Total Synthesis of Bistratamide D†

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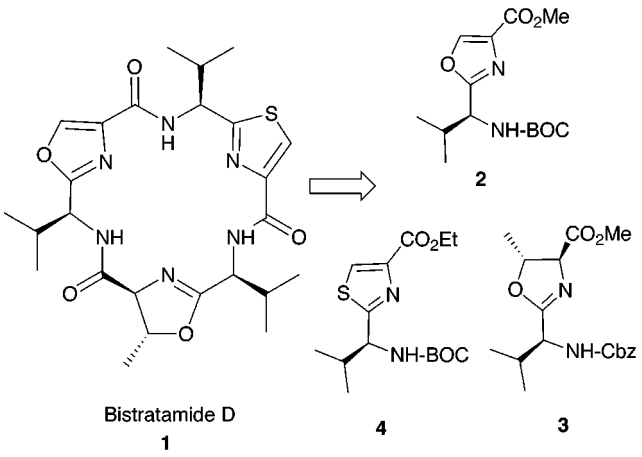
The total synthesis of the macrocyclic hexapeptide bistratamide D is reported. The synthetic strategy involved assembly of enantiomerically pure oxazole, thiazole, and oxazoline segments derived from amino acids. Macrocyclization of the hexapeptidic aminooxazoline-oxazole-thiazole carboxylic acid fragment was accomplished by activation with *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU).

A large number of oxazole- and/or thiazole-containing natural products have been isolated from marine organisms, mainly sponges and ascidians, over the last two decades. The cytotoxic and antineoplastic activities that they exhibit, as well as the possibility of acting as metal ion chelating metabolites, have inspired a considerable amount of both structural and synthetic studies.[1]

We have focused our attention on the synthesis of some of these natural products and have recently reported the total synthesis of bistratamide C.[2] We next turned our attention to the synthesis of the closely related macrocyclic hexapeptide bistratamide D (**1**), isolated from a Philippine collection of the ascidian *Lissoclinum bistratum*.[3] While oxazole-containing products are known from nudibrach egg masses[4] and from a number of sponges,[5] bistratamide D is only the third example of an oxazole-containing product from an ascidian.[3,6] Furthermore, bistratamide D is one of the more cytotoxic of the cyclic hexapeptides isolated from *L. bistratum* and has been found to induce depressant effects in mice when administered by intracerebral injection.[3]

A retrosynthetic approach to bistratamide D, consisting of disconnection at each of the amide linkages and therefore similar to the one performed for bistratamide C[2], is outlined in Scheme 1. However, the presence of the trans-4,5-disubstituted oxazoline **3** in the bistratamide D skeleton required that we use different protecting groups during the synthetic process. The trans-substituted oxazoline **3** is an acid-sensitive and readily opened moiety,[7] and for these reasons the oxazoline ring closure

Scheme 1



in earlier work on peptidic macrocycles[8] was delayed until the final step. However, there were instances where the preconstructed trans-4,5-disubstituted oxazoline was utilized[9] successfully. We chose to follow this course since it represented a more convergent strategy.

Synthesis of the oxazole moiety **2** could be achieved by radical oxidation of the valine-serine-derived oxazoline **5**[2] by a procedure recently developed in our laboratory, allowing us to obtain oxazole **2** in 67% yield on a 2.5 g scale without affecting the chiral center α to the 2-position of the oxazole ring. This procedure[10] involves refluxing of oxazoline **5** in benzene in the presence of copper(I) bromide, copper(II) acetate, and *tert*-butylperoxybenzoate (Scheme 2). It offers a high degree of reproducibility, being therefore much more reliable than MnO_2 or NiO_2 for the oxidation of oxazolines. However, by following a procedure recently reported by Williams,[11] involving use of bromotrichloromethane and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), oxazole **2** was obtained in quantitative yield. Saponification with lithium hydroxide in aqueous methanol gave the oxazole carboxylic acid **6**, in

† Dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday.

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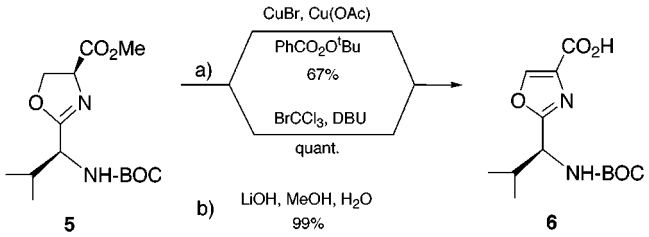
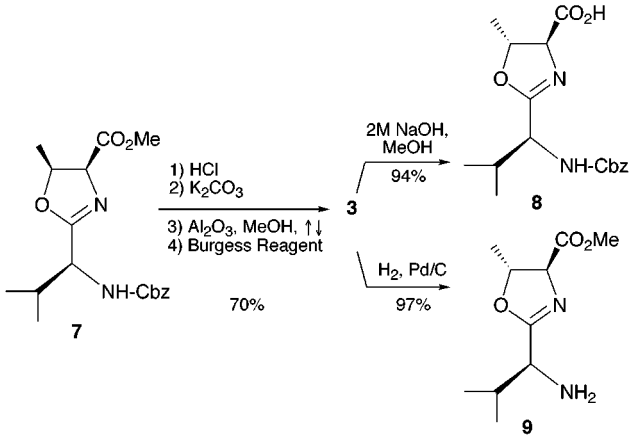
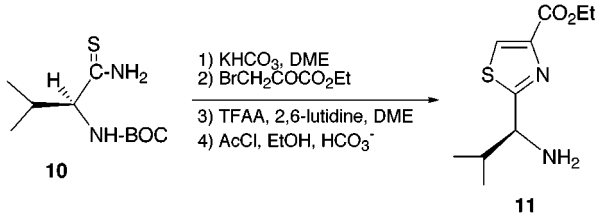
Scheme 2



Scheme 3



Scheme 4



near-quantitative yield, which is now ready to be coupled to the thiazole **4**.

