a thioester, which underwent macrocyclization with the secondary hydroxyl group mediated by silver(I) trifluoroacetate to give derivatives of the pyrrolizidine alkaloids.

Introduction

Ketene dithioacetals are frequently used as latent carboxylic acids in addition to other applications.[1] We previously carried out a stereoselective synthesis of ketene dithioacetal **2** via the reaction of ethyl pyruvate with the 2-propenyl-1,3-dithian-2-ylzinc reagent derived from dithiane **1** (Scheme 1).[2] The stereochemistry in **2** results from the strong chelating ability of the zinc cation and oxygen atoms of pyruvate. As a masked form of 2-hydroxy-2,3-dimethylglutaric acid, ester **2** is readily converted to crobarbatic acid ethyl ester **3** on hydrolysis with HgCl₂ catalysis.[3] Crobarbatic acid has been shown to bear two *trans*-methyl groups;[3,4] however, its absolute configuration is still unknown. Ester **2** has the potential for regioselective elaboration to an 11-membered dilactonic pyrrolizidine alkaloid, crobarbatine (**9d** or **10d**),[5] by esterification of retronecine at the allylic hydroxyl group and macrocyclization subsequent to hydrolysis of the ketene dithioacetal moiety. We report herein the results of this investigation. In the present case, the ketene dithioacetal not only functions as a masked carboxylic acid at an early stage of the synthesis but also was readily transformed to an activated thioester for the ultimate formation of the macrocyclic lactone. It is well documented[6] that ω-hydroxy acids are generally activated as the corresponding ω-hydroxy thioesters, which undergo macrolactonization by catalysis with thiophilic metal ions such as Ag(I), Cu(I), Hg(II), and Tl(I). The use of ω-hydroxy thioesters in the synthesis of pyrrolizidine alkaloids has been reported.[4a,7]

Results and Discussion

In order to avoid formation of γ-lactones such as crobarbatic acid derivatives **3**, the tertiary hydroxyl group of ketene dithioacetal **2** was protected as an ether. Alcohol **2** was treated with NaH and PhCH₂Br in refluxing THF to give, in 95% yield, benzyl ether **4a**, which was saponified to the acid **5a**. After activation to imidazolide **6a**, regioselective esterification with (+)-retronecine was carried out to give ester **7a** in a 93% yield. The side product imidazole was readily removed on stirring with IR-120 resin (acidic form). No esterification with the secondary alcohol of retronecine was observed. The ratio of the two diastereomers in **7a** was deduced to be 1:1 on the basis of analysis of **9a/10a** (see below).

Ketene dithioacetals are usually difficult to hydrolyze but readily form spiro orthodithioesters by assistance of a neighboring hydroxyl group.[3,8] The first transformation of a ketene dithioacetal to a thioester was demonstrated by the conversion of **7a** to **8a**. On treatment with concentrated hydrochloric acid for a short period, ketene dithioacetals **7a** were smoothly converted to thioesters **8a** (88%) bearing an activated carboxyl group suitable for the formation of macrocyclic lactones. Hydrolysis with organic acid catalysts such as AcOH, TFA, and TsOH required prolonged periods and gave lower yields. The diastereomeric mixture of **8a** was treated with silver-(I) trifluoroacetate and 4-DMAP in refluxing THF to give **9a** and **10a** (1:1) in 55% yield. In the absence of 4-DMAP, the yield was lower (22%).[9a] The reaction did not occur in hot toluene presumably due to poor solubility of the substrates. Treatment of **8a** with copper(I) trifluoromethanesulfonate in refluxing benzene failed to produce the macrocycle.[9b]

The diastereomers **9a** and **10a** were separated by HPLC, and their structures were assigned by comparison of their polarity and NMR data with those of analogs **9c** and **10c** (Table 1).[4a] In addition to other signals, the H-8 and C-8 resonances of **10a** appeared at higher fields (δ_H 5.08−5.14 and δ_C 76.79) than those of **9a** (at δ_H 5.59 and δ_C 78.64). Alcohol **2** was similarly alkylated with 4-meth-

⊗ Abstract published in *Advance ACS Abstracts,* February 1, 1996.

(1) (a) Kolb, M. *Synthesis* **1990,** 171. (b) Lee, T.-J.; Holtz, W. J.; Smith, R. L. *J. Org. Chem.* **1982,** *47,* 4750. (c) Chamberlin, A. R.; Chung, J. Y. L. *J. Org. Chem.* **1985,** *50,* 4425.

(2) (a) Fang, J.-M.; Hong, B.-C. *J. Org. Chem.* **1987,** *52,* 3162. (b) Chen, M.-Y.; Fang, J.-M. *J. Org. Chem.* **1992,** *57,* 2937.

(3) (a) Fang, J.-M.; Liao, L.-F.; Hong, B.-C. *J. Org. Chem.* **1986,** *51,* 2828. (b) Fang, J.-M.; Hong, B.-C.; Liao, L.-F. *J. Org. Chem.* **1987,** *52,* 855.

