An Improved Synthesis of a Template for α-Helix Formation

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Received September 26, 1994

Previously we described the utility of the tricyclic-diprolyl structure **1a** as a template for inducing helicity in short *N*-terminally linked peptides (cf. **1b** Figure 1).[1,2] Peptides of predictable structure find application in medicinal chemistry[3] and as models for probing the energetics that underlie the protein folding process. By extending the range of peptides that can exhibit demonstrable helicity, *N*-terminal helical templates potentially provide a means of extending the scope of these applications. Unfortunately, the availability of **1** was limited by our previous synthesis.[4] Herein, we report a greatly improved synthesis of **1c** starting from L-proline and 4-hydroxy-L-proline by a novel tandem intramolecular acyl-transfer–cyclization process.

The formation of the central eight-membered ring of **1c** was initially explored through synthesis of a model compound that lacked the carbomethoxy group,[5] since prior work had shown that *trans*-2,5-disubstituted inductively deactivated pyrrolidines can be difficult to acylate.[6] Although the ring formation was expected to be facilitated by the absence of the electron-withdrawing carbomethoxy group, the lactamization nevertheless proceeded in low yield and required careful choice of activated acyl derivative, high dilution, elevated temperature, and long reaction time. The substantial ring strain of the product is the likely origin of these difficulties.

For **1c** itself, molecular mechanics calculations give a strain energy estimate of 15–17 kcal/mol, and severe angular distortions and close van der Waals contacts are evident in the X-ray structure of **1a**.[4] The lactamization that generates **1c** proved to be more difficult than with the model. Despite systematic efforts to optimize conditions for ring closure, yields never exceeded 28% and more typically fell in the range of 5–15%. Thus, further improvement of this lactamization approach to **1c** was deemed unlikely.

An alternative route to **1c** could be envisioned wherein the acylation step would be separated from the reaction

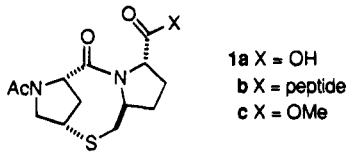
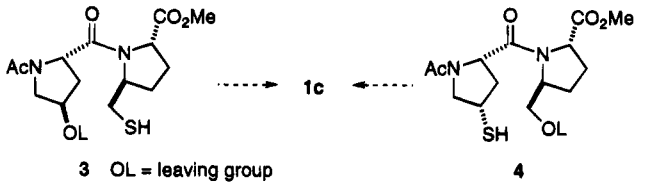


Figure 1.

Scheme 1



in which the eight-membered ring would be closed. Thus, with the prolyl-amide bond in place, the macrocycle would be formed by one of two possible internal thiol alkylation reactions (see **3** or **4** → **1c**, Scheme 1). Two potential problems could arise with such an approach. The unveiling of a thiol in the presence of a good leaving group could lead to unwanted side reactions. Also, given the significant strain energy in the product **1c**, a good leaving group might sooner participate in elimination than substitution under forcing cyclization conditions. We now report the synthesis of **1c** by the intramolecular thiol alkylation implied by the transformation of **3** → **1c** (Scheme 1).

As in the previous synthesis of **1c** the pyrrolidine subunits **5** and **6** (Figure 2) were logical candidates for the construction of a compound like **3**. The synthesis of **5** was efficiently accomplished from 4-hydroxy-L-proline.[4] By contrast, the original synthesis of **6** was a lengthy process starting from adipic acid, that required both the desymmetrization of the two carbonyl groups, as well as a resolution of enantiomers.