The oxazoline portion **3** of the target was obtained as follows by a slight modification of the epimerization conditions reported by Wipf.[12] Sequential treatment of *cis*-oxazoline **7** with 1 M HCl, K_2CO_3, and basic Al_2O_3 in refluxing MeOH provided the dipeptide with the *allo*-threonine configuration (not shown), which upon cyclization with Burgess reagent[13] gave the required trans-oxazoline fragment **3** in good (70%) yield from *cis*-oxazoline **7** (Scheme 3). *trans*-Oxazoline **3** was easily transformed to the free acid **8** by basic hydrolysis or to the amine **9** by catalytic hydrogenolysis of the Cbz group in very good yields.

The requisite thiazole fragment **4** was prepared from thioamide **10** by using Holzapfel's modified Hantzsch procedure,[14] as outlined in Scheme 4. Amine deprotection was achieved with acetyl chloride in absolute ethanol, as described by North,[15] to provide primary amine **11** in quantitative yield.

To couple the three fragments, it was decided to first join oxazole **6** with thiazole amine **11**. This was accomplished by forming mixed acyl carbonates with both isobutyl and isopropyl chloroformates, and mixed anhydrides with both pivaloyl and 2,4,6-trichlorobenzoyl chloride. However, both these routes resulted in low to moderate yields of the desired product **12**, often accompanied by large amounts of undesired side products. Activation of oxazole acid **6** with (1,1′)-carbonyldiimidazole (CDI)[16] resulted in a 78% yield of adduct **12**, while use of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) in the presence of 1-hydroxybenzotriazole (HOBt) proved to be superior, finally providing adduct **12** in 94% yield (Scheme 5). The primary amine **13** or the carboxylic acid **14** could be obtained from **12** in almost quantitative yields by employment of well-known deprotection protocols, as shown in Scheme 5.

To arrive at the final product, **1**, two alternative routes were explored. Coupling of the tetrapeptidic acid **14** with oxazoline amine **9** was accomplished in 53% yield by using EDCI in the presence of 4-(dimethylamino)pyridine (DMAP) in dichloromethane (Scheme 6). However, amine deprotection of **15** did not provide the amino ester **16**. Only products derived from the opening of the oxazoline moiety were obtained. This result prompted us to explore the alternative coupling of oxazoline acid **8** with tetrapeptidic amine **13**. Carboxyl activation of **8** via a mixed anhydride or the employment of dicyclohexylcarbodiimide (DCC) with DMAP were found to be inefficient. The use of EDCI with DMAP, 2-chloro-1,3-dimethyl-imidazolidium hexafluorophosphate (CIP) with 1-hydroxy-7-azabenzotriazole (HOAt),[17] or of triphenylphosphine with hexachloroacetone[18] did produce the hexapeptide **17** in a modest 31−40% yield (Scheme 7). However, the yield was eventually improved to 79% by using EDCI with HOBt in DMF.

Removal of the Cbz group in **17** proved to be one of the critical steps of the synthesis. Any attempt to carry out an acid-catalyzed cleavage (BBr_3, TFA, bromocatecholborane) resulted in opening of the oxazoline moiety rather than loss of the Cbz group. On the other hand, catalytic hydrogenolysis under standard conditions (10% Pd/C, $Pd(OH)_2$, atmospheric pressure) was an ineffective and low-yielding alternative because of the poisoning effect of the sulfur-containing thiazole moiety. The employment of liquid ammonia as solvent did little to improve matters.[19] This problem was eventually solved by using higher pressure (100 psi), a more active catalyst (Pd black), and EtOH/Et_3N as the solvent system to achieve an 83% yield of amine **18** (Scheme 8). The final ring-closure step was successfully implemented after ester hydrolysis of **18** using LiOH−aqueous EtOH, by treatment of the crude amino acid with HATU and Hunigs base in dry DMF. Isolation of the product produced bistratamide D (**1**) in 48% yield.

As mentioned earlier, our first route to bistratamide D, involving the *N*-Boc cleavage of hexapeptide **15**, was found to be unsuccessful. However, we felt that further study may prove useful. For our second route described above, a reliable method to cleave the *N*-Cbz group from hexapeptide **17** had been obtained, despite the presence

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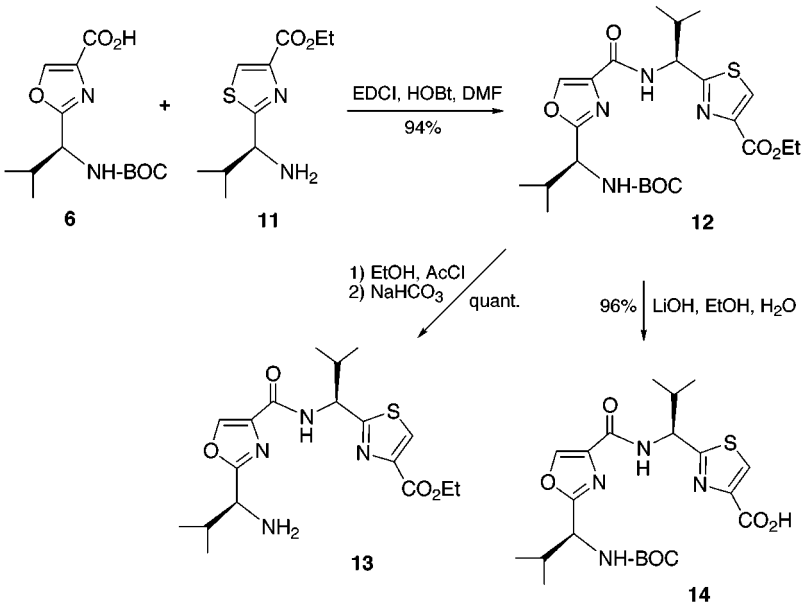
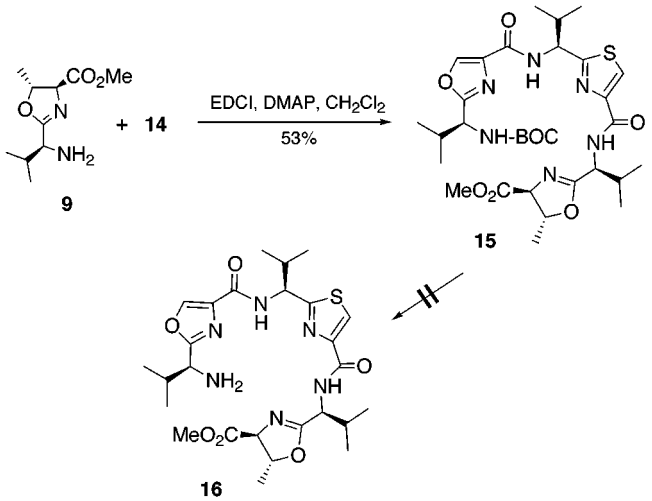
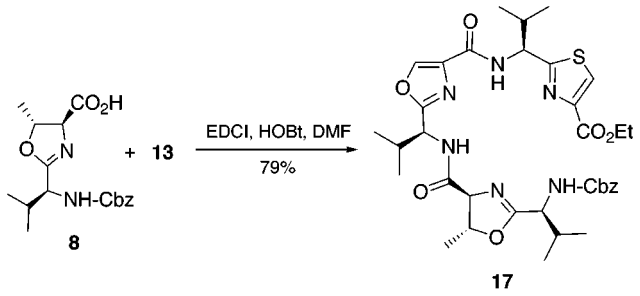
Scheme 5