(4) (a) Huang, J.; Meinwald, J. *J. Am. Chem. Soc.* **1981,** *103,* 861. (b) Adams, R.; Rogers, E. F. *J. Am. Chem. Soc.* **1939,** *61,* 2815.
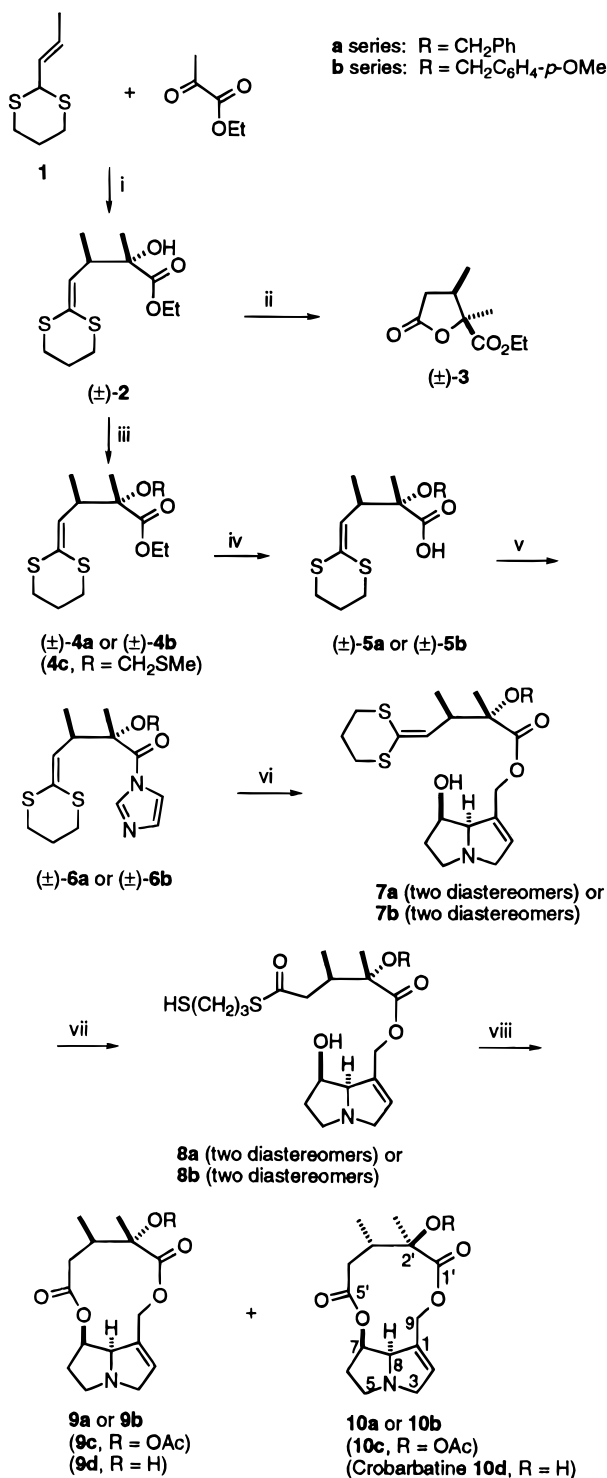
(5) (a) Puri, S. C.; Sawhney, R. S.; Atal, C. K. *Experientia* **1973,** *29,* 390. (b) For a recent review of pyrrolizidine alkaloids, see: Robins, D. J. *Nat. Prod. Rep.* **1989,** 221.

(6) For reviews of macrolide syntheses, see: (a) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977,** *16,* 585. (b) Nicolaou, K. C. *Tetrahedron* **1977,** *33,* 683. (c) Back, T. G. *Terahedron* **1977,** *33,* 3041.

(7) Brown, K.; Delvin, J. A.; Robins, D. J. *J. Chem. Soc., Perkin Trans. 1* **1983,** 1819.

(8) Lee, T.-J.; Holtz, W. J.; Smith, R. L. *J. Org. Chem.* **1982,** *47,* 4750.

(9) Use of 4-DMAP to facilitate macrolactonization: (a) Niwa, H.; Okamoto, O.; Yamada, K. *Tetrahedron Lett.* **1988,** *29,* 5139. The use of Ag(I) is superior to other metal ions in the transformation of thioesters to esters; see: (b) Gerlach, H.; Thalmann, A. *Helv. Chim. Acta* **1974,** *57,* 293.

Scheme 1[a]

a series: R = CH₂Ph

a series: R = CH$_2$Ph
b series: R = CH$_2$C$_6$H$_4$-*p*-OMe

Table 1. Some Pertinent ¹H and ¹³C NMR Data of Crobarbatine Derivatives 9a–10c (CDCl₃, δ Values)

compd[a]	H-2	H-8	Me-2′	C-2	C-7	C-8	C-2′
9a	5.88	5.59	1.53	134.94	72.54	78.64	80.83
10a	6.00	5.08–5.14	1.49	133.88	74.56	76.79	79.49
9b	5.91	5.58	1.50	134.86	72.47	78.74	80.70
10b	5.98	5.07–5.11	1.46	133.68	74.43	76.89	79.39
9c[b]	5.96–6.06	5.34–5.39	1.56	134.90	73.24	78.23	82.17
10c[b]	5.96–6.02	5.08–5.24	1.51	134.41	74.37	76.98	81.74

[a] Compound **9a** (or **9b** or **9c**) was less polar on silica gel than the corresponding isomer **10a** (or **10b** or **10c**). [b] Data are adapted from ref 4a.

compound **10a** (or **10b**) was tentatively assigned to have the (2′*R*,3′*S*,7*R*,8*R*) configuration by analogy to **10c**.[4a]

Attempts to remove the benzyl protecting groups in **10a** or **10b** failed. Hydrogenation of **10a** over 5% Pd/C saturated the double bond of the retronecine moiety without cleavage at the benzyl group. Treatment of **10a** with Me₃SiI[10] in CH₂Cl₂ gave a product **11a**,[11] which was considered to be the C-8 epimer of **10a** as it showed all the characteristic proton and carbon resonances, except the chemical shifts on the retronecine ring were distinct from those of **10a**. Treatment of **10a** with dissolving metal (Li/NH₃),[12] of **10b** with DDQ[13] or CAN,[14] or photolysis (λ = 300 nm) sensitized with 1,4-dicyanonaphthalene[15] all caused rupture of the macrolides and led to intractable products. (Methylthio)methyl ether **4c**,[16] prepared by treating (±)-**2** with Me₂SO–Ac₂O,[17] was unsuitable for the total synthesis. The (methylthio)methyl protecting group decomposed upon saponification of **4c** followed by acidification with aqueous HCl.