Because of their use as C_2 symmetric chiral auxiliaries, much effort has been devoted to obtaining *trans*-2,5-disubstituted pyrrolidines from chiral precursors.[7] Recently Wistrand described a short synthesis of (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid from L-proline, that generates aldehyde **10** relevant to our synthesis of **6** (see Scheme 2).[8] Thus, with only minor modifications to the work of Wistrand, **6** was synthesized in four-steps starting from *N*-(*tert*-butoxycarbonyl)-L-proline methyl ester (**7**).[9] Anodic oxidation of **7** in methanol produced the aminal **8**[10] as a mixture of diastereomers. Boron trifluoride-mediated cuprate addition to **8** using the organocopper reagent derived from (*Z*)-1-lithio-1-propene[11] generated adduct **9** stereospecifically.[12] Finally, ozonolysis

(1) Kemp, D. S.; Curran, T. P.; Boyd, J. G.; Allen, T. J. *J. Org. Chem.* **1991**, *56*, 6683–6697.

(2) Kemp, D. S.; Boyd, J. G.; Muendel, C. C. *Nature (London)* **1991**, *352*, 451–454.

(3) (a) Felix, A. M.; Zhao, Z.; Lee, Y.; Cambell, R. M. in *Proceedings of the Second International Peptide Symposium;* Du, Y.-C., Tam, J. P., Zhang, Y.-S., Eds., 1993; pp 255–258. (b) Felix, A. M.; Wang, C.-T.; Cambell, R. M.; Toome, V.; Fry, D.; Madison, V. S. In *Proceedings of the 12th American Peptide Symposium;* Smith, J. A., Rivier, J. E., Eds.; 1992; pp 77–79. (c) Felix, A. M.; Heimer, E. P.; Wang, C.-T.; Lambros, T. J.; Fournier, A.; Mowles, T. F.; Maines, S.; Campbell, R. M.; Wegrzynski, B. B.; Toome, V.; Fry, D.; Madison, V. S. *Int. J. Pept. Protein Res.* **1988**, *32*, 441–454. (d) For a recent review see: Olson, G. L.; Bolin, D. R.; Bonner, P. M.; Bös, M.; Cook, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P.; Voss, M. E. *J. Med. Chem.* **1993**, *36*, 3039–3049.

(4) Kemp, D. S.; Curran, T. P.; Davis, W. M.; Boyd, J. G.; Muendel, C. C. *J. Org. Chem.* **1991**, *56*, 6672–6682.

(5) Curran, T. P. Ph. D. Thesis, Massachusetts Institute of Technology, 1988.

(6) Kemp, D. S.; Curran, T. P. *J. Org. Chem.* **1988**, *53*, 5729–5731.

(7) (a) Ezquerra, J.; Rubio, A.; Pedregal, C.; Sanz, G.; Rodriguez, J. H.; Ruano, J. L. G. *Tetrahedron Lett.* **1993**, *34*, 4989–4992. (b) Langlois, N.; Rojas, A. *Tetrahedron* **1993**, *49*, 77–82. (c) Takano, S.; Moriya, M.; Iwabuchi, Y.; Ogasawara, K. *Tetrahedron Lett.* **1989**, *30*, 3805–3806. (d) Uchikawa, M.; Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 4577–4580. (e) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1977**, *42*, 1663–1664.

(8) Thaning, M.; Wistrand, L.-G. *Acta Chem. Scand.* **1992**, *46*, 194–199.

(9) Miles, N. J.; Sammes, P. G.; Kennewell, P. D.; Westwood, R. *J. Chem. Soc. Perkin Trans. 1* **1985**, 2299–2305.

(10) Based on ^{1}H NMR analysis, it is believed that **8** is contaminated with small amounts of the regioisomeric aminal.

(11) See: (a) Grovenstein, E. Jr.; Black, K. W.; Goel, S. C.; Hughes, R. L.; Northrop, J. H.; Streeter, D. L.; VanDerveer, D. *J. Org. Chem.* **1989**, *54*, 1671–1679. (b) Linstrumelle, G.; Kreiger, J. K.; Whitesides, G. M. *Org. Synth.* **1976**, *55*, 103–113.

(12) Wistrand, L.-G.; Skrinjar, M. *Tetrahedron* **1991**, *47*, 573–582.