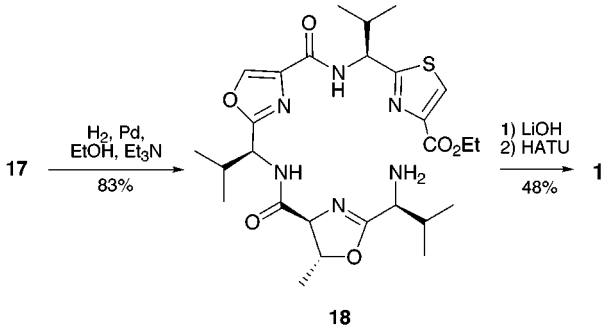
Scheme 6



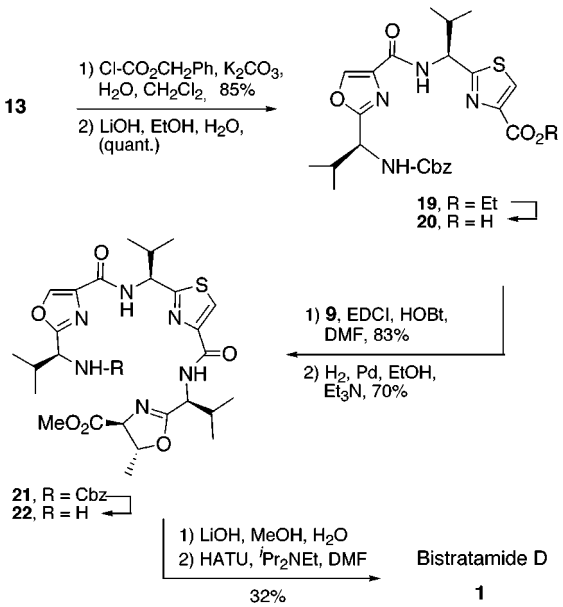
Scheme 7



Scheme 8



Scheme 9



of the thiazole moiety. Given these circumstances, it seemed that a reexamination of the first route, involving a change in protecting group for **14**, could overcome the earlier failure.

If amine **13** was reprotected as the *N*-Cbz derivative and then the ester, **19**, hydrolyzed to provide acid **20**, it seemed we should have a coupling partner in hand that could later be N-deprotected (Scheme 9). This indeed was shown to be the case. Coupling of amine **9** with carboxylic acid **20** using EDCI with HOBt proceeded in good yield, and the resulting hexapeptide **21** was smoothly hydrogenolyzed to amine **22** using the conditions described for **17** to **18**. Amine **22** was then carried on, after ester hydrolysis, to bistratamide D in 32% yield using the HATU/Hünigs sequence outlined above. Given the greater steric demands of this cyclization, a lower yield of bistratamide D from this hexapeptidic fragment was expected.

In summary, the first total synthesis of bistratamide D has been accomplished wherein employment of EDCI with HOBt for fragment coupling proved to be superior to other coupling methods explored. Our convergent approach allowed for easy access to either of two hexapeptidic fragments (**17** and **21**), cyclization of which with HATU provided the final compound in 48% (from **17**) or 32% (from **21**) yields.

Experimental Section

General and Starting Materials Used. Commercially available copper(I) bromide was purified by refluxing in dry THF, decanting the liquid, and repeating the procedure until a colorless liquid was obtained. Methyl *N*-((triethylammonio)-sulfonyl)carbamate (Burgess reagent), prepared according to literature procedures,[13] was stored in brown bottles under argon at −20 °C and checked by NMR prior to each use.

Oxazoline **5** was prepared as previously described.[2] *cis*-Oxazoline **7** was prepared as described by Wipf.[12] Thioamide **10** was synthesized following the procedure described by Holzapfel.[14] All other reagents were commercially available (Aldrich) and used without any further purification.