11a

In summary, we have demonstrated a route for the synthesis of dilactones in a regioselective manner. As an example, ketene dithioacetal **2** functioned as an equivalent of 2-hydroxy-2,3-dimethylglutaric acid, so that esterification with retronecine occurred regioselectively at the desired allylic position. Upon acid-catalyzed hydrolysis, the ketene dithioacetal moiety was readily converted to a thioester suitable for the subsequent

[a] Reagents and conditions: (i) BuLi, THF, −30 °C; ZnCl₂ (3 equiv), −100 °C; 85% (92% de); (ii) aqueous EtOH, HgCl₂; 86%; (iii) for **4a**, NaH, PhCH₂Br, THF, reflux, 4 h; 95%; for **4b**, NaH, *p*-MeOC₆H₄CH₂I, THF, reflux, 16 h; 75%; (iv) *t*-BuOK (8 equiv), H₂O (2 equiv), THF, 26 °C, 0.5 h; then HCl; **5a**, 100%; **5b**, 96%; (v) *N,N*-carbonyldiimidazole (1.1 equiv), THF, 26 °C, 4 h; **6a**, 95%; **6b**, 98%; (vi) NaH (0.2 equiv), retronecine (1 equiv), THF, 26 °C, 2 h; then NH₄Cl (aq); **7a**, 93%; **7b**, 100%; (vii) HCl, CH₂Cl₂, 26 °C, 0.5 h; **8a**, 88%; **8b**, 53%. (viii) silver trifluroacetate (6 equiv), DMAP (12 equiv), THF, reflux, 40 h; **9a/10a** (1:1), 55%; **9b/10b** (1:1), 67%.

oxybenzyl iodide to give **4b**, which was subsequently transformed into the macrolides **9b** and **10b** (1:1). These two isomers also showed characteristic resonances in their ¹H and ¹³C NMR spectra (Table 1). The more polar
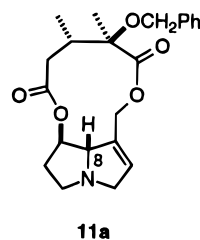
(10) (a) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761. (b) Olah, G. A.; Narang, S. C. *Tetrahedron* **1982**, *38*, 2225.

(11) Compound **11a**: ¹H NMR (CDCl₃) δ 1.07 (d, *J* = 6.9 Hz, 3 H), 1.52 (s, 3 H), 2.29 (dd, *J* = 3.6, 15.6 Hz, 1 H), 2.46–2.52 (m, 4 H), 2.77 (dd, *J* = 15.6, 11.1 Hz, 1 H), 3.00–3.12 (m, 1 H), 3.68 (d, *J* = 16.4 Hz, 1 H), 4.10–4.20 (m, 1 H), 4.42, 4.68 (AB quartet, *J* = 11.0 Hz, 2 H), 4.70–4.80 (m, 1 H), 4.48, 5.16 (AB quartet, *J* = 12.3 Hz, 2 H), 5.33 (br s, 1 H), 6.10 (s, 1 H), 7.27–7.42 (m, 5 H); ¹³C NMR (CDCl₃) δ 15.31 (q), 20.65 (q), 33.68 (t), 37.55 (t), 38.25 (d), 54.35 (t), 56.10 (t), 59.99 (t), 66.45 (t), 72.00 (d), 78.20 (d), 79.44 (s), 127.37 (d, 3 C), 128.25 (d, 2 C), 129.70 (d), 131.77 (s), 138.64 (s), 169.64 (s), 173.58 (s).

(12) Philips, K. D.; Zemlicka, J.; Horowitz, J. P. *Carbohydr. Res.* **1973**, *30*, 281.

(13) Trost, B. M.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1985**, *107*, 4586.

(14) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371.

(15) Pandey, G.; Krishna, A. *Synth. Commun.* **1988**, *18*, 2309.

(16) Compound **4c**: ¹H NMR (CDCl₃) δ 0.99 (d, *J* = 6.9 Hz, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 1.41 (s, 3 H), 2.08–2.15 (m, 2 H), 2.20 (s, 3 H), 2.78–2.87 (m, 4 H), 3.11–3.20 (m, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.48, 4.62 (AB quartet, *J* = 10.4 Hz, 2 H), 5.94 (d, *J* = 10.0 Hz, 1 H).

(17) Pojer, P. M.; Angyal, S. J. *Aust. J. Chem.* **1978**, *31*, 1031.

macrolactonization. This is the first report that a ketene dithioacetal can be hydrolyzed to a thioester and used in the synthesis of pyrrolizidine alkaloids.

Experimental Section

Mass spectra were recorded at an ionizing voltage 70 or 20 eV. A quartz cuvette (length 10 cm) was used for optical rotation measurements. Merck silica gel 60F sheets were used for analytical TLC. Column chromatography was conducted on silica gel 60 (Merck, 70−230 mesh ASTM). A μ-Porasil column (25 cm × 7.8 mm i.d.) was used for HPLC; the flow rate of indicated eluent was 5 mL/min. Retronecine, $[\alpha]^{26}{}_{D} = +50.1°$ (*c* 1.2, ethanol), was prepared by hydrolysis of monocrotaline according to the literature procedure.[4] Preparation of (±)-**2** was reported.[2]

Ethyl 2-(Benzyloxy)-2,3-dimethyl-4-(1,3-dithianylidene)butanoate (4a). Under an atmosphere of argon, a suspension of NaH (0.45 g of 60% oil dispersion, 11.3 mmol) in anhydrous THF (20 mL) was placed in a 50 mL round-bottomed flask equipped with a refluxing condenser and capped with a septum. A solution of alcohol (±)-**2** (1.57 g, 5.7 mmol) in THF (5 mL) was added dropwise at 25 °C. The evolution of H_2 was apparent. The mixture was stirred for 10 min to give a turbid solution, after which $PhCH_2Br$ (0.5 mL, 5 mmol) in THF (5 mL) was added dropwise. The mixture was heated at reflux for 4 h and cooled, and saturated NH_4Cl aqueous solution (5 mL) was added. THF was removed by rotary evaporation, and the residue was extracted with EtOAc (2 × 30 mL). The organic phase was washed with brine, dried (Na_2SO_4), and filtered, and the filtrate was concentrated by rotary evaporation. The residue was chromatographed on a silica gel column by elution with EtOAc/hexane (1:9) to give benzyl ether (±)-**4a** (1.98 g, 95%): oil; R_f 0.35 (EtOAc/hexane (1:9)); IR (neat) 1725, 697 cm^{-1}; MS m/z (rel intensity) 366 (0.5, M$^+$), 293 (3), 159 (100) , 132 (14), 91 (27); ^{1}H NMR (CDCl$_3$) δ 1.05 (d, $J = 6.9$ Hz, 3 H), 1.29 (t, $J = 7.2$ Hz, 3 H), 1.47 (s, 3 H), 2.04−2.19 (m, 2 H), 2.78−2.87 (m, 4 H), 3.24 (dq, $J = 10.1$, 6.9 Hz, 1 H), 4.19 (q, $J = 7.2$ Hz, 2 H), 4.45, 4.57 (AB quartet, $J = 11.3$ Hz, 2 H), 6.45 (d, $J = 10.1$ Hz, 1 H), 7.21−7.42 (m, 5 H); ^{13}C NMR (CDCl$_3$) δ 14.04 (q), 14.33 (q), 18.82 (q), 24.83 (t), 29.36 (t), 29.96 (t), 42.06 (d), 60.53 (t), 66.16 (t), 81.85 (s), 126.77 (s), 126.87 (d, 3 C), 127.81 (d, 2 C), 134.17 (d), 138.80 (s), 173.06 (s); HRMS for C$_{19}$H$_{26}$O$_3$S$_2$ calcd 366.1323, found 366.1329.