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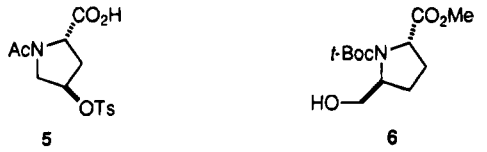
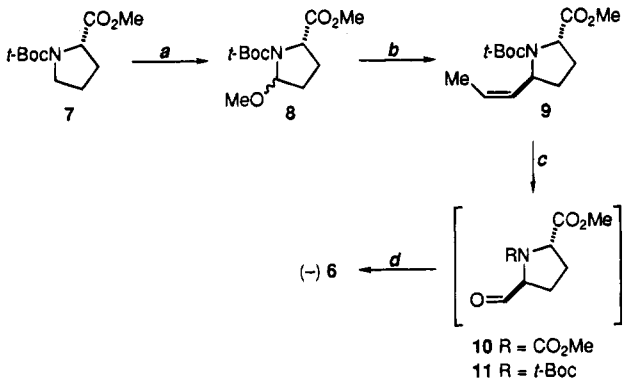


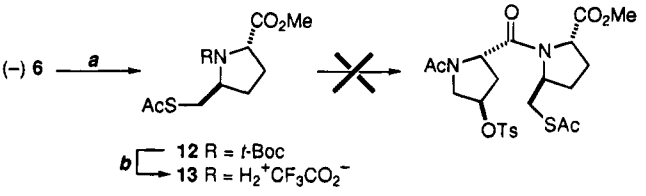
Figure 2.

Scheme 2



[a] (a) −2e, catalytic Bu_4NBF_4, MeOH, 23 °C, 93% (crude); (b) (*Z*)-1-lithio-1-propene, CuBr·DMS, Et_2O, −40 to −50 °C, $BF_3{\cdot}Et_2O$, −78 °C, and then **8**, 5 h, 60%; (c) O_3, MeOH, −78 °C, then DMS, 10 h; (d) $NaBH_4$, MeOH, 0 °C, 1 h, 88% from **9**.

Scheme 3



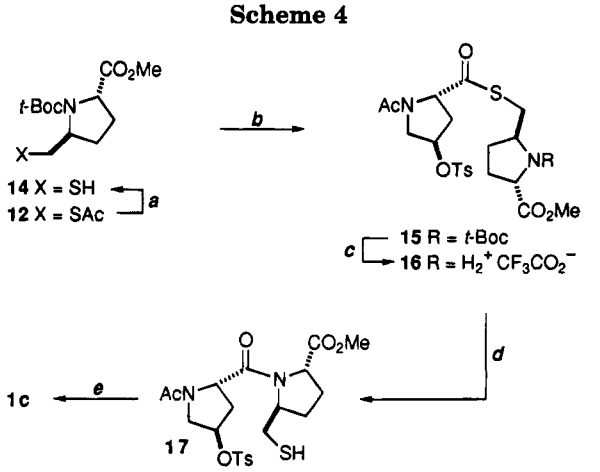
[a] (a) PPh_3, diisopropyl azodicarboxylate, AcSH and **6**, THF, 0 °C 2 h → 23 °C, 1 h, 94%; (b) TFA, CH_2Cl_2, 0 °C.

followed by sodium borohydride reduction of the crude aldehyde **11** gave the desired alcohol **6**.

From alcohol **6** the requisite sulfur was incorporated by a Mitsunobu reaction with thiolacetic acid to give **12** (Scheme 3).[13] Attempts were then made to acylate amine salt **13** with acid **5**. In these efforts it was observed that the acetate in **13** migrated to the resident nitrogen. Apparently the activated forms of **5** proved to be less effective at acylating the hindered amine than the neighboring thiolacetate. Wieland had earlier recognized that such intramolecular *S*−*N* acyl transfer processes could be useful for peptide couplings involving cysteine.[14] Applied to our system this method offered a potential solution to the otherwise difficult acylation of amine **13**.

