Synthesis of an Enantiomerically Pure Serine-Derived Thiazole

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Previously reported methods for preparing enantiomerically pure thiazoles are inadequate for the synthesis of inherently labile *O*-alkyl serine-derived thiazoles. The intermediate *N*-Boc-(*O*-methylseryl) thiazolines are very susceptible to tautomerization, even under neutral conditions (Scheme 5). Herein, it is demonstrated that the choice of *N*-protecting group is critical to the preservation of enantiomeric purity. Thus, using an *N*-trityl protecting group, *O*-methyl serine was converted to the corresponding *N*-Boc-(*O*-methylseryl) thiazole **3** with no appreciable epimerization as indicated by ^{19}F and ^{1}H NMR of the corresponding Mosher's amide.

Introduction

In recent years, many thiazole-containing secondary metabolites from marine sources have been isolated and characterized.[1] These compounds include the potent antineoplastic agent dolastatin 10,[2] the cytotoxin bistatramide C,[3] the antifungal pateamine,[4] and the antitumor agent ulithiacyclamide.[5] Several of these peptides contain a chiral 2-(1-aminoalkyl)thiazole possessing either the *R* or *S* configuration. A number of methods for the synthesis of these optically active amino acid-derived thiazoles have been described. Examples include the following: (a) condensation of an amino acid-derived thioamide with ethyl bromopyruvate (Hantzsch reaction);[6] (b) conversion of aminoaldehydes into thiazoles *via* the thiazolidine;[7] and (c) cyclodehydration of *β*-hydroxythioamides using Burgess reagent,[8] followed by oxidation of the intermediate thiazoline.[9] While each of these general methods has been used in the synthesis of 2-(1-aminoalkyl)thiazoles, none of these methods has been applied successfully to the preparation of chiral serine-derived thiazole amino acids due to extensive epimerization at the α-carbon. As part of our ongoing investigation into the synthesis of the marine cyclic peptides keramamide F (**1**)[10] and keramamide J (**2**),[11] we needed a way to prepare (*O*-methylseryl) thiazole derivative **3** in enantiomerically pure form (Figure 1). Herein, we describe the first synthesis of a serine-derived thiazole with preservation of stereochemical integrity.

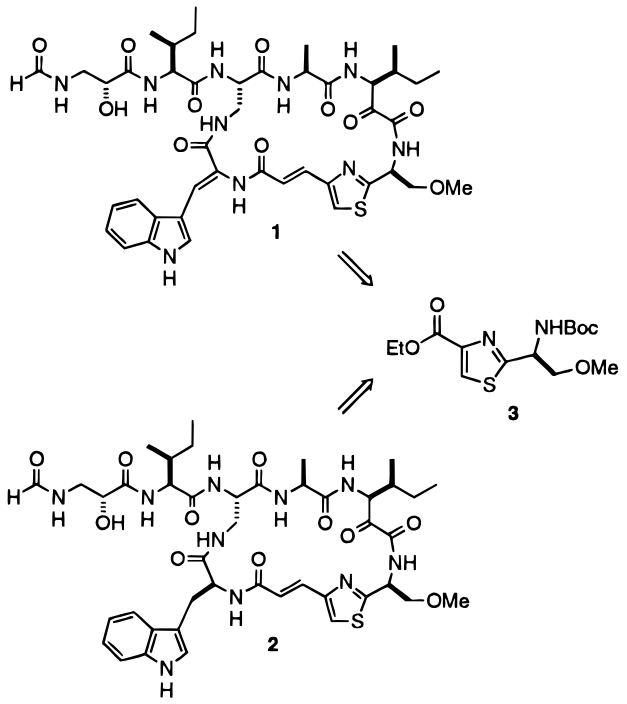

Figure 1.

Results and Discussion

We have reported previously our progress toward the total synthesis of the cytotoxic cyclic peptide keramamide F (**1**).[12] In this communication, we described a synthesis of thiazole **3** *via* a modified Hantzsch reaction which provided **3** as a 4:1 mixture of enantiomers, as determined by ^{1}H and ^{19}F NMR analysis of the corresponding (−)-α-methoxy-α-(trifluoromethyl)phenylacetyl derivative[13] (Mosher's amide). Upon further investigation, it was determined that the starting acid we had used was a mixture of enantiomers due to epimerization (*ca.* 33%) during the saponification of *N*-Boc-*O*-Me-L-serine methyl ester. To circumvent this problem, enantiomerically pure acid **6** was prepared from serine benzyl ester as illustrated in Scheme 1. However, use of enantiomerically

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(6) For recent examples, see: (a) Kelly, R. C.; Gebhard, I.; Wicnienski, N. *J. Org. Chem.* **1986**, *51*, 4590. (b) Schmidt, U.; Utz, R.; Lieberknecht, A.; Griesser, H.; Potzolli, B.; Bahr, J.; Wagner, K.; Fischer, P. *Synthesis* **1987**, 233. (c) Bredenkamp, M. W.; Holzapfel, C. W.; van Zyl, W. J. *Synth. Commun.* **1990**, *20*, 2235. (d) Hamada, Y.; Hayashi, K.; Shioiri, T. *Tetrahedron Lett.* **1991**, *32*, 931. (e) Pattenden, G.; Thom, S. M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1629. (f) Martin, B. J.; Clough, J. M.; Pattenden, G.; Waldron, I. R. *Tetrahedron Lett.* **1993**, *34*, 5151.