Ethyl 2,3-Dimethyl-4-(1,3-dithianylidene)-2-[(4-methoxybenzyl)oxy]butanoate (4b). *p*-Methoxybenzyl iodide was prepared from *p*-methoxybenzyl bromide and NaI in Me$_2$CO. Alcohol **2** (0.83 g) was treated with NaH and *p*-methoxybenzyl iodide by a procedure similar to that for **4a** to give *p*-methoxybenzyl ether (±)-**4b** (0.89 g, 75%): oil; R_f 0.22 (MeOH/CH$_2$Cl$_2$ (1:9)); IR (neat) 1726 cm^{-1}; MS m/z (rel intensity) 396 (12, M$^+$), 323 (4), 289 (1), 260 (35), 159 (100), 132 (148), 121 (78), 91 (8); ^{1}H NMR (CDCl$_3$) δ 1.01 (d, $J = 6.9$ Hz, 3 H), 1.28 (t, $J = 7.3$ Hz, 3 H), 1.44 (s, 3 H), 2.05−2.17 (m, 2 H), 2.75−2.85 (m, 4 H), 3.20 (dq, $J = 10.1$, 6.9 Hz, 1 H), 3.78 (s, 3 H), 4.17 (q, $J = 7.3$ Hz, 2 H), 4.35, 4.46 (AB quartet, $J = 10.7$ Hz, 2 H), 6.01 (d, $J = 10.1$ Hz, 1 H), 6.84 (d, $J = 8.5$ Hz, 2 H), 7.29 (d, $J = 8.5$ Hz, 2 H); ^{13}C NMR (CDCl$_3$) δ 14.29 (q), 14.57 (q), 19.09 (q), 25.13 (t), 29.64 (t), 30.27 (t), 42.30 (d), 55.21 (q), 60.78 (t), 66.16 (t), 82.08 (s), 113.53 (d, 2 C), 126.83 (s), 128.70 (d, 2 C), 131.21 (s), 134.71 (d), 158.81 (s), 173.50 (s); HRMS for C$_{20}$H$_{28}$O$_4$S$_2$ calcd 396.1429, found 396.1430.

2-(Benzyloxy)-2,3-dimethyl-4-(1,3-dithianylidene)butanoic Acid (5a). To a solution of ester (±)-**4a** (280 mg, 0.76 mmol) and H$_2$O (27 mg, 1.53 mmol) in THF (10 mL) was added *t*-BuOK (0.68 g, 6.1 mmol) at 0 °C. The orange solution was stirred at 25 °C for 0.5 h, HCl (0.55 mL of 12 N solution) was added, and the solution was concentrated by rotary evaporation. The residue was extracted with EtOAc (2 × 30 mL), the combined extracts were washed with brine, dried (Na$_2$SO$_4$), and filtered, and the filtrate was concentrated by rotary evaporation. The residue was chromatographed on a silica gel column by elution with EtOAc to give acid (±)-**5a** (795 mg, 96%): oil; R_f 0.55 (EtOAc); IR (neat) 3500−2400 , 1705, 1277, 697 cm^{-1}; MS m/z (rel intensity) 339 (7, M$^+$ + 1), 338 (5, M$^+$)

293 (4), 232 (12), 187 (1), 159 (100), 132 (18), 91 (23); ^{1}H NMR (CDCl$_3$) δ 0.99 (d, $J = 6.6$ Hz, 3 H), 1.38 (s, 3 H), 2.00−2.12 (m, 2 H), 2.70−2.85 (m, 4 H), 3.24 (dq, $J = 10.1$, 6.6 Hz, 1 H), 4.42, 4.51 (AB quartet, $J = 11.6$ Hz, 2 H), 6.09 (d, $J = 10.1$ Hz, 1 H), 7.17−7.34 (m, 5 H), 9.52 (br s, 1 H); ^{13}C NMR (CDCl$_3$) δ 15.05 (q), 19.07 (q), 25.17 (t), 29.67 (t), 30.29 (t), 41.16 (d), 65.70 (t), 83.12 (s), 126.53 (s), 126.94 (d, 3 C), 128.16 (d, 2 C), 135.61 (d), 139.05 (s), 178.06 (s); HRMS for C$_{17}$H$_{22}$O$_3$S$_2$ calcd 338.1010, found 338.0983.