The implementation of this strategy is shown in Scheme 4. The acetate of **12** was removed and the resultant thiol **14** was coupled[15] with **5** to give the thioester **15**. Removal of the *tert*-butoxycarbonyl group with TFA led to amine salt **16**. Heating a solution of **16** in toluene and *N*,*N*-diisopropylethylamine then gave the desired thiol **17**, which in spite of our earlier concerns could be isolated as stable compound. Remarkably, with the prolyl-amide bond now in place, the internal thiol alkylation to form the eight-membered ring proceeded in

Scheme 4



[a] (a) NH_3 in MeOH, 23 °C, 2 h, 85%; (b) **5** and 1,1-carbonyldiimidazole, CH_3CN, 0 °C, 1 h, and then **14**, 0 °C, 2 h → 23 °C, 22 h, 91%; (c) TFA, anisole, CH_2Cl_2, 0 °C, 1 h; (d) *i*-Pr_2NEt, PhMe, 60 °C, 2 h, 90% from **15**; (e) KOMe, CH_3CN, reflux, 1 h, 91%.

excellent yield with no detectable elimination of the tosylate.[16] Thus, the thiolate, generated by the addition of KOMe[17] to **17**, cyclized in acetonitrile (3×10^{-3} M at reflux)[18] to provide **1c** in 91% yield. In this way, greater than 1 g of **1c** could be conveniently prepared in a single cyclization reaction.

An efficient synthesis of the helix template **1c** has thus been accomplished. Thiol **14** and acid **5** were coupled to provide the thioester **15**. An internal *S*−*N* acyl transfer reaction then gave thiol **17**. This acyl transfer process proved more effective at forming the problematic amide bond than direct acylation methods. Cyclization of thiol **17** under high dilution conditions gave the helix template **1c** in excellent yield. Although the generality of this synthesis is untested, it is hoped that related helical template structures will prove accessible using this chemistry.

Experimental Section.

Unless otherwise noted, commercially available anhydrous ether, toluene, CH_2Cl_2, and acetonitrile were used directly. THF was distilled from sodium-benzophenone ketyl. The (*Z*)-1-lithio-1-propene was prepared from *cis*-1-bromo-1-propene (Aldrich) and lithium powder (high sodium, Aldrich) in Et_2O at −25 °C under an argon atmosphere in ca. 65% yield (based on the bromide).[11] Concentrations of the nearly colorless ethereal solutions of the alkenyllithium were typically 0.7 M as determined by titration.[19] Aminal **8** and alcohol **6** were evaporated twice from benzene and dried under high vacuum prior to use. Combustion analyses were performed by Robertson Microlit Laboratories Inc, Madison, NJ.

[2*S*-*trans*-(*Z*)]-5-Propenyl-1,2-pyrrolidinedicarboxylic Acid 1-(1,1-Dimethylethyl) 2-Methyl Diester (9). A 250 mL water-cooled cell was charged with a magnetic stir-bar, 20 g (82.7 mmol) of *N*-(*tert*-butoxycarbonyl)-L-proline methyl ester, 180 mL of methanol, and 130 mg (0.39 mmol) of Bu_4NBF_4. Two graphite plates (5 × 5 cm) were immersed in the methanolic solution and separated by 5 cm. A constant current of 260 mA was then passed through the solution (the regular addition of methanol during the electrolysis was necessary to maintain a reasonably constant volume). Progress of the anodic oxidation was monitored by ^1H NMR analysis of small aliquots removed from the