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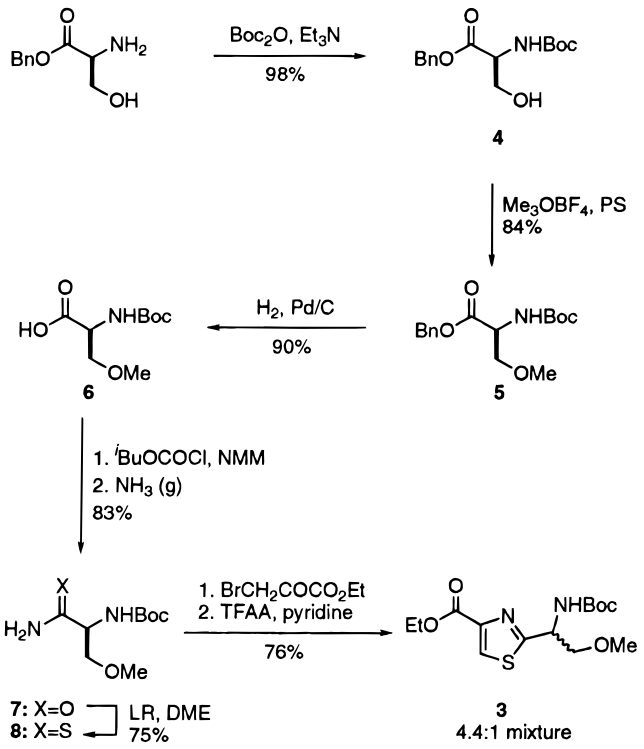
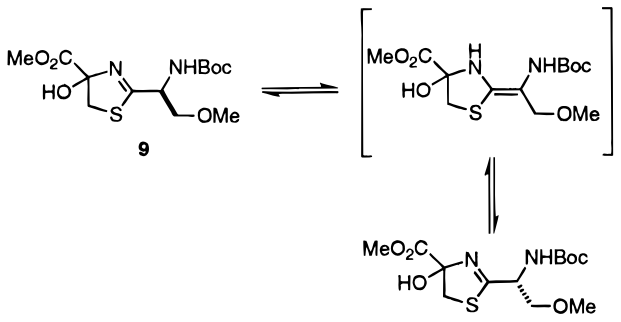
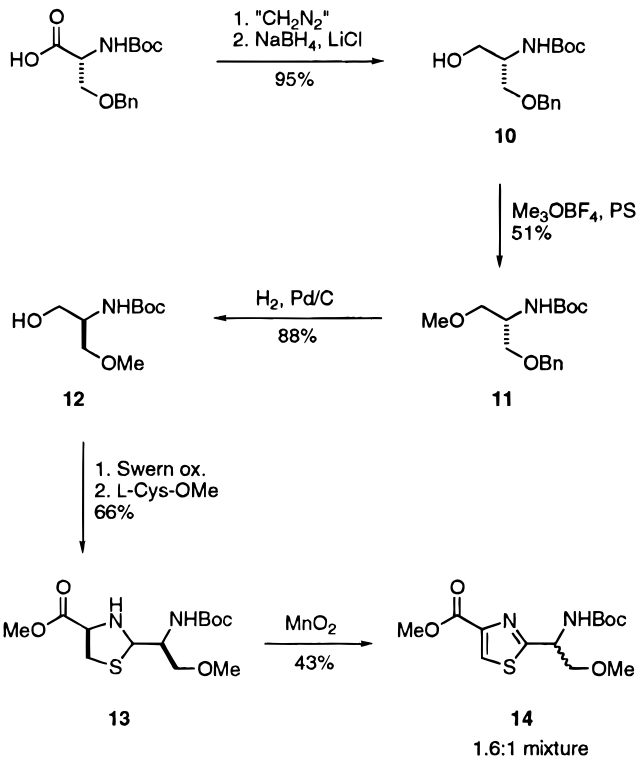
Scheme 1



Scheme 2



Scheme 3



pure **6** in the preparation of thiazole **3** *via* a modified Hantzsch synthesis similarly produced an enantiomeric mixture of products. Thus, *N*-Boc-L-serine benzyl ester was methylated using trimethyloxonium tetrafluoroborate and proton sponge (PS). Hydrogenolysis provided acid **6**, which was converted to the thioamide **8** *via* treatment of amide **7** with Lawesson's reagent (LR). Subsequent reaction of thioamide **8** with ethyl bromopyruvate under the conditions reported by Meyers and co-workers[14] afforded thiazole **3** as a 4.4:1 mixture of enantiomers, as determined by Mosher's amide analysis (^{1}H and ^{19}F NMR). Further modifications of the Hantzsch reaction, including those reported by Holzapfel[15] and Schmidt[16] also afforded thiazole **3** as a mixture of enantiomers (2−4:1).

It has been proposed that epimerization during the Hantzsch reaction occurs through an acid-catalyzed imine−enamine tautomerization of the intermediate hydroxythiazoline **9**, as illustrated in Scheme 2.[15] Since a long lifetime of this intermediate presumably would result in complete racemization, we reasoned that a procedure in which the thiazole ring is formed quickly and under near-neutral conditions should reduce the extent of epimerization.

Shioiri has reported the convenient and efficient conversion of *N*-Boc and *N*-Z α-aminoaldehydes into their corresponding 2-(1-aminoalkyl)thiazole-4-carboxylic acids, with no appreciable racemization, by condensation with cysteine followed by oxidation of the resulting thiazolidine.[7] Following this approach, *N*-Boc-*O*-Bn-D-serine[17] was converted to the corresponding methyl ester which was reduced with sodium borohydride-lithium chloride in methanol−THF to give the amino alcohol derivative **10** (Scheme 3). *O*-Methylation using trimethyloxonium tetrafluoroborate, followed by hydrogenolysis, afforded methyl ether **12** as a single enantiomer as determined by ^{1}H NMR analysis of the corresponding (1*S*)-(−)-camphanate ester. Oxidation of compound **12** under Swern conditions and immediate condensation with L-cysteine methyl ester smoothly afforded the thiazoline derivative **13** as a mixture of C-2 epimers with no apparent epimerization of the α-center. Oxidation of thiazolidine **13** (MnO_2, benzene, 55 °C, 4 h) afforded the corresponding thiazole **14** as a 1.6 to 1 mixture of enantiomers, as determined by Mosher's amide analysis (^{1}H and ^{19}F NMR). Epimerization presumably results from the relatively harsh conditions required to perform the oxidation step.

Wipf and co-workers have developed a mild and reliable method for the preparation of 2-(1-aminoalkyl)-thiazoline-4-carboxylic acids with high diastereomeric excess.[9,18] These thiazolines may be oxidized to the corresponding thiazoles with MnO_2 at room temperature. Since this procedure does not require the use of elevated temperatures during the oxidation step, it represented an attractive option for the synthesis of thiazole **3**. Thus,