2-[(*S*)-1-*tert*-Butyloxycarbonylamino-2-methylpropyl]-4-carbomethoxyoxazole 2. Oxazoline **5** (1.67 g, 5.56 mmol), dissolved in CH_2Cl_2 (56 mL), was cooled to 0 °C in an ice bath. DBU (0.91 mL, 6.08 mmol) was added and then $BrCCl_3$ (0.71 mL, 7.20 mmol), dropwise. This was allowed to stir overnight while warming to room temperature. The mixture was washed with saturated (aqueous) NH_4Cl (2 × 27 mL), and the aqueous phase was extracted with EtOAc (2 × 14 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to provide 1.66 g (100%) of **2** as a yellow solid that required no further purification: mp 120−124 °C; R_f = 0.68 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ −44.4 (*c* 0.8, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.84 (app t, J = 6.4 Hz, 6H), 1.34 (s, 9H), 2.12 (m, 1H), 3.82 (s, 3H), 4.71 (dd, J = 6.3 Hz, 9.2 Hz, 1H), 5.30 (br d, J = 9.5 Hz, 1H), 8.13 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.0, 18.8, 28.3, 32.9, 52.2, 54.4, 80.0, 133.2, 144.0, 155.4, 161.6, 165.2; IR (neat) 3353, 1714 cm^{-1}; MS *m*/*z* 298. Anal. Calcd for $C_{14}H_{22}N_2O_5$: C, 56.36; H, 7.43; N, 9.39. Found: C, 56.31; H, 7.43; N, 9.31.

4-[2-[(*S*)-1-*tert*-Butyloxycarbonylamino-2-methylpropyl]]-oxazole Carboxylic Acid 6. Lithium hydroxide monohydrate (95 mg, 2.26 mmol) was added to a stirred solution of oxazole ester **2** (0.29 g, 0.97 mmol) in 4 mL of MeOH/H_2O (3:1) at 0 °C and stirred for 1 h with gradual warming to room temperature. TLC monitoring shows complete consumption of starting material. The solvents were concentrated, and the residue was partitioned between EtOAc (10 mL) and H_2O (10 mL). The organic phase was separated, and the aqueous phase was acidified to pH 2 with 1 M HCl and then extracted with EtOAc (4 × 3 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to give 274 mg (99%) of **6** as a pale yellow solid that was used without purification: mp 154−155 °C; R_f = 0.12 (CH_2Cl_2/MeOH 95:5); $[\alpha]^{23}_D$ −28.9 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.89 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 1.37 (s, 9H), 2.17 (m, 1H), 4.82 (app t, J = 8.2 Hz, 1H), 6.41 (d, J = 9.8 Hz, 1H), 8.28 (s, 1H), 12.44 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.5, 19.1, 28.5, 33.0, 54.8, 80.2, 133.4, 144.9, 156.2, 163.9, 167.1; IR (neat) 3314, 3107, 2552, 1745 cm^{-1}; MS *m*/*z* 284; HRMS calcd for $C_{13}H_{20}N_2O_5$ 284.13722, found 284.13720.

2-(1-Benzyloxycarbonylamino-2-methylpropyl)-4-carbomethoxy-5-methyl-*trans*-oxazoline 3. To *cis*-oxazoline **7** (4.20 g, 12.1 mmol) in 200 mL of THF was added 1 M HCl (aqueous) (80 mL), and the mixture was stirred for 30 min. The solution was then made alkaline (pH 9) by addition of solid K_2CO_3. The THF was evaporated, the residue was extracted with EtOAc (3 × 150 mL), and the combined organic phases were concentrated. To the residue were added MeOH (150 mL) and basic alumina (10.0 g, 98.0 mmol), and the mixture was heated to reflux for 4 h. The mixture was cooled to room temperature, sonicated for 5 min, and then vacuum filtered to remove the alumina. The filtrate was concentrated and the residue dissolved in THF (200 mL). Burgess reagent[13] (3.16 g, 13.2 mmol) was added and the solution heated at 80 °C in a pressure tube for 3 h. The mixture was cooled, the solvent concentrated, and the residue purified by chromatography to provided 2.95 g (70%) of **3** as a clear oil, whose spectroscopic data are in agreement with those reported by Wipf:[12] R_f = 0.29 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ +62.5 (*c* 2.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.93 (d, J = 5.9 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 1.43 (d, J = 6.2 Hz, 3H), 2.14 (m, 1H), 3.77 (s, 3H), 4.27 (d, J = 7 Hz, 1H), 4.42 (m, 1H), 4.85 (m, 1H), 5.11 (m, 2H), 5.47 (d, J = 9.2 Hz, 1H), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 17.4, 19.0, 21.1, 32.0, 52.8, 54.6, 67.2, 74.3, 80.0, 128.3, 128.3, 128.7, 136.6, 156.4, 169.2, 171.5; IR (neat) 3370, 3221, 1721 cm^{-1}.

4-[2-(1-Benzyloxycarbonylamino-2-methylpropyl)]-5-methyl-*trans*-oxazoline Carboxylic Acid 8. A solution of **3** (360 mg, 1.03 mmol) in MeOH (3 mL) was treated with 2 M NaOH (0.57 mL, 1.14 mmol) at 0 °C. After 1 h, the solvent was evaporated in vacuo, and the residue was partitioned between water and CH_2Cl_2. The organic layer was discharged, and the aqueous layer was acidified and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were evaporated to give 324 mg (94%) of **8** that was used without further purification: $[\alpha]^{23}_D$ −2.3 (*c* 0.80, MeOH); ^{1}H NMR (CD_3OD) δ 0.92 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 1.40 (d, J = 7.1 Hz, 3H), 2.14 (m, 1H), 3.61 (d, J = 5.5 Hz, 1H), 4.13 (d, J = 5.9 Hz, 1H), 5.09 (s, 2H), 5.33 (m, 1H), 7.33 (m, 5H); ^{13}C NMR (CD_3OD) δ 17.8, 18.3, 19.6, 31.9, 60.0, 61.1, 67.8, 71.6, 128.9, 129.1, 129.5, 138.1, 158.9, 170.9, 172.1; IR (neat) 3404, 1736, 1702, 1654, 1640 cm^{-1}.