(13) Volante, R. P. *Tetrahedron Lett.* **1981**, *33*, 3119−3122.
(14) (a) Wieland, T. V.; Bokelmann, E. *Liebigs Ann. Chem.* **1952**, *576*, 20−34. (b) Wieland, T. V.; Bokelmann, E.; Bauer, L.; Lang, H. U.; Lau, H. *Liebigs Ann. Chem.* **1953**, *583*, 129−149.
(15) Gais, H.-J. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 244−246.
(16) Elimination of the tosylate was observed in attempted cyclizations using amine bases in toluene at reflux.
(17) Sodium methoxide can also be used.
(18) Lower yields were observed when reactions were run at higher concentrations (ca. 2×10^{-2}; 70% yield).
(19) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165−168.

reaction mixture. After 18 h (the passage of 0.17 F) the electrolysis was stopped, and the reaction mixture was concentrated in vacuo. The resulting residue was passed through a plug of silica eluting with 1:1 EtOAc/hexanes, and the effluent was concentrated to give 20 g (93%) of a faintly colored oil. The crude aminal **8** thus obtained was used in the subsequent reaction without further purification.

To a vigorously stirred suspension of CuBr·DMS (23.3 g, 113 mmol) in 130 mL of Et_2O was added a solution of (*Z*)-1-lithio-1-propene (0.7 M in Et_2O, 140 mL, 98 mmol) via cannula at −50 °C under an argon atmosphere. The resulting dark brown mixture was stirred for 30 min at −40 to −50 °C before being cooled to −78 °C. Boron trifluoride etherate (13.0 mL, 105 mmol) was then added slowly. After 10 min, a solution of aminal **8** (12.5 g, 48.2 mmol) in 20 mL of Et_2O was then added dropwise via cannula. The black reaction mixture was slowly allowed to warm to ambient temperature over ca. 5 h. The mixture was cooled to ca. 10 °C, and a mixture of saturated aqueous NH_4Cl (80 mL) and concentrated NH_4OH (80 mL) was then added. The mixture was then transferred to a 1 L Erlenmeyer flask charged with a stirring-bar and 200 mL each of saturated aqueous NH_4Cl and concentrated NH_4OH. The mixture was vigorously stirred for 45 min and extracted with EtOAc (4 × 150 mL). The combined extracts were washed with water (3×) and brine (1×), and the mixture was dried over $MgSO_4$. Filtration, concentration, and purification of the residue by flash column chromatography (15:85 EtOAc/hexanes) gave 7.80 g (60%) of **9** as a colorless oil: $[\alpha]^{22}_D$ +8.3° (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) 1740, 1690, 1391, 1366, 1200, 1171 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, two conformations present) δ 5.56−5.29 (m, 2 H), 4.83 (t, *J* = 8.0 Hz, 0.5 H), 4.74 (t, *J* = 7.7 Hz, 0.5 H), 4.42−4.39 (m, 0.5 H), 4.34−4.30 (m, 0.5 H), 3.73 (s, 1.5 H), 3.72 (s, 1.5 H), 2.31−2.16 (m, 2 H), 1.98−1.91 (m, 1 H), 1.75 (dd, *J* = 6.8, 1.4 Hz, 1.5 H), 1.68 (dd, *J* = 6.5, 1.1 Hz, 1.5 H), 1.65−1.58 (m, 1 H), 1.42 (s, 1.5 H), 1.40 (s, 1.5 H). Anal. Calcd for $C_{14}H_{23}NO_4S$: C, 62.4; H, 8.6; N, 5.2. Found: C, 62.7; H, 8.8; N, 5.2.