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(15) Bredenkamp, M. W.; Holzapfel, C. W.; Snyman, R. M.; van Zyl, W. J. *Synth. Commun.* **1992**, *22*, 3029.
(16) Schmidt, U.; Gleich, P.; Griesser, H.; Utz, R. *Synthesis* **1986**, 992.
(17) Commercially available from Bachem (California).
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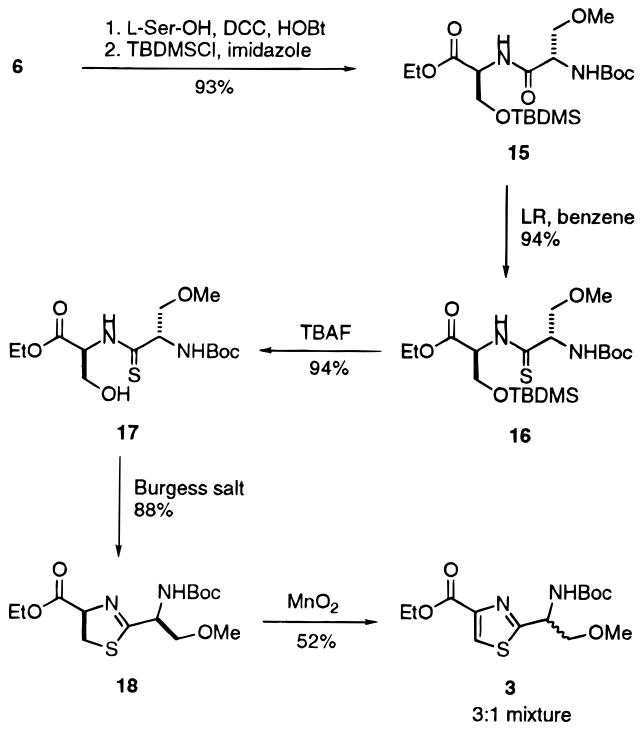
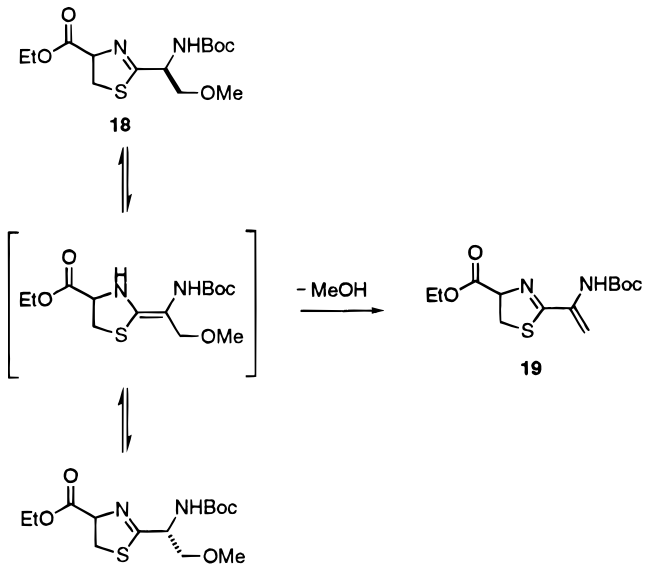
Scheme 4



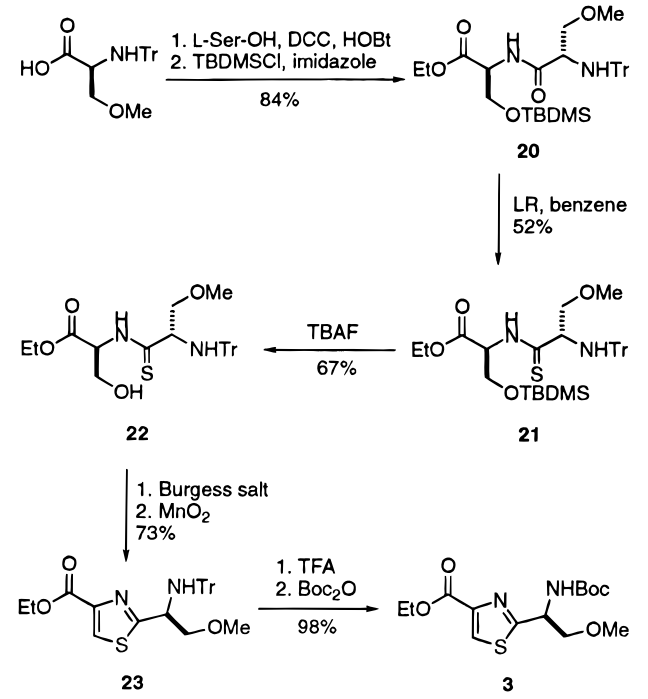
N-Boc-*O*-Me-L-serine (**6**) was converted into the necessary thiazoline **18** as outlined in Scheme 4. Acid **6** was condensed with L-serine ethyl ester, and the alcohol was protected as its *tert*-butyldimethylsilyl ether affording dipeptide **15** which was smoothly converted to the thioamide **16** with Lawesson's reagent.[19] Subsequent removal of the silicon protecting group and reaction with Burgess reagent yielded thiazoline **18**. Oxidation of thiazoline **18** (MnO_2, CH_2Cl_2, rt, 36 h) afforded thiazole **3** as a mixture of enantiomers (3:1) as determined by Mosher's amide analysis (^1H and ^{19}F NMR).

Interestingly, upon standing at 4 °C (*ca* 7 days), thiazoline **18** underwent complete conversion to the didehydro peptide **19** (Scheme 5). We propose that this elimination occurs *via* an imine−enamine tautomerization with subsequent loss of methanol. Elimination reactions are a well-documented problem commonly associated with serine derivatives. For example, reaction of *O*-tosyl and β-halo *N*-Boc or *N*-Z L-serine derivatives with organocuprates or amines affords the corresponding didehydroalanine.[20] Furthermore, attempts to methylate *N*-Boc or *N*-Z L-serine derivatives have resulted in high yields of the corresponding β-elimination products.[21] While Mitsunobu reactions of *N*-Boc or *N*-Z L-serine derivatives also commonly afford the elimination product,[22] Cherney recently reported that neither *N*-phenylfluorenyl nor *N*-trityl (Tr) serines undergo elimination under Mitsunobu conditions.[23] This result followed previous work demonstrating that the phenylfluorenyl and trityl protecting groups protect the α-center of amino

Scheme 5



Scheme 6



acids from deprotonation.[24,25] We postulated that the use of such a protecting group also might suppress epimerization of serine-derived thiazolines (Scheme 5).

To test whether using the *N*-trityl protecting group would preserve enantiomeric purity in our chemistry, we prepared the *N*-Tr protected thioamide **22** as illustrated in Scheme 6. *N*-Tr-*O*-Me-L-serine[26] was coupled to L-serine ethyl ester and protected as its *tert*-butyldimethylsilyl ether (**20**). Compound **20** was subsequently converted into the thioamide **21**. Conversion of dipeptide **20** to thioamide **21** proceeds in poor yield, presumably due to instability of the *N*-trityl group during treatment with Lawesson's reagent.[27] Furthermore, variations in solvent (THF, DME, HMPA) and thionation reagent

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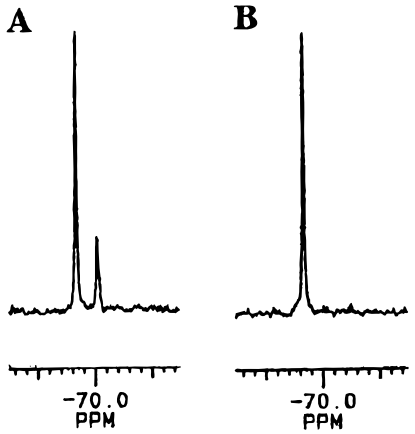

Figure 2. ^{19}F-NMR (282 Hz, $CDCl_3$) spectra of (*R*)-(−)-Mosher's amide of (A) **3** as a mixture of enantiomers (δ −69.69 and −70.06), and (B) enantiomerically pure **3** (δ −69.69). Chemical shifts (δ) reported in parts per million (ppm) with respect to a C_6F_6 external reference (δ_F −162.90).