2-(1-Amino-2-methylpropyl)-4-carbomethoxy-5-methyl-*trans*-oxazoline 9. A solution of **3** (124 mg, 0.36 mmol) in MeOH (2 mL) was hydrogenated over 15 mg of 5% Pd/C. After 2 h, the reaction mixture was filtered over Celite and evaporated to yield 75 mg (97%) of crude **9** that was used without further purification: ^{1}H NMR ($CDCl_3$) δ 0.92 (m, 6H), 1.42 (d, J = 6.4 Hz, 3H), 2.02 (m, 1H), 3.44 (d, J = 5.2 Hz, 1H), 3.76 (s, 3H), 4.25 (d, J = 5.7 Hz, 1H), 4.84 (m, 1H); IR (neat) 3379, 3303, 2965, 1730, 1654 cm^{-1}.

2-[(*S*)-1′-*tert*-Butyloxycarbonylamino-2′-methylpropyl]-4-carbethoxythiazole 4, was prepared using Holzapfel's procedure.[14] Thioamide **10** (0.50 g, 2.15 mmol) and $KHCO_3$ (1.72 g, 17.2 mmol) were stirred vigorously in 13 mL of DME for 8 min at room temperature. Ethyl bromopyruvate (0.81 mL, 6.45 mmol) was added via syringe and the mixture stirred at room temperature for 45 min before being cooled to ∼0 °C in an ice bath. A solution of trifluoroacetic anhydride (1.21 mL, 8.58 mmol) and 2,6-lutidine (2.12 mL, 18.3 mmol) in 3.3 mL of DME was transferred to the mixture dropwise via cannula over a period of 10 min. After the addition was complete, the mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature. The solvents were concentrated, and the residue was partitioned between H_2O (25 mL) and EtOAc (50 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (4 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (EtOAc/hexanes 5:1) followed with ninhydrin stain gave, after recrystallization ($CHCl_3$/hexanes), 0.50 g (71%) of **4** as a white solid: mp 116−117 °C; R_f = 0.81 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ −37.1 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.86 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.40 (s, 9H), 2.39 (m, 1H), 4.36 (q, J = 7.1 Hz, 2H), 4.85 (m, 1H), 5.30 (br d, J = 9 Hz, 1H), 8.04 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 17.0, 19.2, 28.0, 33.0, 57.8, 61.1, 79.7, 126.6, 147.1, 155.2, 161.1, 173.0; IR ($CDCl_3$): 3350, 3097, 1712, 1477 cm^{-1}; MS *m*/*z* 285, 229, 185; HRMS calcd for $C_{15}H_{24}N_2O_4S$ 328.14568, found 328.14576. Anal. Calcd for $C_{15}H_{24}N_2O_4S$: C, 54.85; H, 7.36; N, 8.53. Found: C, 54.58; H, 7.51; N, 8.49.

2-[(*S*)-1-Amino-2-methylpropyl]-4-ethoxycarbonylthiazole 11. Acetyl chloride (2.5 mL, 35.3 mmol) was added dropwise to absolute ethanol (17 mL) at 0 °C. Thiazole **4** (1.16 g, 3.53 mmol) was added as a solid in one portion and the reaction allowed to stir overnight at room temperature. Concentration of the reaction mixture gave 0.93 g (100%) of

11·HCl as a white foam. Purified material was obtained by partitioning the crude material between CH_2Cl_2 (5 mL) and saturated (aqueous) $NaHCO_3$ (5 mL). The phases were separated, and the organic phase was dried (Na_2SO_4) and concentrated to provide the free amine **11** as a colorless oil: R_f = 0.18 (EtOAc); $[\alpha]^{23}_D$ −24.4 (*c* 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 1.40 (t, J = 7.1 Hz, 3H), 2.02 (br s, 2H), 2.27 (m, 1H), 4.19 (m, 1H), 4.42 (q, J = 7.1 Hz, 2H), 8.11 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.6, 17.0, 19.8, 34.8, 59.6, 61.6, 127.4, 147.2, 161.9, 191.2; IR (neat) 3387, 3318, 3116, 1728, 1618 cm^{-1}; HRMS calcd for $C_{10}H_{16}N_2O_2S$ 228.09325, found 228.09315.

***N*-Boc-oxazole-thiazole-ethyl Ester 12.** To thiazole amine **11** (0.20 g, 0.88 mmol) in DMF (13 mL) at −10 °C were added 1-hydroxybenzotriazole (0.38 g, 2.81 mmol) and oxazole acid **6** (0.28 g, 0.98 mmol), and this was stirred at −10 °C for 20 min. EDCI (0.20 g, 1.05 mmol) was added and the mixture stirred at room temperature for 21 h. After this time, the reaction mixture was diluted with 26 mL of EtOAc, and 13 mL of brine was added. The phases were separated, and the aqueous phase was extracted with EtOAc (2 × 26 mL). The organic phases were then washed successively with 10% citric acid (2 × 13 mL), saturated aqueous $NaHCO_3$ (2 × 13 mL), and brine (2 × 13 mL) and then dried (Na_2SO_4). Flash chromatography of the residue (hexanes/EtOAc 2:1) gave 0.41 g (94%) of **12** as a white solid: mp 144.5−145.8 °C; R_f = 0.40 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ −49.0 (*c* 1.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.91−1.00 (m, 12H), 1.34−1.42 (m, 12H), 2.15 (m, 1H), 2.57 (m, 1H), 4.38 (q, J = 7.1 Hz, 2H), 4.75 (m, 1H), 5.15 (br d, J = 9.1 Hz, 1H), 5.26 (m, 1H), 7.51 (d, J = 9.1 Hz, 1H), 8.06 (s, 1H), 8.11 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.5, 18.1, 18.3, 18.9, 19.8, 28.5, 32.8, 33.2, 54.4, 56.2, 61.6, 80.3, 127.1, 135.7, 141.5, 147.7, 155.5, 160.4, 161.4, 164.1, 171.4; IR ($CDCl_3$) 3325, 3127, 1716, 1596, 1505 cm^{-1}; HRMS calcd for $C_{23}H_{34}N_4O_6S$ 494.21991, found 494.22019. Anal. Calcd for $C_{23}H_{34}N_4O_6S$: C, 55.85; H, 6.93; N, 11.33. Found: C, 55.93; H, 6.87; N, 11.27.