2,3-Dimethyl-4-(1,3-dithianylidene)-2-[(4-methoxybenzyl)oxy]butanoic Acid (5b). Ester (±)-**4b** (0.89 g) was saponified by a procedure similar to that for **5a** to give acid (±)-**5b** (0.80 g, 96%): oil; R_f 0.28 (EtOAc/hexane (1:1)); IR (neat) 3500−2400 , 1708, 1505, 1245 cm^{-1}; MS m/z (rel intensity) 368 (4, M$^+$), 323 (0.5), 159 (100), 132 (30), 121 (46); ^{1}H NMR (CDCl$_3$) δ 1.03 (d, $J = 6.9$ Hz, 3 H), 1.47 (s, 3 H), 1.98−2.11 (m, 2 H), 2.76−2.84 (m, 4 H), 3.26 (dq, $J = 10.1$, 6.9 Hz, 1 H), 3.75 (s, 3 H), 4.41, 4.48 (AB quartet, $J = 10.6$ Hz, 2 H), 6.03 (d, $J = 10.1$ Hz, 1 H), 6.82 (d, $J = 8.5$ Hz, 2 H), 7.26 (d, $J = 8.5$ Hz, 2 H), 9.30 (br s, 1 H); ^{13}C NMR (CDCl$_3$) δ 14.56 (q), 19.08 (q), 25.00 (t), 25.59 (t), 30.17 (t), 41.40 (d), 55.13 (q), 65.97 (t), 82.24 (s), 113.60 (d, 2 C), 127.75 (s), 128.90 (d, 2 C), 130.27 (s), 134.00 (d), 158.94 (s), 177.71 (s); HRMS for C$_{18}$H$_{24}$O$_4$S$_2$ calcd 368.1116, found 368.1119.

2-(Benzyloxy)-2,3-dimethyl-4-(1,3-dithianylidene)butanoyl Imidazolide (6a). Under argon atmosphere, a solution of acid (±)-**5a** (258 mg, 0.76 mmol) in THF (5 mL) was added to a solution of 1,1′-carbonyldiimidazole (136 mg, 0.84 mmol) in THF (5 mL). The mixture was stirred at 25 °C for 4 h, after which it was concentrated by rotary evaporation. The residue was partitioned between CH$_2$Cl$_2$ and water, and the aqueous layer was extracted with Et$_2$O (2 × 30 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated by rotary evaporation to yield the corresponding imidazolide (±)-**6a** (282 mg, 95%). Further purification was conducted by chromatography on a silica gel column with elution of EtOAc/hexane (1:1): oil; R_f 0.43 (EtOAc/hexane (1:1)); IR (neat) 1715, 1462, 1284, 1234 cm^{-1}; MS m/z (rel intensity) 388 (4, M$^+$), 297 (4), 293 (14), 159 (100), 91 (12); ^{1}H NMR (CDCl$_3$) δ 0.96 (d, $J = 6.9$ Hz, 3 H), 1.55 (s, 3 H), 2.10−2.16 (m, 2 H), 2.61−2.70 (m, 1 H), 2.79−2.88 (m, 3 H), 3.53 (dq, $J = 9.9$, 6.9 Hz, 1 H), 4.25, 4.55 (AB quartet, $J = 11.4$ Hz, 2 H), 5.89 (d, $J = 9.9$ Hz, 1 H), 7.03 (s, 1 H), 7.23−7.35 (m, 5 H), 7.81 (s, 1 H), 8.70 (s, 1 H); ^{13}C NMR (CDCl$_3$) δ 15.03 (q), 16.25 (q), 24.58 (t), 29.27 (t), 29.74 (t), 41.24 (d), 66.50 (t), 85.92 (s), 117.21 (d), 126.86 (d, 2 C), 127.29 (d), 127.97 (d, 2 C), 129.54 (d), 130.31 (s), 131.44 (d), 136.80 (s), 137.95 (d), 171.88 (s); HRMS for C$_{20}$H$_{24}$N$_2$O$_2$S$_2$ calcd 388.1279, found 388.1277.

2,3-Dimethyl-4-(1,3-dithianylidene)-2-[(4-methoxybenzyl)oxy]butanoyl Imidazolide (6b). Acid (±)-**5b** (194 mg) was treated with 1,1′-carbonyldiimidazole by a procedure similar to that for **6a** to give imidazolide (±)-**6b** (215 mg, 98%): oil; R_f 0.30 (EtOAc/hexane (35:65)); IR (neat) 3142, 1714, 1508, 1246 cm^{-1}; MS m/z (rel intensity) 418 (0.5, M$^+$), 323 (2), 159 (100), 132 (38), 121 (36), 68 (35); ^{1}H NMR (CDCl$_3$) δ 0.91 (d, $J = 6.8$ Hz, 3 H), 1.50 (s, 3 H), 2.03−2.11 (m, 2 H), 2.58−2.65 (m, 1H), 2.77−2.83 (m, 3 H), 3.46 (dq, $J = 9.9$, 6.8 Hz, 1 H), 3.75 (s, 3 H), 4.13, 4.45 (AB quartet, $J = 10.7$ Hz, 2 H), 5.84 (d, $J = 9.9$ Hz, 1 H), 6.78 (d, $J = 8.5$ Hz, 2 H), 6.98 (s, 1 H), 7.11 (d, $J = 8.5$ Hz, 2 H), 7.75 (s, 1 H), 8.64 (s, 1 H); ^{13}C NMR (CDCl$_3$) δ 15.30 (q), 16.66 (q), 24.91 (t), 29.61 (t), 30.13 (t), 41.53 (d), 55.15 (q), 66.63 (t), 86.03 (s), 113.67 (d, 2 C), 117.55 (d), 128.91 (d, 2 C), 129.05 (s), 130.40 (s), 130.40 (d), 132.05 (d), 138.37 (d), 159.11 (s), 172.39 (s); HRMS for C$_{21}$H$_{26}$N$_2$O$_3$S$_2$ calcd 418.1385, found 418.1390.