(P_2S_5) did not increase the yield of thioamide **21**. Removal of the silyl protecting group and treatment with Burgess reagent provided the thiazoline, which was oxidized to afford the enantiomerically pure *N*-trityl protected thiazole **23**. Thiazole **23** was smoothly deprotected (TFA, $CHCl_3$/MeOH, −10 °C), and the resulting amine was reprotected as its *tert*-butyl carbamate **3** in high yield and with no loss of stereochemical integrity as determined by ^{1}H and ^{19}F NMR analysis of the corresponding Mosher's amide (Figure 2). Thus, the *N*-trityl group does indeed appear to prevent removal of the adjacent proton providing access to enantiomerically pure product under conditions which otherwise yield product mixtures.

In summary, we have shown that previously overlooked serine-derived thiazole amino acids may be prepared enantiomerically pure by judicious choice of the *N*-protecting group. Due to the inherent lability of the α-proton of *O*-alkylated serines, very bulky, non-urethane protecting groups (e.g. trityl) appear to be the *N*-protecting groups of choice. This observation may be extended to other cases where epimerization is a problem during thiazole ring formation.

Experimental Section

General Procedures. Anhydrous ether and tetrahydrofuran (THF) were distilled from sodium and benzophenone. Dichloromethane (CH_2Cl_2), benzene, and acetonitrile (CH_3CN) were distilled from calcium hydride (CaH_2). Other solvents used were HPLC or reagent grade. Organic acids and bases were reagent grade. Triethylamine and diisopropylethylamine were distilled and stored over 4 Å molecular sieves. All other reagents were commercial compounds of the highest purity available.

***N*-Boc-L-Serine Benzyl Ester (4).** L-Serine benzyl ester (1.50 g, 6.47 mmol) was dissolved in CH_2Cl_2 (50 mL) under nitrogen and cooled to 0 °C. Triethylamine (2.70 mL, 19.41 mmol) was added followed by a solution of di-*tert*-butyl dicarbonate (1.40 g, 6.47 mmol) in CH_2Cl_2 (5 mL). After 2 h, the solution was washed with 1 M HCl followed by brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (1:1 hexanes/EtOAc) afforded the title compound (1.87 g, 98%) as a colorless oil: R_f = 0.42 (1:1 hexanes/EtOAc); IR (film) 3426, 2977, 1717, 1505, 1165, 1061; ^{1}H NMR (360 MHz) δ 7.39−7.32 (m, 5H), 5.52 (d, 1H, J = 8.6 Hz), 5.20 (s, 2H), 4.44−4.38 (m, 1H), 3.97 (dd, 1H, J = 3.8, 11.1 Hz), 3.89 (dd, 1H, J = 3.5, 11.1 Hz), 2.53−2.45 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (90 MHz) δ 170.7, 155.7, 135.1, 128.4, 128.2, 128.0, 80.1, 67.1, 63.1, 55.7, 28.1; MS *m*/*z* (rel int) 296 (21, M + H), 257 (100), 240 (31), 196 (66); HRMS (CI) calcd for $C_{15}H_{22}NO_5$ (M + H) 296.1498, found 296.1484; $[\alpha]^{25}_D$ = +0.5 (*c* 1, CH_2Cl_2).

***N*-Boc-*O*-Methyl-L-serine Benzyl Ester (5).** Compound **4** (1.74 g, 5.89 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C under nitrogen in the dark. Trimethyloxonium tetrafluoroborate (1.13 g, 7.67 mmol) was added. After 5 min, proton sponge (1.64 g, 7.67 mmol) was added and the resulting solution was allowed to reach ambient temperature over 18 h. The solution was filtered through a pad of Celite and the filtrate washed with 1 M HCl and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (2:1 hexanes/EtOAc) afforded **5** (1.52 g, 84%) as a colorless oil: R_f = 0.47 (2:1 hexanes/EtOAc); IR (film) 2980, 2933, 1718, 1498, 1163; ^{1}H NMR (360 MHz) δ 7.38−7.30 (m, 5H), 5.40 (d, 1H, J = 8.6 Hz), 5.27 (d, 1H, J = 12.3 Hz), 5.14 (d, 1H, J = 12.4 Hz), 4.47−4.45 (m, 1H), 3.81 (dd, 1H, J = 3.0, 9.1 Hz), 3.60 (dd, 1H, J = 3.2, 9.3 Hz), 3.29 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (90 MHz) δ 170.4, 155.3, 135.8, 128.3, 128.1, 127.9, 79.9, 72.3, 66.9, 59.0, 53.9, 28.1; MS *m*/*z* (rel int) 310 (51, M + H), 254 (87), 210 (100); HRMS (CI) calcd for $C_{16}H_{24}NO_5$ (M + H) 310.1654, found 310.1654; $[\alpha]^{25}_D$ = −4.3 (*c* 1, CH_2Cl_2).

***N*-Boc-*O*-Methyl-L-serinamide (7).** Compound **5** (1.50 g, 4.85 mmol) and Pd/C (150 mg) were combined and methanol (30 mL) was added. The resulting heterogeneous mixture was stirred under hydrogen (1 atm) for 1 h. The palladium was removed by filtration through Celite and the filtrate concentrated *in vacuo*. The resulting residue was dissolved in water, adjusted to pH 9 with 1 M NaOH, and washed with diethyl ether. The aqueous layer was adjusted to pH 4 with 10% citric acid and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford **6** (952 mg, 90%) as a white foam; R_f = 0.57 (10% MeOH/CH_2Cl_2). A solution of the crude acid **6** (952 mg, 4.37 mmol) in THF (25 mL) was cooled to −15 °C, and 4-methylmorpholine (0.48 mL, 4.37 mmol) was added. Isobutyl chloroformate (0.57 mL, 4.37 mmol) was added and the resulting solution stirred 15 min at −15 °C. Ammonia gas was bubbled through the reaction and condensed using a dry ice/acetone cold finger. After 10 min, the flask was allowed to warm to room temperature over 30 min. The reaction mixture was purged with nitrogen, diluted with EtOAc, and washed with 5% aqueous $NaHCO_3$, 1 M HCl, and then brine. Flash chromatography (EtOAc) afforded the title compound (790 mg, 83%) as a white solid: R_f = 0.38 (EtOAc); IR (film) 3400, 2986, 2914, 2386, 2314, 1772, 1736, 1701, 1664; ^{1}H NMR (300 MHz) δ 6.45 (br s, 1H), 5.69 (br s, 1H), 5.43 (d, 1H, J = 7.0 Hz), 4.25−4.22 (m, 1H), 3.76 (dd, 1H, J = 4.1, 9.3 Hz), 3.47 (dd, 1H, J = 4.7, 9.0 Hz), 3.35 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (90 MHz) δ 173.1, 155.4, 80.0, 72.0, 58.9, 53.4, 28.1; MS *m*/*z* (rel int) 219 (55, M + H), 163 (100), 119 (45). Anal. Calcd for $C_9H_{18}N_2O_4$ C, 49.53; H, 8.31; N, 12.84. Found: C, 49.50; H, 8.46; N, 12.84. $[\alpha]^{25}_D$ = +19.6 (*c* 1, $CHCl_3$).