Aminooxazole-thiazole-ethyl Ester 13. Acetyl chloride (2.51 mL, 35.3 mmol) was added dropwise to absolute ethanol (20 mL) at 0 °C. **12** (666 mg, 1.35 mmol) was added to the solution, and the reaction was allowed to stir at room temperature overnight. Evaporation of the solvents in vacuo provided 579 mg of **13**·HCl (100%) as a white solid. A portion of the compound was dissolved in CH_2Cl_2, and aqueous saturated $NaHCO_3$ was added; the organic layer was separated, dried over Na_2SO_4, filtered and evaporated to provide **13** as the free amine, R_f = 0.20 (EtOAc); $[\alpha]^{25}_D$ −31.4 (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87−0.99 (m, 12H), 1.33 (t, J = 7.2 Hz, 3H), 1.76 (bs, 2H), 2.05 (m, 1H), 2.55 (m, 1H), 3.46 (d, J = 5.7 Hz, 1H), 4.35 (q, J = 7.2 Hz, 2H), 5.25 (dd, J = 7.0 and 9.2 Hz, 1H), 7.54 (d, J = 9.2 Hz, 1H), 8.02 (s, 1H), 8.09 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 17.7, 18.0, 18.9, 19.5, 33.0, 33.3, 55.7, 56.0, 61.3, 126.8, 135.2, 141.0, 147.3, 160.3, 161.1, 167.0, 171.2; IR (film) 3568, 3405, 1728, 1668, 1596 cm^{-1}.

***N*-Boc-oxazole-thiazole carboxylic Acid 14.** Lithium hydroxide monohydrate (19 mg, 0.43 mmol) was added to a solution of **12** (100 mg, 0.20 mmol) in 4 mL of EtOH/H_2O (3:1). After 1 h, the solvents were concentrated, and the residue was partitioned between H_2O and CH_2Cl_2. The organic phase was separated, and the aqueous layer was acidified and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were evaporated to give 90 mg (96%) of **14** as a solid: mp 164−166 °C; R_f = 0.21 (CH_2Cl_2/EtOAc 95:5); $[\alpha]^{25}_D$ −54.4 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.81−1.07 (m, 12H), 1.39 (s, 9H), 2.10−2.24 (m, 1H), 2.48−2.63 (m, 1H), 4.75 (bs, 1H), 5.12−5.35 (m, 2H), 7.62 (d, J = 9.1 Hz, 1H), 8.13 (s, 2H), 10.14 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 17.9, 18.1, 18.6, 19.5, 28.2, 32.5, 32.9, 54.2, 56.0, 80.1, 128.2, 135.2, 141.6, 146.8, 155.3, 160.4, 163.6, 164.1, 171.4; IR (film) 3310, 1709, 1693, 1678, 1666 cm^{-1}. This material was used in the next step without further purification.

***N*-Boc-oxazole-thiazole-oxazoline-methyl Ester 15.** EDCI (150 mg, 0.78 mmol) was added to a solution of **9** (186 mg, 0.87 mmol) and **14** (365 mg, 0.78 mmol) in CH_2Cl_2 (5 mL) at 0 °C. A catalytic amount of DMAP was then added. The reaction was allowed to warm to room temperature, and after 3 h, water was added and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated to give 275 mg (53%) of **15**: ^{1}H NMR ($CDCl_3$) δ 0.89−1.03 (m, 18H), 1.41 (s, 9H), 1.41 (d, J = 6.1 Hz, 3H), 2.16−2.29 (m, 1H), 2.48−2.59 (m, 1H), 3.75 (s, 3H), 4.28 (d, J = 6.8 Hz, 1H), 4.75−4.84 (m, 3H), 5.09 (d, J = 8.6 Hz, 1H), 5.29 (dd, J = 6.3 and 9.2 Hz, 1H), 7.35 (d, J = 9.2 Hz, 1H), 7.71 (d, J = 9.1 Hz, 1H), 7.99 (s, 1H), 8.13 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.7, 17.8, 18.0, 18.7, 18.8, 19.5, 20.8, 28.2, 31.8, 32.4, 32.7, 52.3, 52.4, 54.3, 55.9, 74.2, 79.3, 80.7, 123.3, 135.4, 141.3, 149.6, 155.2, 160.2, 160.6, 163.8, 168.4, 171.1, 171.3.

***N*-Cbz-oxazoline-oxazole-thiazole-ethyl Ester 17.** Amine **13** (504 mg, 1.28 mmol) and acid **8** (428 mg, 1.28 mmol) were dissolved in toluene, and then the solution was concentrated. DMF (18 mL) was added, the solution cooled to −10 °C, and HOBt (553 mg, 4.10 mmol) was added. This was stirred for 20 min at −10 °C before EDCI (294 mg, 1.54 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 14 h, after which the solvent was evaporated under reduced pressure and the residue partitioned between EtOAc (40 mL) and brine (20 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed successively with 10% citric acid (2 × 10 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL), and brine (2 × 10 mL), dried ($MgSO_4$), and concentrated. Radial chromatographic purification of the crude residue provided 718 mg (79%) of **17** as a light yellow foam: R_f = 0.16 (hexanes/EtOAc 1:1); $[\alpha]^{25}_D$ −5.53 (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.80−0.97 (m, 18H), 1.30 (t, J = 7.1 Hz, 3H), 1.41 (d, J = 6.1 Hz, 3H), 2.04−2.19 (m, 2H), 2.46−2.55 (m, 1H), 4.15 (d, J = 7.4 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 4.73 (m, 1H), 4.95−5.07 (m, 3H), 5.23 (dd, J = 7.1, 9.1 Hz, 1H), 5.59 (d, J = 8.6 Hz, 1H), 7.10 (d, J = 9.1 Hz, 1H), 7.25 (m, 5H), 7.58 (d, J = 9.1 Hz, 1H), 8.00 (s, 1H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 17.7, 17.9, 18.0, 18.6, 18.7, 19.4, 21.6, 31.3, 31.9, 32.9, 52.1, 54.7, 56.0, 61.2, 66.8, 74.3, 80.5, 126.8, 127.9, 128.0, 128.3, 135.4, 136.0, 141.4, 147.2, 155.9, 160.1, 161.1, 162.7, 168.7, 170.8, 171.1; IR (film) 3302, 1721, 1659, 1596 cm^{-1}. This material was used without further purification.