Retronecine Ester of 2-(Benzyloxy)-2,3-dimethyl-4-(1,3-dithianylidene)butanoic Acid (7a). To a suspension of NaH (5 mg of 80% oil dispersion, 0.17 mmol) in anhydrous THF (10 mL) was added (+)-retronecine (124 mg, 0.80 mmol) at 25 °C under argon atmosphere. The suspension was stirred at 25 °C for 5 min, and evolution of H_2 ceased, after which a solution of (±)-**6a** (311 mg, 0.80 mmol) in THF (10 mL) was added dropwise over a period of 1 min. The reaction mixture was stirred for 2 h, and aqueous NH$_4$Cl (9 mg in 0.1 mL of water, 0.17 mmol) was added, after which the mixture was stirred for 5 min. The solution was concentrated by rotary

evaporation, and the residue was chromatographed on a silica gel column by elution with MeOH/CH$_2$Cl$_2$ (1:9) to give crude ester **7a** contaminated with imidazole. The crude ester was dissolved in CH$_2$Cl$_2$ (20 mL), IR-120 resin (acidic form) was added, and the resulting mixture was stirred for 1 h. The mixture was filtered, and the filtrate was concentrated to give pure **7a** (351 mg, 93%): oil; R_f 0.26 (MeOH/CH$_2$Cl$_2$ (1:9)); IR (neat) 3200, 1730, 1063 cm^{-1}; MS m/z (rel intensity) 476 (10, M$^+$ + 1), 475 (1, M$^+$), 339 (5), 159 (100), 138 (20), 106 (10), 91 (36); ^{1}H NMR (CDCl$_3$) δ 1.06 (d, J = 6.8 Hz, 3 H), 1.51 (s, 3 H), 2.00–2.17 (m, 4 H), 2.76–2.97 (m, 5 H), 3.21–3.30 (m, 1 H), 3.43–3.58 (m, 2 H), 4.10 (br d, J = 15.3 Hz, 1 H), 4.37-4.44 (m, 2 H), 4.50–4.52 (m, 2 H), 4.65–4.90 (m, 2 H), 5.82 (br s, 1 H), 6.01 (d, J = 10.1 Hz, 1 H), 7.22–7.38 (m, 5 H); ^{13}C NMR (CDCl$_3$) δ 14.28 (q), 18.87 (q), 24.71 (t), 29.30 (t), 29.86 (t), 35.71 (t), 41.93 (d), 53.26 (t), 61.36 (t), 61.72 (t), 66.10 (t), 70.10 (d), 77.96 (d), 82.09 (s), 126.74 (d, 3 C), 126.79 (d), 127.42 (s), 127.84 (d, 2 C), 132.84 (s), 133.40 (d), 138.42 (s), 172.85 (s); HRMS for C$_{25}$H$_{33}$NO$_4$S$_2$ calcd 475.1851, found 475.1842.

Retronecine Ester of 2,3-Dimethyl-4-(1,3-dithianyl-idene)-2-[(4-methoxybenzyl)oxy]butanoic Acid (7b). Treatment of imidazolide (±)-**6b** (401 mg) with (+)-retronecine by a procedure similar to that for **7a**, after removal of residual imidazole with IR-120 resin, gave ester **7b** (484 mg, 100%): oil; R_f 0.24 (MeOH/CH$_2$Cl$_2$ (1:9)); IR (neat) 3200, 1730 cm^{-1}; MS m/z (rel intensity) 506 (1, M$^+$ + 1), 505 (0.1, M$^+$), 367 (2), 232 (2), 159 (60), 132 (15), 121 (21); ^{1}H NMR (CDCl$_3$) δ 1.00 (d, J = 6.7 Hz, 3 H), 1.46 (s, 3 H), 1.89–2.00 (m, 2 H), 2.05–2.13 (m, 2 H), 2.71–2.90 (m, 5 H), 3.14–3.25 (m, 1 H), 3.42–3.53 (m, 2 H), 3.76 (s, 3 H), 4.10 (br d, J = 15.6 Hz, 1 H), 4.28–4.35 (m, 2 H), 4.37–4.50 (m, 2 H), 4.65–4.85 (m, 2 H), 5.78 (br s, 1 H), 5.94 (d, J = 10.1 Hz, 1 H), 6.86 (d, J = 8.7 Hz, 2 H), 7.24 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 14.53 (q), 19.24 (q), 24.97 (t), 29.58 (t), 30.12 (t), 35.67 (t), 42.07 (d), 53.95 (t), 55.21 (q), 61.45 (t), 61.91 (t), 66.07 (t), 70.39 (d), 78.70 (d), 82.31 (s), 113.59 (d, 2 C), 127.35 (d), 127.65 (s), 128.76 (d, 2 C), 130.47 (s), 132.55 (s), 133.70 (d), 158.93 (s), 173.18 (s); HRMS for C$_{26}$H$_{35}$NO$_5$S$_2$ calcd 505.1957, found 505.1955.

Retronecine Ester of 2-(Benzyloxy)-2,3-dimethyl-4-[[(3-mercaptopropyl)sulfanyl]carbonyl]butanoic Acid (8a). To a stirring solution of **7a** (321 mg, 0.68 mmol) in CH$_2$Cl$_2$ (20 mL) was added HCl (37%, 0.25 mL) at 25 °C; the solution turned pink immediately. After 0.5 h, the solution was concentrated by rotary evaporation, and the residue was chromatographed on a silica gel column by elution with MeOH/CH$_2$Cl$_2$ (1:9) to give thioester **8a** (294 mg, 88%): oil; R_f 0.26 (MeOH/CH$_2$Cl$_2$ (1:9)); IR (neat) 3341, 1726 (ester), 1682 (thioester), 699 cm^{-1}; MS (20 eV) m/z (rel intensity) 493 (4, M$^+$), 386 (4), 369 (4), 278 (10), 200 (21), 138 (100), 113 (97); ^{1}H NMR (CDCl$_3$) δ 0.97 (d, J = 6.5 Hz, 3 H), 1.46 (s, 3 H), 1.85 (quin, J = 7.0 Hz, 2 H), 2.01–2.10 (m, 2 H), 2.40–2.70 (m, 2 H), 2.55 (t, J = 7.0 Hz, 2 H), 2.79–2.99 (m, 2 H), 2.96 (t, J = 7.0 Hz, 2 H), 3.50–3.70 (m, 2 H), 4.21 (br d, J = 15.4 Hz, 1 H), 4.50–4.62 (m, 4 H), 4.70, 4.81 (AB quartet, J = 13.8 Hz, 2 H), 5.78 (br s, 1 H), 7.26–7.35 (m, 5 H); ^{13}C NMR (CDCl$_3$) δ 14.42 (q), 17.21 (q), 23.27 (t), 27.27 (t), 33.39 (t), 35.83 (t), 38.10 (d), 45.86 (t), 53.93 (t), 61.27 (t), 61.40 (t), 66.57 (t), 70.21 (d), 78.53 (d), 82.44 (s), 126.73 (d, 3 C), 127.13 (d), 128.26 (d, 2 C), 132.80 (s), 138.10 (s), 173.18 (s), 198.64 (s); HRMS for C$_{25}$H$_{35}$NO$_5$S$_2$ calcd 493.1957, found 493.1968.