***N*-Boc-*O*-Methyl-L-serine Thioamide (8).** Amide **7** (700 mg, 3.21 mmol) was dissolved in ethylene glycol dimethyl ether (20 mL) at ambient temperature. Lawesson's reagent[19] (779 mg, 1.93 mmol) was added, and the mixture was stirred overnight under an atmosphere of dry nitrogen. The solvent was evaporated *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 and washed with 1% aqueous NaOH. The aqueous layer was further extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to yield a residue which was purified by flash chromatography (1:1 hexanes/EtOAc). The title compound (563 mg, 75%) was obtained as a white solid: R_f = 0.38 (1:1 hexanes/EtOAc); IR (film) 3336, 2854, 2818, 1640, 1619; ^{1}H NMR (300 MHz) δ 7.94 (br s, 1H), 7.79 (br s, 1H), 5.63 (d, 1H, J = 6.5 Hz), 4.55 (dt, 1H, J = 4.4, 6.5 Hz), 3.86 (dd, 1H, J = 4.7, 9.0 Hz), 3.56 (dd,

(27) Attempts to form the thioamide from *N*-Tr-*O*-methyl-L-serinamide were unsuccessful. The polarity of the primary thioamide formed prohibited its separation from decomposition products; consequently, the Hantzsch method was not investigated using the *N*-trityl protecting group.

1H, J = 4.4, 9.0 Hz), 3.38 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (90 MHz) δ 205.9, 155.1, 80.3, 74.0, 58.9, 28.1; MS m/z (rel int) 235 (43, M + H), 219 (31), 195 (12), 179 (100), 163 (75). Anal. Calcd for $C_9H_{18}N_2SO_3$: C, 46.30; H, 7.34; N, 12.0. Found: C, 46.01; H, 7.61; N, 11.83. $[\alpha]^{25}_D = +38.0$ (c 1, $CHCl_3$).

(*S*)-(−)-*N*-Boc-*O*-Benzylserinol (10). *N*-Boc-*O*-Bn-D-Serine[17] (1.18 g, 4.00 mmol) was treated with Diazald (1.00 g, *ca.* 4 mmol) in a typical diazomethane procedure to yield the corresponding *N*-Boc-*O*-Bn-D-serine methyl ester (1.12 g, 99%) as a colorless oil: R_f = 0.30 (4:1 hexanes/EtOAc). The ester was dissolved in THF (6 mL), and LiCl (339 mg, 8.00 mmol) was added. The solution was cooled to −10 °C. After 30 min, $NaBH_4$ (303 mg, 8.00 mmol) was added. Methanol (11 mL) was added dropwise over 15 min and the mixture allowed to warm to ambient temperature with stirring. After 2 h, the solution was cooled to 0 °C and adjusted to pH 4 by addition of 10% citric acid. The volatile components were removed *in vacuo*, the resulting residue was dissolved in water, and the product was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (1:1 EtOAc/hexanes) afforded the title compound (1.06 g, 95%) as a colorless oil: R_f = 0.34 (1:1 hexanes/EtOAc); IR (film) 3393, 2977, 2932, 2869, 1695, 1501, 1363, 1169; ^{1}H NMR (360 MHz) δ 7.35−7.29 (m, 5H), 5.19−5.17 (m, 1H), 4.52 (s, 2H), 3.81−3.79 (m, 2H), 3.69−3.62 (m, 3H), 1.44 (s, 9H); ^{13}C NMR (90 MHz) δ 155.9, 137.6, 128.3, 127.6, 127.5, 79.4, 73.2, 70.0, 63.1, 51.5, 28.2; MS m/z (rel int) 282 (7, M + H), 226 (80), 208 (60), 182 (90), 91 (100); HRMS (CI) calcd for $C_{15}H_{24}NO_4$ (M + H) 282.1705, found 282.1699; $[\alpha]^{25}_D = -8.5$ (c 1, CH_2Cl_2).

(*S*)-(−)-*N*-Boc-*O*-Benzyl-*O*-methylserinol (11). Alcohol **10** (400 mg, 1.42 mmol) was dissolved in CH_2Cl_2 (10 mL) at room temperature in a foil-covered flask. Trimethyloxonium tetrafluoroborate (315 mg, 2.13 mmol) was added, followed by the portionwise addition of proton sponge (456 mg, 2.13 mmol). After stirring 24 h, the solution was concentrated, the residue dissolved in EtOAc, and the solution filtered through a pad of Celite. The filtrate was washed with 1 M HCl and brine. The organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Flash chromatography (3:2 hexanes/EtOAc) afforded the methyl ether (214 mg, 51%) as a colorless oil: R_f = 0.42 (2:1 hexanes/EtOAc); IR (film) 2979, 2923, 1716, 1497, 1457, 1366, 1167; ^{1}H NMR (360 MHz) δ 7.37−7.27 (m, 5H), 4.92−4.89 (m, 1H), 4.52 (s, 2H), 3.94−3.91 (m, 1H), 3.79−3.77 (m, 1H), 3.58 (dd, 2H, J = 4.1, 9.4 Hz), 3.44 (dd, 1H, J = 5.9, 9.3 Hz), 3.34 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (90 MHz) δ 155.4, 138.1, 128.3, 127.8, 127.5, 79.3, 73.1, 71.2, 68.9, 58.9, 49.5, 28.3; MS m/z (rel int) 296 (2, M + H), 240 (21), 196 (100), 91 (84); HRMS (CI) calcd for $C_{16}H_{26}NO_4$ (M + H) 296.1863, found 296.1862; $[\alpha]^{25}_D = -6.8$ (c 1, CH_2Cl_2).

(*R*)-(−)-*N*-Boc-*O*-Methylserinol (12). To compound **11** (200 mg, 0.678 mmol) was added 10% Pd/C (20 mg) followed by methanol (10 mL). The resulting heterogeneous solution was stirred under a hydrogen atmosphere for 24 h. The palladium was removed by filtration through Celite and the filtrate concentrated *in vacuo*. Purification by flash chromatography (1:1 hexanes/EtOAc) afforded the title compound (122 mg, 88%) as a colorless oil: R_f = 0.21 (1:1 hexanes/EtOAc); IR (film) 3351, 2976, 2934, 1693, 1512, 1364, 1248, 1172, 1062; ^{1}H NMR (360 MHz) δ 5.26−5.21 (m, 1H), 3.76−3.73 (m, 2H), 3.64−3.62 (m, 1H), 3.53 (dd, 1H, J = 3.8, 9.5 Hz), 3.49 (dd, 1H, J = 4.2, 9.5 Hz), 3.34 (s, 3H), 2.99−2.96 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (90 MHz) δ 156.0, 79.6, 73.0, 63.7, 59.1, 51.4, 28.3; MS m/z (rel int) 206 (37, M + H), 150 (100), 132 (14), 106 (82); HRMS (CI) calcd for $C_9H_{20}NO_4$ (M + H) 206.1392, found 206.1390; $[\alpha]^{25}_D = -3.3$ (c 1, CH_2Cl_2).