Aminooxazoline-oxazole-thiazole-ethyl Ester 18. A solution of **17** (97 mg, 0.14 mmol) in 4 mL of EtOH/Et_3N (3:1) was hydrogenated over Pd black at 100 psi. After 5 h, the reaction mixture was sonicated for 5 min and filtered through Celite. The solvents were concentrated, and the crude residue was chromatographied to give 65 mg (83%) of **18**: R_f = 0.33 (CH_2Cl_2/MeOH 90:10); ^{1}H NMR ($CDCl_3$) δ 0.86−1.03 (m, 18H), 1.37 (t, J = 7.1 Hz, 3H), 1.48 (d, J = 6.2 Hz, 3H), 2.02−2.25 (m, 4H), 2.51−2.60 (m, 1H), 3.43 (d, J = 5.1 Hz, 1H), 4.19 (d, J = 7.7 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 4.76 (m, 1H), 5.05 (dd, J = 6.4, 9.1 Hz, 1H), 5.27 (dd, J = 7.1, 9.2 Hz, 1H), 7.14 (d, J = 9.1 Hz, 1H), 7.59 (d, J = 9.2 Hz, 1H), 8.05 (s, 1H), 8.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.3, 17.4, 18.0, 18.2, 18.8, 19.0, 19.7, 21.8, 32.0, 32.2, 32.9, 52.3, 55.3, 56.1, 61.4, 74.5, 80.3, 127.0, 135.6, 141.4, 147.3, 160.2, 161.3, 163.0, 171.2, 171.3, 171.6.

***N*-Cbz-oxazole-thiazole-ethyl Ester 19.** Potassium carbonate (140 mg, 1.01 mmol) was added to a stirred solution of **13** (399 mg, 1.01 mmol) in 2 mL of CH_2Cl_2/H_2O (1:1). Benzyl chloroformate (0.17 mL, 1.21 mmol) was added via syringe, and the mixture was stirred for 12 h at room temperature. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), and chromatographed (hexanes/EtOAc 5:3) to provide 454 mg (85%) of **19** as a colorless solid: mp 169.7−170.7 °C; R_f = 0.35 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ −34.1 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.81−1.02 (m, 12H), 1.31 (t, J = 7.0 Hz, 3H), 2.10−2.20 (m, 1H), 2.49−2.56 (m, 1H), 4.33 (q, J = 6.9 Hz, 2H), 4.78 (app t, J = 7.1 Hz, 1H), 5.06 (m, 2H), 5.22 (t, J = 8.1 Hz, 1H), 5.40 (d, J = 8.8 Hz, 1H), 7.24−7.28 (m, 5H), 7.43 (d, J = 8.6 Hz, 1H), 8.00 (s, 1H), 8.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.8, 13.6, 13.8, 14.1, 15.1, 28.1, 28.5, 50.2, 51.5, 56.8, 62.7, 122.4, 123.6,

124.0, 131.0, 131.5, 136.8, 142.9, 151.4, 155.6, 156.7, 158.9, 166.7; IR (neat) 3321, 3148, 3100, 1725 cm^{-1}.

***N*-Cbz-oxazole-thiazole Carboxylic Acid 20.** Lithium hydroxide monohydrate (28 mg, 0.67 mmol) was added to a stirred solution of **19** (155 mg, 0.29 mmol) in 3.7 mL of MeOH/H_2O (4.5:1) at 0 °C and allowed to stir for 2 h with gradual warming to room temperature, after which the previously cloudy solution had cleared. The solvents were concentrated, and the residue was partitioned between water and $CHCl_3$. The organic layer was discharged, and the aqueous layer was acidified and extracted with $CHCl_3$ (3 × 5 mL). The combined organic extracts were evaporated to give 145 mg (100%) of **20** that was used without further purification: ^{1}H NMR ($CDCl_3$) δ 0.75−1.05 (m, 12H), 2.09−2.21 (bs, 1H), 2.43−2.55 (bs, 1H), 4.78 (bs, 1H), 4.96−5.19 (m, 2H), 5.24 (bs, 1H), 5.59 (bs, 1H), 7.25 (bs, 5H), 7.59 (bs, 1H), 8.12 (bs, 1H), 8.15 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 13.4, 13.7, 14.2, 15.0, 28.0, 28.4, 50.3, 51.6, 62.7, 123.7, 123.9, 130.7, 131.4, 137.3, 142.5, 151.5, 155.8, 159.2, 166.7; IR (neat) 3401, 3314, 3117, 2965, 1714 cm^{-1}.