Retronecine Ester of 2,3-Dimethyl-4-[[(3-mercapto-propyl)sulfanyl]carbonyl]-2-[(4-methoxybenzyl)oxy]butanoic Acid (8b). Ester **7b** (784 mg) was treated with concd HCl by a procedure similar to that for **8a** to give thioester **8b** (432 mg, 53%): oil; IR (neat) 3358, 1723 (ester), 1675 (thioester) cm^{-1}; MS m/z (rel intensity) 524 (2, M$^+$ + 1), 523 (0.3, M$^+$), 369 (1), 278 (2), 249 (3), 228 (4), 137 (25), 121 (100); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.92 (d, J = 6.7 Hz, 3 H), 1.41 (s, 3 H), 1.81 (quin, J = 7.0 Hz, 2 H), 1.93–2.00 (m, 2 H), 2.38–2.60 (m, 2 H), 2.52 (t, J = 7.0 Hz, 2 H), 2.76–2.85 (m, 2 H), 2.92 (t, J = 7.0 Hz, 2 H), 3.35–3.46 (m, 2 H), 3.76 (s, 3 H), 4.01 (br d, J = 15.6 Hz, 1 H), 4.25–4.40 (m, 4 H), 4.62–4.80 (m, 2 H), 5.81 (br s, 1 H), 6.83 (d, J = 8.6 Hz, 2 H), 7.23 (d, J = 8.6 Hz, 2 H); ^{13}C NMR (CDCl$_3$) δ 14.39 (q), 17.17 (q), 23.96 (t), 27.26

(t), 33.47 (t), 35.95 (t), 38.05 (d), 45.84 (t), 53.91 (t), 55.23 (q), 61.83 (t), 62.43 (t), 66.33 (t), 70.70 (d), 78.54 (d), 82.24 (s), 113.66 (d, 2 C), 128.80 (d, 2 C), 128.95 (d), 130.22 (s), 132.75 (s), 159.03 (s), 173.44 (s), 198.60 (s); HRMS for C$_{26}$H$_{37}$NO$_6$S$_2$ calcd 523.2062, found 523.2060.

Crobarbatine Derivatives 9a and 10a. Under an argon atmosphere, a solution of thioester **8a** (56 mg, 0.11 mmol) in anhydrous THF (10 mL) was added dropwise over a period of 2 h to a refluxing THF (30 mL) solution containing 4-(di-methylamino)pyridine (166 mg, 1.36 mmol) and silver(I) trifluoroacetate (145 mg, 0.68 mmol). The resulting green solution was heated at reflux for an additional 40 h, cooled, and stirred at room temperature for 2 h. The mixture was bubbled with H$_2$S (prepared from FeS and dilute H$_2$SO$_4$) until no more black precipitate appeared. The black precipitate was filtered, and the filtrate was concentrated and chromatographed on a silica gel column by elution with MeOH/CH$_2$Cl$_2$ (1:9), R_f 0.37, to give dilactones **9a** and **10a** (24 mg, 55%, 1:1 ratio). Two isomers were separated by HPLC. **9a**: oil; t_R 7.83 min (MeOH/CH$_2$Cl$_2$ (2:8)); [α]$^{26}_D$ = +32.3° (c 1.12, CHCl$_3$); IR (neat) 1731, 699 cm^{-1}; MS m/z (rel intensity) 385 (6, M$^+$), 279 (32), 251 (35), 220 (23), 135 (52), 119 (100), 91 (28); ^{1}H NMR (CDCl$_3$) δ 1.10 (d, J = 7.1 Hz, 3 H), 1.53 (s, 3 H), 1.92–2.15 (m, 2 H), 2.02 (dd, J = 16.6, 1.6 Hz, 1 H), 2.45 (ddq, J = 10.1, 7.1, 1.6 Hz, 1 H), 2.72–2.79 (m, 1H), 3.03 (dd, J = 16.6, 10.7 Hz, 1 H), 3.28 (ddd, J = 8.9, 6.9, 2.0 Hz, 1 H), 3.50 (dd, J = 20.3, 5.5 Hz, 1 H), 3.94 (dd, J = 20.3, 1.9 Hz, 1 H), 4.34, 4.46 (AB quartet, J = 11.3 Hz, 2 H), 4.45–4.47 (m, 1 H), 4.43, 4.55 (AB quartet, J = 11.6 Hz, 2 H), 5.59 (ddd, J = 5.2, 5.2, 1.8 Hz, 1 H), 5.88 (br d, J = 1.9 Hz, 1H), 7.25–7.41 (m, 5 H); ^{13}C NMR (CDCl$_3$) δ 16.10 (q), 20.37 (q), 33.17 (t), 37.24 (t), 38.75 (d), 54.18 (t), 59.27 (t), 61.13 (t), 66.97 (t), 72.54 (d), 78.64 (d), 80.83 (s), 127.36 (d, 3 C), 128.10 (d, 2 C), 132.40 (s), 134.94 (d), 138.89 (s), 173.08 (s), 174.19 (s); HRMS for C$_{22}$H$_{27}$NO$_2$ calcd 385.1890, found 385.1895. **10a**: oil, t_R 9.83 min (MeOH/CH$_2$Cl$_2$ (2:8)); [α]$^{26}_D$ = −41.5° (c 0.53, CHCl$_3$); IR (neat) 1738, 699 cm^{-1}; MS m/z (rel intensity) 385 (0.1, M$^+$), 279 (8), 251 (35), 220 (10), 136 (40), 119 (60), 91 (28); ^{1}H NMR (CDCl$_3$) δ 1.03 (d, J = 6.9 Hz, 3 H), 1.49 (s, 3 H), 2.00–2.11 (m, 2 H), 2.19 (dd, J = 15.7, 3.2 Hz, 1 H), 2.45–2.65 (m, 2 H), 2.79 (dd, J = 15.7, 11.1 Hz, 1 H), 3.19–3.30 (m, 1 H), 3.46 (dd, J = 16.4, 5.6 Hz, 1 H), 3.97 (br d, J = 16.4 Hz, 1 H), 4.38–4.44 (m, 1 H), 4.39, 5.11 (AB quartet, J = 11.4 Hz, 2 H), 4.40, 4.73 (AB quartet, J = 11.1 Hz, 2 H), 5.08–5.14 (m, 1 H), 6.00 (br d, J = 1.9 Hz, 1 H), 7.25–7.46 (m, 5 H); ^{13}C NMR (CDCl$_3$) δ 15.43 (q), 20.81 (q), 33.70 (t), 37.36 (t), 38.65 (d), 53.79 (t), 57.52 (t), 61.51 (t), 66.28 (t), 74.56 (d), 76.79 (d), 79.49 (s), 127.14 (d, 3 C), 128.16 (d, 2 C), 133.58 (s), 133.88 (d), 139.15 (s), 170.64 (s), 173.50 (s); HRMS for C$_{22}$H$_{27}$NO$_2$ calcd 385.1890, found 385.1895.