(2*S*-*trans*)-5-(Hydroxymethyl)-1,2-pyrrolidinedicarboxylic Acid 1-(1,1-Dimethylethyl) 2-Methyl Diester (6). Ozone-oxygen was bubbled through a stirred, cold (−78 °C), colorless solution of the olefin **9** (4.40 g, 16.3 mmol) in 80 mL of methanol until a blue color persisted. The solution was then purged with argon until the color had dissipated. A mixture of 12 mL of dimethyl sulfide and 12 mL of CH_2Cl_2 was slowly added, and the mixture was allowed to warm to ambient temperature overnight (12 h). The reaction mixture was then concentrated and the lightly colored residue was dissolved in 55 mL of methanol and cooled to 0 °C under an argon atmosphere. To the resulting stirred, cold solution was added sodium borohydride (1.26 g, 32.6 mmol) in portions over several minutes and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with 50 mL of water; the mixture was stirred for 30 min and then extracted with EtOAc (4×). The combined extracts were washed with water (2×), brine (1×), and the mixture was dried over Na_2SO_4. Filtration, concentration, and purification of the residue by flash chromatography (85:15 Et_2O/hexanes) gave 3.74 g (88%) of **6** as a colorless oil: $[\alpha]^{24}_D$ −63.8° (*c* 1.71, $CHCl_3$), lit.[5] $[\alpha]_D$ −65° (*c* 0.64, $CHCl_3$).

(2*S*-*trans*)-5-[(Acetylthio)methyl]-1,2-pyrrolidinedicarboxylic Acid 1-(1,1-Dimethylethyl) 2-Methyl Diester (12). To a stirred, cold (0 °C), colorless solution of triphenylphosphine (4.00 g, 15.3 mmol) in 38 mL of THF was added diisopropyl azodicarboxylate (2.9 mL, 14.7 mmol) under an argon atmosphere. The resulting colorless paste was vigorously stirred for 30 min. A solution of the alcohol **6** (3.46 g, 13.3 mmol) and thiolacetic acid (1.1 mL, 16.0 mmol) in 33 mL of THF was then added dropwise via cannula. The colorless solution was stirred for 2 h at 0 °C and 1 h at ambient temperature, and the mixture was concentrated in vacuo. The residue was purified by flash chromatography (4:6 Et_2O/hexanes) to give 4.00 g (94%) of thiolacetate **12** as a colorless oil: $[\alpha]^{23}_D$ −58.3° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 1737, 1690, 1384, 1366, 1166, 1131 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, two conformations present) δ 4.36 (dd, *J* = 8.9, 1.1 Hz, 0.4 H), 4.29 (dd, *J* = 9.0, 1.2 Hz, 0.6 H), 4.17 (td, *J* = 8.5, 3.4 Hz, 0.6 H), 4.07 (td, *J* = 8.4, 3.1 Hz, 0.4 H), 3.72 (s, 1.2 H), 3.71 (s, 1.8 H), 3.28 (dd, *J* = 13.4, 3.2 Hz, 0.4 H), 3.22 (dd, *J* = 13.4, 3.4 Hz, 0.6 H), 3.13 (dd, *J* = 13.4, 9.0 Hz, 0.6 H), 2.94 (dd, *J* = 13.4, 9.3 Hz, 0.4 H), 2.42−2.24 (m, 1 H), 2.36 (s, 1.2 H), 2.35 (s, 1.8 H), 2.14−1.98 (m, 1 H), 1.93−1.88 (m, 1 H), 1.75−1.66 (m, 1 H), 1.50 (s, 3.6 H), 1.40 (s, 5.4 H). Anal. Calcd for $C_{14}H_{23}NO_5S$: C, 53.0; H, 7.3; N, 4.4. Found: C, 52.8; H, 7.2; N, 4.2.