Thiazolidine 13. To a −78 °C solution of oxalyl chloride (0.24 mL, 0.48 mmol) in CH_2Cl_2 (3.5 mL) was added DMSO (0.07 mL, 1.0 mmol). After 15 min, a solution of alcohol **12** (66 mg, 0.32 mmol) in CH_2Cl_2 (2.5 mL) was added *via* cannula. The resulting solution was stirred for 15 min and then treated with triethylamine (0.26 mL, 1.90 mmol). The dry ice/acetone bath was removed, and the solution allowed to gradually warm to ambient temperature over 2.5 h. The reaction was quenched by the addition of NH_4Cl (aqueous saturated, 4.7 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted several times with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford the corresponding aldehyde (64 mg, 99%) as a colorless solid. The aldehyde was immediately dissolved in benzene (2.5 mL) at room temperature under nitrogen. A solution of L-cysteine methyl ester (43 mg, 0.32 mmol) in benzene (2.5 mL) was added. After stirring 18 h, the mixture was diluted with EtOAc and washed with NH_4Cl (aqueous saturated) and then brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (3:2 hexanes/EtOAc) afforded **13** (67 mg, 66%) as a colorless oil: R_f = 0.17 (3:2 hexanes/EtOAc); IR (film) 2979, 2929, 1744, 1714, 1505, 1368, 1166; ^{1}H NMR (360 MHz) δ 5.18−5.12 (m, 1H), 4.77−4.79 and 4.73−4.71 (m, 1H), 4.27−4.24 and 4.03−4.01 (m, 1H), 3.73 and 3.72 (s, 3H), 3.75−3.71 and 3.63−3.59 (m, 1H), 3.55−3.48 (m, 1H), 3.31 and 3.30 (s, 3H), 3.29−3.27 (m, 1H), 3.24−3.20 (m, 1H), 2.81 and 2.68 (t, 1H, J = 10.3 Hz), 1.40 (s, 9H); ^{13}C NMR (90 MHz) δ 171.1, 155.5, 79.8, 73.5, 73.1, 71.8, 65.3, 65.0, 59.1, 59.0, 52.3, 52.3, 50.6, 37.7, 37.5, 28.1 (diastereomers present in NMR); MS m/z (rel int) 321 (42, M + H), 265 (56), 233 (32), 221 (58), 172 (20), 146 (100), 86 (20); HRMS (CI) calcd for $C_{13}H_{25}N_2SO_5$ (M + H) 321.1484, found 321.1470.

***N*-Boc-*O*-Methyl-L-seryl-*O*-TBDMS-L-serine Ethyl Ester (15).** L-Serine ethyl ester hydrochloride (773 mg, 4.56 mmol), acid **6** (994 mg, 4.56 mmol), and HOBt (678 mg, 5.01 mmol) were dissolved in CH_2Cl_2 (35 mL) and cooled to 0 °C. Triethylamine (0.64 mL, 4.45 mmol) was added, followed by a solution of DCC (941 mg, 4.56 mmol) in CH_2Cl_2 (5 mL). The resulting mixture was allowed to reach ambient temperature with stirring over 4 h. The solution was filtered through a pad of Celite, and the filtrate was washed with 1 M HCl, $NaHCO_3$ (aqueous), and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to yield the dipeptide (1.44 g, 95%) as a white solid. The dipeptide (495 mg, 1.1 mmol) was dissolved in DMF (30 mL) at ambient temperature. *tert*-Butyldimethylsilyl chloride (1.43 g, 9.53 mmol) was added, followed by imidazole (1.30 g, 19.05 mmol). After stirring 18 h, the mixture was diluted with benzene/EtOAc (1:1) and washed with 10% citric acid and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Flash chromatography (3:1 hexanes/EtOAc) afforded the title compound (1.90 g, 98%) as a colorless oil: R_f = 0.50 (1:1 hexanes/EtOAc); IR (film) 2928, 2856, 1723, 1684, 1490, 1390, 1366, 1251, 1169, 1116; ^{1}H NMR (360 MHz) δ 7.36−7.33 (m, 1H), 5.42−5.40 (m, 1H), 4.58 (dt, 1H, J = 2.7, 8.4 Hz), 4.26−4.21 (m, 1H), 4.17 (q, 2H, J = 7.2 Hz), 4.06 (dd, 1H, J = 2.5, 10.0 Hz), 3.80−3.73 (m, 2H), 3.45 (dd, 1H, J = 7.3, 8.9Hz), 3.36 (s, 3H), 1.42 (s, 9H), 1.24 (t, 3H, J = 7.2 Hz), 0.87 (s, 9H), 0.00 (d, 6H, J = 6.0 Hz); ^{13}C NMR (90 MHz) δ 170.2, 169.9, 155.5, 79.9, 72.0, 63.3, 61.3, 58.9, 54.3, 53.3, 28.2, 25.5, 18.0, 14.0, −5.6, −5.7; MS m/z (rel int) 449 (56, M + H), 393 (84), 375 (61), 349 (100), 317 (10), 178 (15), 164 (13), 134 (15), 119 (51); HRMS (CI) calcd for $C_{20}H_{41}N_2SiO_7$ (M + H) 449.2688, found 449.2664; $[\alpha]^{25}_D = +44.3$ (c 1, CH_2Cl_2).

Thioamide 16. To a stirred solution of **15** (240 mg, 0.536 mmol) in benzene (3 mL) was added Lawesson's reagent[19] (130 mg, 0.321 mmol), and the mixture was stirred at 80 °C for 1 h. After cooling to ambient temperature, the reaction mixture was poured into a solution of saturated $NaHCO_3$ (aqueous saturated, 4 mL, 0 °C). The aqueous layer was extracted several times with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (4:1 hexanes/EtOAc) afforded the title compoud (235 mg, 94%) as a yellow oil: R_f = 0.43 (4:1 hexanes/EtOAc); IR (film) 2929, 2857, 1724, 1522, 1471, 1366, 1251, 1163, 1113; ^{1}H NMR (200 MHz) δ 5.72−5.65 (m, 1H), 5.17 (dt, 1H, J = 2.6, 7.7 Hz), 4.52 (dt, 1H, J = 4.0, 9.2 Hz), 4.23 (q, 2H, J = 7.2 Hz), 4.12 (dd, 1H, J = 2.4, 10.2 Hz), 4.02 (dd, 1H, J = 2.8, 10.2 Hz), 3.89 (dd, 1H, J = 4.0, 9.2 Hz), 3.57 (dd, 1H, J = 9.1, 9.2 Hz), 3.37 (s, 3H), 1.46 (s, 9H), 1.28 (t, 3H, J = 7.2 Hz), 0.86 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (50 MHz) δ 201.2, 168.9, 160.7, 80.3, 74.3, 62.3, 61.6, 59.8, 59.0, 28.2, 25.6, 18.1, 14.1, −5.6, −5.7; MS m/z (rel int) 465 (11, M + H), 437 (10), 409 (46), 391 (22), 365 (100), 333 (21), 307 (18), 277 (21), 259

(23), 233 (34), 173 (27); HRMS (CI) calcd for $C_{20}H_{41}N_2SiSO_6$ (M + H) 465.2437, found 465.2437; $[\alpha]^{25}_D = +66.7$ (*c* 1, CH_2Cl_2).