Crobarbatine Derivatives 9b and 10b. Thioester **8b** (73 mg) was treated with silver trifluoroacetate and 4-(dimethyl-amino)pyridine by a procedure similar to that for **9a/10a** to give dilactones **9b** and **10b** (1:1; 39 mg, 67%). **9b**: t_R 14.5 min (MeOH/CH$_2$Cl$_2$ (1:9)); [α]$^{23}_D$ = +39.0° (c 0.20, CHCl$_3$); IR (neat) 1735, 1247 cm^{-1}; MS m/z (rel intensity) 416 (8, M$^+$ + 1), 415 (1, M$^+$), 294 (4), 279 (19), 250 (41), 220 (23), 136 (47), 121 (100); ^{1}H NMR (CDCl$_3$) δ 1.06 (d, J = 7.0 Hz, 3 H), 1.50 (s, 3 H), 1.93–2.07 (m, 2 H), 1.97 (dd, J = 16.5, 1.2 Hz, 1 H), 2.42 (ddq, 10.9, 7.0, 1.2 Hz, 1 H), 2.65–2.80 (m, 1 H), 2.99 (dd, J = 10.5, 16.5 Hz, 1 H), 3.25 (ddd, J = 8.8, 6.7, 2.2 Hz, 1 H), 3.49 (dd, J = 16.6, 4.3 Hz, 1 H), 3.78 (s, 3 H), 3.93 (br d, J = 16.6 Hz, 1 H), 4.24, 4.36 (AB quartet, J = 10.7 Hz, 2 H), 4.34–4.45 (m, 1 H), 4.46, 4.62 (AB quqrtet, J = 11.7 Hz, 2 H), 5.58 (ddd, J = 5.3, 5.3, 1.9 Hz, 1 H), 5.91 (br d, J = 1.8 Hz, 1 H), 6.84 (d, J = 8.7 Hz, 2 H), 7.30 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (CDCl$_3$) δ 16.11 (q), 20.43 (q), 33.20 (t), 37.20 (t), 38.72 (d), 54.24 (t), 55.30 (q), 59.27 (t), 61.13 (t), 66.70 (t), 72.47 (d), 78.74 (d), 80.70 (s), 113.53 (d, 2 C), 128.90 (d, 2 C), 130.97 (s), 132.51 (s), 134.86 (d), 159.03 (s), 173.13 (s), 174.33 (s); HRMS for C$_{23}$H$_{29}$NO$_6$ calcd 415.1995, found 415.2020. **10b**: t_R 16.3 min (MeOH/CH$_2$Cl$_2$ (1:9)); [α]$^{23}_D$ −46.8° (c 0.47, CHCl$_3$); IR (neat) 1735, 1246 cm^{-1}; MS m/z (rel intensity) 416 (5, M$^+$ + 1), 415 (1, M$^+$), 294 (2), 279 (10), 250 (27), 220 (13), 136 (29), 121 (100); ^{1}H NMR (CDCl$_3$) δ 0.99 (d, J = 7.0 Hz, 3 H), 1.46 (s, 3 H), 2.00–2.09

(m, 2 H), 2.15 (dd, $J = 15.8$, 3.2 Hz, 1 H), 2.42−2.68 (m, 2 H), 2.73 (dd, $J = 11.2$, 15.8 Hz, 1 H), 3.25−3.31 (m, 1 H), 3.46 (dd, $J = 16.0$, 5.3 Hz, 1 H), 3.78 (s, 3 H), 3.98 (br d, $J = 16.0$ Hz, 1 H), 4.40−4.48 (m, 1 H), 4.30, 4.61 (AB quartet, $J = 10.5$ Hz, 2 H), 4.37, 5.09 (AB quartet, $J = 11.6$ Hz, 2 H), 5.07- 5.11 (m, 1 H), 5.98 (br s, 1 H), 6.87 (d, $J = 8.5$ Hz, 2 H), 7.34 (d, $J = 8.5$ Hz, 2 H); ^{13}C NMR (CDCl$_3$) δ 15.40 (q), 20.82 (q), 33.70 (t), 37.33 (t), 38.61 (d), 53.81 (t), 55.27 (q), 57.42 (t), 61.41 (t), 66.01 (t), 74.43 (d), 76.89 (d), 79.39 (s), 113.64 (d, 2 C), 128.73 (d, 2 C), 131.26 (s), 133.54 (s), 133.68 (d), 158.87 (s), 170.64 (s), 173.60 (s); HRMS for C$_{23}$H$_{29}$NO$_6$ calcd 415.1995, found 415.2002.

Supporting Information Available: NMR spectra of new compounds (30 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.

JO951363Y