(2*S*-*trans*)-5-(Mercaptomethyl)-1,2-pyrrolidinedicarboxylic Acid 1-(1,1-Dimethylethyl) 2-Methyl Diester (14). To a stirred solution of the thiolacetate **12** (4.00 g, 12.6 mmol) in 23 mL of methanol was added 23 mL of a saturated solution of ammonia in methanol at ambient temperature. The flask was then sealed with a plastic cap, and the colorless solution was stirred for 2 h. The mixture was then concentrated in vacuo, and the residue was purified by flash chromatography (15:85 EtOAc/hexanes) to give 2.96 g (85%) of the thiol **14** as a colorless oil: $[\alpha]^{23}_D$ −59.9° (*c* 2.01, $CHCl_3$); IR ($CHCl_3$) 1744, 1695, 1392, 1368, 1207, 1169, 1125 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, two conformations present) δ 4.37 (dd, *J* = 9.0, 1.1 Hz, 0.4 H), 4.29 (dd, *J* = 9.0, 1.2 Hz, 0.6 H), 4.14−4.10 (m, 0.6 H), 4.04−4.00 (m, 0.4 H), 3.73 (s, 1.2 H), 3.72 (s, 1.8 H), 2.93 (ddd, *J* = 13.4, 8.5, 2.9 Hz, 0.6 H), 2.81 (ddd, *J* = 12.9, 8.7, 3.1 Hz, 0.4 H), 2.58−2.49 (m, 1 H), 2.36−2.24 (m, 1 H), 2.19−2.07 (m, 1 H), 1.96−1.90 (m, 2 H), 1.48 (s, 3.6 H), 1.40 (s, 5.4 H), 1.31 (t, *J* = 8.8 Hz, 0.6 H), 1.26 (t, *J* = 8.7 Hz, 0.4 H). Anal. Calcd for $C_{12}H_{21}NO_4S$: C, 52.3; H, 7.7; N, 5.1. Found: C, 52.3; H, 7.6; N, 5.0.

Thioester 15. To a stirred, cold (0 °C), colorless solution of acid **5** (3.86 g, 11.8 mmol) in 40 mL of dry acetonitrile (distilled form CaH_2) was added a solution of 1,1'-carbonyldiimidazole (1.91 g, 11.8 mmol) in 25 mL acetonitrile under an argon atmosphere. After 1 h, a solution of the thiol **14** (2.70 g, 9.8 mmol) in 30 mL acetonitrile was added. The resulting solution was stirred for 2 h at 0 °C and 22 h at ambient temperature, and then the mixture was concentrated in vacuo. The residue was purified by flash chromatography (15:85 EtOAc/Et_2O) to give 5.21 g (91%) of the thioester **15** as a colorless foam: $[\alpha]^{22}_D$ −62.8° (*c* 1.31, $CHCl_3$); IR ($CHCl_3$) 1744, 1697, 1661, 1392, 1365, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, four conformations present) δ 7.93−7.76 (m, 2 H), 7.39−7.36 (m, 2 H), 5.13−5.09 (m, 0.8 H), 5.04−5.03 (m, 0.2 H), 4.74−4.70 (m, 0.8 H), 4.63−4.60 (m, 0.2 H), 4.34−4.26 (m, 1 H), 4.20−3.95 (m, 1 H), 3.87−3.85 (m, 1 H), 3.72 (s, 0.2 H), 3.71 (s, 0.5 H), 3.70 (s, 0.8 H), 3.69 (s, 1.5 H), 3.32−3.18 (m, 1 H), 3.14−3.07 (m, 0.6 H), 3.01−2.94 (m, 0.4 H), 2.47 (s, 2.4 H), 2.46 (s, 0.6 H), 2.43−2.26(m, 2 H), 2.14−2.05 (m, 2 H), 2.04 (s, 0.9 H), 2.02 (s, 1.6 H), 1.97 (s, 0.5 H), 1.90−1.86 (m, 1 H), 1.70−1.64 (m, 1 H), 1.59 (s, 2.1 H), 1.49 (s, 0.6 H), 1.47 (s, 2.2 H), 1.39 (s, 4.1 H). Anal. Calcd for $C_{26}H_{36}N_2O_9S_2$: C, 53.3; H, 6.2; N, 4.8. Found: C, 53.1; H, 6.0; N, 4.8.