Alcohol 17. A solution of **16** (235 mg, 0.51 mmol) in THF (3 mL) at 0 °C was treated with tetrabutylammonium fluoride (146 mg, 0.56 mmol). After stirring 1 h at 0 °C, the solvent was evaporated and the residue partitioned between CH_2Cl_2 and water. The aqueous layer was extracted three times with CH_2Cl_2, and the combined organic layers washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (3:2 hexanes/EtOAc) afforded 168 mg (94%) of the title compound as a light yellow oil: $R_f = 0.23$ (1:1 hexanes/EtOAc); IR (film) 3338, 2980, 2932, 1721, 1693, 1519, 1392, 1166, 1118; ^{1}H NMR (360 MHz) δ 5.66 (d, 1H, $J = 5.7$ Hz), 5.16 (dt, 1H, $J = 3.6$, 7.1 Hz), 4.55 (dd, 1H, $J = 5.3$, 11.3 Hz), 4.27 (q, 2H, $J = 7.2$ Hz), 4.20−4.17 (m, 1H), 4.01 (dd, 1H, $J = 2.7$, 11.6 Hz), 3.86 (dd, 1H, $J = 4.7$, 9.4 Hz), 3.60−3.56 (m, 1H), 3.36 (s, 3H), 1.43 (s, 9H), 1.29 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (50 MHz) δ 201.4, 169.4, 155.2, 80.6, 74.4, 62.0, 61.2, 60.4, 59.7, 59.1, 28.1, 14.0; MS *m*/*z* (rel int) 351 (11, M + H), 333 (10), 317 (41), 295 (14), 261 (21), 251 (54), 233 (20), 217 (62), 201 (17), 187 (20), 162 (18), 145 (20), 135 (100); HRMS (CI) calcd for $C_{14}H_{27}N_2SO_6$ (M + H) 351.1590, found 351.1583; $[\alpha]^{25}_D = +32.6$ (*c* 1, CH_2Cl_2).

Thiazoline 18. A solution of compound **17** (159 mg, 0.45 mmol) in THF (3 mL) was treated with Burgess reagent[8] (118 mg, 0.50 mmol) and heated for 15 min at 65 °C. The reaction mixture was cooled to room temperature and concentrated *in vacuo*, and the residue was chromatographed (1:1 hexanes/EtOAc) to afford 131 mg (88%) of the title compound as a colorless solid: $R_f = 0.30$ (1:1 hexanes/EtOAc); IR (film) 2978, 2932, 1719, 1621, 1507, 1367, 1237, 1165; ^{1}H NMR (360 MHz) δ 5.49 (d, 1H, $J = 6.5$ Hz), 5.11 (t, 1H, $J = 9.5$ Hz), 4.69−4.66 (m, 1H), 4.24 (q, 2H, $J = 7.2$ Hz), 3.81−3.77 (m, 1H), 3.62−3.59 (m, 1H), 3.55−3.46 (m, 2H), 3.35 (s, 3H), 1.44 (s, 9H), 1.29 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (90 MHz) δ 175.6, 170.4, 155.1, 105.3, 80.0, 78.3, 61.7, 59.2, 53.1, 35.21, 28.2, 14.1; MS *m*/*z* (rel int) 333 (100, M + H), 301 (23), 277 (81), 245 (72), 233 (88), 201 (17), 187 (9); HRMS (CI) calcd for $C_{14}H_{25}N_2SO_5$ (M + H) 333.1484, found 333.1474; $[\alpha]^{25}_D = +54.4$ (*c* 1, CH_2Cl_2).

***N*-Tr-*O*-Methyl-L-seryl-*O*-TBDMS-L-serine Ethyl Ester (20).** Prepared from *N*-Tr-*O*-Me-L-Ser-OH[26] as described for compound **15**. Purification by flash chromatography (2:1 hexanes/EtOAc) afforded compound **20** (84%, two steps) as a colorless foam: $R_f = 0.26$ (2:1 hexanes/EtOAc); IR (film) 2928, 2952, 2118, 1743, 1676, 1492, 1446, 1112; ^{1}H NMR (360 MHz) δ 8.72 (d, 1H, $J = 8.1$ Hz), 7.57−7.54 (m, 6H), 7.29−7.12 (m, 9H), 4.72−4.69 (m, 1H), 4.31−4.22 (m, 3H), 4.18 (dd, 1H, $J \sim 2.4$, 9.9 Hz), 3.83 (dd, 1H, $J = 2.8$, 9.9 Hz), 3.38 (dd, 1H, $J = 1.9$, 8.9 Hz), 3.29−3.27 (m, 1H), 2.93 (s, 3H), 1.59 (d, 1H, $J = 10.3$ Hz), 1.31 (t, 3H, $J = 7.1$ Hz), 0.91 (s, 9H), 0.06 (d, 6H, $J = 2.6$ Hz); ^{13}C NMR (90 MHz) δ 173.2, 170.1, 145.9, 128.6, 128.0, 126.5, 71.7, 71.3, 63.9, 61.3, 58.5, 57.5, 54.3, 25.6, 14.2, −5.6, −5.7; MS *m*/*z* (rel int) 591 (2, M + H), 213 (1), 349 (25), 243 (100), 165 (8); HRMS (CI) calcd for $C_{34}H_{47}N_2SiO_5$ (M + H) 591.3254, found 591.3231; $[\alpha]^{25}_D = -69.8$ (*c* 1, CH_2Cl_2).