***N*-Cbz-oxazole-thiazole-oxazoline-methyl Ester 21.** To amine **9** (75 mg, 0.35 mmol) and acid **20** (141 mg, 0.29 mmol) in DMF (4 mL) at −10 °C was added HOBt (126 mg, 0.93 mmol), and the mixture was stirred for 20 min. EDCI (73 mg, 0.38 mmol) was added, and stirring was continued for 10.5 h at room temperature. The reaction mixture was then diluted with EtOAc (8 mL), brine (4 mL) was added, the phases were separated, and the aqueous phase was extracted with EtOAc (2 × 8 mL). The organic phases were washed successively with 10% citric acid (2 × 4 mL), saturated aqueous $NaHCO_3$ (2 × 4 mL), and brine (2 × 4 mL) and dried (Na_2SO_4). Flash chromatography of the residue (EtOAc/hexanes 5:4) provided 168 mg (83%) of **21** as a white foam that consisted of a mixture (approximately 1:1) of two rotomers: R_f = 0.06 (hexanes/EtOAc 1:1); $[\alpha]^{23}_D$ −1.25 (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.80−0.99 (m, 18H), 1.33−1.37 (m, 3H), 2.12−2.23 (m, 1H), 2.41−2.50 (m, 2H), 3.69 (s, 3H), 4.20 (d, *J* = 6.9 Hz, 0.47H), 4.24 (d, *J* = 6.7 Hz, 0.52H), 4.72−4.85 (m, 3H), 5.00−5.11 (m, 2H), 5.26 (dd, *J* = 3.0, 6.3 Hz, 1H), 5.36 (d, *J* = 9.2 Hz, 0.48H), 5.48 (d, *J* = 9.1 Hz, 0.52H), 7.20−7.32 (m, 5H), 7.38 (d, *J* = 9.0 Hz, 1H), 7.67 (d, *J* = 9.1 Hz, 0.48H), 7.73 (d, *J* = 9.3 Hz, 0.53H), 7.96 (s, 1H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.2, 13.4, 13.5, 14.1, 14.2, 14.3, 14.8, 14.9, 16.3, 27.3, 28.0, 28.1, 28.4, 28.5, 47.8, 48.0, 50.3, 51.3, 62.7, 69.7, 69.8, 74.6, 118.7, 118.8, 123.5, 123.6, 123.8, 124.0, 131.0, 131.4, 136.9, 145.2, 151.4, 155.5, 156.0, 156.1, 158.9, 159.1, 163.4, 164.0, 166.1, 166.2, 166.6, 166.9; IR (neat) 3394, 3297, 2966, 1725 cm^{-1}. Anal. Calcd for $C_{34}H_{44}N_6O_8S$: C, 58.61; H, 6.36; N, 12.06. Found: C, 58.41; H, 6.44; N, 12.06.

Aminooxazole-thiazole-oxazoline-methyl Ester 22. A solution of **21** (101 mg, 0.15 mmol) in 3.3 mL of EtOH/Et_3N (3:1) was hydrogenated over Pd black at 100 psi. After 5 h, the reaction mixture was sonicated for 5 min and filtered through Celite. The solvents were concentrated, and the crude residue was chromatographed to give 57 mg (70%) of **18**: R_f = 0.45 (CH_2Cl_2/MeOH 90:10); ^{1}H NMR ($CDCl_3$) δ 0.86−1.00 (m, 18H), 1.38 (d, *J* = 6.3 Hz, 3H), 1.72 (bs, 2H), 2.06−2.23 (m, 2H), 2.44−2.48 (m, 1H), 3.72 (s, 3H), 3.80 (d, *J* = 6.0 Hz, 1H), 4.23 (d, *J* = 6.8 Hz, 1H), 4.72−4.87 (m, 2H), 5.26 (dd, *J* = 2.5 and 6.6 Hz, 1H), 7.41 (d, *J* = 9.0 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.96 (s, 1H), 8.09 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.3, 13.4, 14.4, 14.4, 15.0, 16.4, 27.4, 28.5, 28.7, 47.9, 48.0, 51.3, 69.8, 74.9, 118.9, 130.7, 136.6, 145.1, 155.9, 156.1, 164.0, 166.3, 166.9; IR (neat) 3401, 3307, 2963, 1744, 1659 cm^{-1}. This material was taken directly to the next step.

Bistratamide D (1). Lithium hydroxide monohydrate (12 mg, 0.29 mmol) was added to a solution of **18** (80 mg, 0.14 mmol) in 3.4 mL of EtOH/H_2O (4:1) at 0 °C. After 3 h, the solution was neutralized with 1 M HCl, and then the solvents were evaporated to dryness by azeotropic distillation with toluene. The solid residue was dissolved in DMF (26 mL) and cooled to −10 °C, and diisopropylethylamine (0.05 mL, 0.31 mmol) and HATU (56 mg, 0.15 mmol) were added. The mixture was stirred at −10 °C for 2 h and then at room temperature for 3 days. After this time, the solvents were concentrated in vacuo, and the residue was partitioned between brine (25 mL) and EtOAc (30 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2 × 13 mL). The combined organic extracts were washed successively with 10% aqueous citric acid (2 × 13 mL), saturated aqueous $NaHCO_3$ (2 × 13 mL), and brine (2 × 13 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (EtOAc) afforded 38 mg (48%) of **1** as a colorless solid, whose NMR data are in agreement with that reported:[3] R_f = 0.25 (EtOAc); $[\alpha]^{25}_D$ −29.8 (*c* 0.60, $CHCl_3$) (lit.[3] $[\alpha]^{25}_D$ −31 (*c* 0.33, $CHCl_3$)); λ_{max} = 230 nm (lit.[3] λ_{max} = 232 nm); ^{1}H NMR ($CDCl_3$) δ 0.87−1.06 (m, 18H), 1.57 (d, *J* = 6.3 Hz, 3H), 2.18−2.25 (m, 1H), 2.34−2.43 (m, 2H), 4.09 (dd, *J* = 2.3, 9.1 Hz, 1H), 4.76 (m, 1H), 4.96 (m, 2H), 5.27 (dd, *J* = 5.2, 7.4 Hz, 1H), 7.89 (d, *J* = 7.4 Hz, 1H), 8.03 (d, *J* = 9.9 Hz, 1H), 8.10 (s, 1H), 8.15 (s, 1H), 8.62 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.2, 17.6, 17.7, 18.1, 18.1, 19.0, 21.8, 31.1, 33.2, 34.4, 51.8, 53.0, 56.4, 74.0, 82.4, 123.6, 135.7, 140.9, 148.5, 159.1, 160.0, 163.2, 167.5, 169.3, 170.4; IR (neat) 3387, 2966, 16779, 1539 cm^{-1}.

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Supporting Information Available: NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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