Thiol 17. To a stirred, cold (0 °C), colorless solution of the thioester **15** (2.77 g, 4.7 mmol) in 55 mL of CH_2Cl_2 and 85 μL of anisole was added 14 mL of TFA. The resulting mixture was stirred for 1 h at 0 °C and then concentrated in vacuo. The residue was then repeatedly (ca. 10×) evaporated from a mixture of CH_2Cl_2 and Et_2O until placement under high-vacuum yielded a foam. The foam was dissolved in 255 mL of toluene and to the stirred solution was added *N*,*N*-diisopropylethylamine (2.5 mL, 14.2 mmol) under an argon atmosphere. The mixture was heated at 60 °C for 2 h and then concentrated in vacuo. The residue was purified by flash chromatography (95:5 EtOAc/MeOH) to give 2.07 g (90%) of **17** as a colorless foam: $[\alpha]^{22}_D$ −24.7° (*c* 1.56, $CHCl_3$); IR ($CHCl_3$) 1744, 1649, 1436, 1366, 1190, 1187 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.83−7.79 (m, 2 H), 7.41−7.27 (m, 2 H), 5.11−5.08 (m, 1 H), 4.67 (t, *J* = 7.6 Hz, 1 H), 4.53 (dd, *J* = 9.4, 1.1 Hz, 1 H), 3.99−3.88 (m, 1 H), 3.87 (dd, *J* = 11.8, 4.5 Hz, 1 H), 3.87 (dt, *J* = 12.0, 1.8 Hz, 1 H), 3.67 (s, 3 H), 3.35−3.30 (m, 1 H), 2.65−2.48 (m, 1 H), 2.47 (s, 3 H), 2.46−2.44 (m, 1 H), 2.31−2.26 (m, 1 H), 2.24−2.18 (m, 1 H), 2.16−2.05 (m, 2 H), 1.99 (s, 3 H), 1.97−1.89 (m, 1 H), 1.56 (t, *J* = 8.7 Hz, 1 H). Anal. Calcd for $C_{21}H_{28}N_2O_7S_2$: C, 52.1; H, 5.8; N, 5.8. Found: C, 51.8; H, 5.8; N, 5.7.

[3*S*-(3α,6α,9α,11aα)]-5-Acetyloctahydro-7-oxo-3,6-methano-1*H*,3*H*-pyrrolo[2,1-c][1,4,7]thiadiazonine-9-carboxylic Acid Methyl Ester (1c). A volume of 1.4 L of stirred acetonitrile was heated at reflux for 30 min under a rigorous argon atmosphere. A solution of thiol **17** (2.10 g, 4.33 mmol) in 50 mL of acetonitrile was then added via cannula. The mixture was allowed several minutes to return to a full boil before a solution of KOMe (0.5 M in MeOH, 9.0 mL, 4.5 mmol) was slowly added over 15 min via syringe. The resulting mixture was heated for 1 h, cooled to ambient temperature, and concentrated in vacuo. The residue was purified by flash chromatography

(9:1 EtOAc/MeOH) to give 1.24 g (91%) of **1c** as a colorless foam: [20] mp 48–50 °C (uncorrected); $[\alpha]^{22}_D$ +145.8 (*c* 1.65, $CHCl_3$); $[\alpha]^{22}_D$ +141.5 (*c* 1.60, CH_2Cl_2), lit.[21] $[\alpha]_D$ +110.6° (*c* 0.50, CH_2Cl_2). Anal. Calcd for $C_{14}H_{20}N_2O_4S$: C, 53.8; H, 6.4; N, 9.0. Found: C, 53.5; H, 6.4; N, 8.9.

Acknowledgment. This research was supported by a National Science Foundation grant (9121702-CHE) and the financial assistance of Pfizer Inc. An NIH postdoctoral fellowship to K.F.M. (grant 5 F32 GM15837-02) and a postdoctoral fellowship to P.R. from the Swiss National Science Foundation and the Roche Research Foundation are gratefully acknowledged.

JO9418644

(20) Previously reported as an oil, see ref 4.

(21) Incorrectedly reported as: $[\alpha]_D$ +11° (*c* 0.50, CH_2Cl_2) in ref 4.