Thioamide 21. Prepared from compound **20** as described for compound **16**. Purification by flash chromatography (3:1 hexanes/EtOAc) afforded the title compound (52%) as a colorless oil: $R_f = 0.59$ (3:1 hexanes/EtOAc); IR (film) 2927, 2858, 1745, 1503, 1440, 1251, 1204, 1113; ^{1}H NMR (360 MHz) δ 10.41 (d, 1H, $J = 6.3$ Hz), 7.50 (d, 6H, $J = 7.2$ Hz), 7.32−7.19 (m, 9H), 5.29−5.26 (m, 1H), 4.33−4.28 (m, 3H), 4.18 (dd, 1H, $J = 2.4$, 10.1 Hz), 4.04 (dd, 1H, $J = 2.7$, 10.1 Hz), 3.74−3.72 (m, 2H), 3.00 (s, 3H), 2.01−1.97 (m, 1H), 1.31 (t, 3H, $J = 7.1$ Hz), 0.92 (s, 9H), 0.06 (d, 6H, $J = 1.4$ Hz); ^{13}C NMR (90 MHz) δ 203.9, 169.1, 145.7, 128.7, 128.0, 126.7, 74.3, 71.9, 67.9, 62.9, 61.6, 59.6, 58.7, 25.6, 14.3, −5.6, −5.7; MS *m*/*z* (rel int) 607 (1, M + H), 529 (1), 350 (19), 243 (100), 165 (5); HRMS (CI) calcd for $C_{34}H_{47}N_2SiSO_4$ (M + H) 607.3026, found 607.3018; $[\alpha]^{25}_D = -56.3$ (*c* 1, CH_2Cl_2).

Alcohol 22. Prepared from compound **21** as described for compound **17**. Purification by flash chromatography (3:2 hexanes/EtOAc) afforded **22** (67%) as a colorless solid: $R_f = 0.29$ (3:2 hexanes/EtOAc); IR (film) 3258, 2931, 2886, 1741, 1507, 1451, 1204, 1114; ^{1}H NMR (360 MHz) δ 10.41 (d, 1H, $J = 6.3$ Hz), 7.47−7.40 (m, 6H), 7.31−7.20 (m, 9H), 5.02−4.99 (m, 1H), 4.38−4.32 (m, 4H), 3.94 (d, 1H, $J = 10.7$ Hz), 3.79 (dd, 1H, $J = 2.7$, 8.9 Hz), 3.71 (dd, 1H, $J = 2.6$, 8.9 Hz), 3.08 (s, 3H), 2.27−2.24 (m, 1H), 1.32 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (90 MHz) δ 203.8, 169.5, 145.3, 128.7, 128.1, 126.8, 75.8, 71.9, 65.5, 62.1, 61.2, 59.2, 59.1, 14.2; MS *m*/*z* (rel int) 493 (2, M + H), 459 (1), 415 (1), 316 (3), 243 (100), 165 (6); HRMS (CI) calcd for $C_{28}H_{33}N_2SO_4$ (M + H) 493.2161, found 493.2169; $[\alpha]^{25}_D = -67.7$ (*c* 1, CH_2Cl_2).

Thiazole 23. Compound **22** (55 mg, 0.11 mmol) was dissolved in THF (4 mL) under nitrogen. Burgess reagent[8] (29 mg, 0.12 mmol) was added and the resulting solution heated to 65 °C for 10 min. The mixture was cooled to room temperature, concentrated *in vacuo*, and purified by flash chromatography (3:2 hexanes/EtOAc) to yield the thiazoline (51 mg, 98%) as a colorless solid: $R_f = 0.36$ (3:2 hexanes/EtOAc). The thiazoline (40 mg, 0.074 mmol) was dissolved in CH_2Cl_2 (3.0 mL), and manganese(IV) oxide (73 mg, 0.84 mmol) was added. After 24 h, the mixture was filtered through a pad of Celite and concentrated *in vacuo*. Purification by flash chromatography (3:1 hexanes/EtOAc) afforded compound **23** (26 mg, 74%) as a white foam: $R_f = 0.44$ (2:1 hexanes/EtOAc); IR (film) 2929, 2821, 1733, 1716, 1491, 1450, 1237, 1208, 1104; ^{1}H NMR (360 MHz) δ 8.13 (s, 1H), 7.55−7.53 (m, 6H), 7.28−7.18 (m, 9H), 4.41 (q, 2H, $J = 7.1$ Hz), 4.32−4.29 (m, 1H), 3.49 (dd, 1H, $J = 2.3$, 9.1 Hz), 3.51−3.45 (m, 1H), 2.95 (s, 3H), 1.96 (dd, 1H, $J = 3.9$, 8.9 Hz), 1.40 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (90 MHz) δ 179.2, 161.7, 146.9, 145.9, 128.6, 128.4, 127.9, 126.6, 74.2, 71.8, 61.1, 58.7, 55.6, 14.3; MS *m*/*z* (rel int) 473 (1, M + H), 427 (1), 395 (1), 243 (100), 231 (12), 185 (5); HRMS (CI) calcd for $C_{28}H_{28}N_2SO_3$ 473.1899, found 473.1890; $[\alpha]^{25}_D = -260.8$ (*c* 1, CH_2Cl_2).

Thiazole 3. To a solution of thiazole **23** (10 mg, 0.021 mmol) in 1:1 chloroform/methanol (1.0 mL) was added TFA (1.0 mL) with stirring at −10 °C. After 40 min, the volatile components were removed *in vacuo* and azeotroped twice with CH_2Cl_2. The resulting residue was dissolved in water and washed with ether. The aqueous layer was lyophilized. The crude TFA salt was dissolved in CH_2Cl_2 (1.0 mL) under nitrogen and cooled to 0 °C. Triethylamine (0.01 mL, 0.063 mmol) was added, followed by a solution of di-*tert*-butyl dicarbonate (4.5 mg, 0.021 mmol) in CH_2Cl_2 (1.0 mL). After 4 h, the solution was washed with 1 M HCl followed by brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (3:2 hexanes/EtOAc) afforded the title compound (6.8 mg, 98%) as a colorless solid: $R_f = 0.24$ (3:2 hexanes/EtOAc); IR (film) 3390, 2431, 2359, 2255, 2205, 1554, 1534, 1516; ^{1}H NMR (360 MHz) δ 8.10 (s, 1H), 5.68−5.65 (m, 1H), 5.27−5.24 (m, 1H), 4.41 (q, 2H, $J = 7.1$ Hz), 3.98−3.94 (m, 1H), 3.73 (dd, 1H, $J = 4.7$, 9.0 Hz), 3.32 (s, 3H), 1.48 (s, 9H), 1.40 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (90 MHz) δ 172.5, 161.1, 155.0, 147.1, 127.3, 80.1, 73.5, 61.1, 58.9, 52.8, 28.1, 14.1; MS *m*/*z* (rel int) 330 (3, M + H), 285 (14), 274 (38), 257 (19), 242 (10), 229 (40), 211 (18), 198 (11), 185 (63), 168 (9), 139 (33), 112 (8), 57 (100); HRMS (CI) calcd for $C_{14}H_{23}N_2SO_5$ (M + H) 330.1249, found 330.1239. Anal. Calcd for $C_{14}H_{22}N_2SO_5$: C, 50.90; H, 6.71; N, 8.48. Found: C, 50.91; H, 6.77; N, 8.30; $[\alpha]^{25}_D = -11.6$ (*c* 1, CH_2Cl_2).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **3**−**5**, **7**, **8**, **10**−**13**, **15**−**18**, and **20**−**23** (34 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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