An Enantioselective Synthesis of Bengamide E

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In 1986, bengamides, novel nonalkaloidal natural products that possess significant antihelminthic activity as well as cytotoxicity, were isolated from a Jaspidae sponge collected in the Fiji Islands by Crews and his co-workers.[1] Spectroscopic analyses and degradation studies showed that bengamide E (1), one of the members of bengamide family, has a unique structure having a cyclo-L-lysine and a C-10 side chain with four contiguous hydroxy groups as well as an *E*-olefin (Figure 1). The absolute configuration of the side chain of the bengamides has been tentatively assigned as 2*R*,3*R*,4*S*,5*R* by ^{1}H NMR study of its *O*-methyl manderate derivative[2] and confirmed very recently by three enantioselective syntheses: one from an optically active cyclitol,[3] another from L-glucose,[4] and a third from D-glucoheptono-γ-lactone.[5]

In this paper, we would like to describe an alternative enantioselective synthesis of bengamide E (1) from D-glucose.[6] Our synthetic plan is to utilize the entire carbon skeleton of D-glucose for preparation of the side chain of 1 (C-1 of D-glucose as C-1 of 1) as shown in Figure 1 and δ-lactone **15** for amide formation.[7]

Since the hydroxy groups at C-3 and C-4 of D-glucose are epimeric compared with those of 1, the inversion of the stereochemistry of these hydroxy groups, namely, the transformation of D-glucose via 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) to 3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (**3**), was accomplished according to the literature procedure[8] (five steps, 50% from D-glucose). Compound **3** was converted to 3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (**4**). Next, treatment of **4** with MeOH in the presence of Dowex 50W at 80 °C for 20 h gave methyl 3-*O*-benzyl-β-D-gulopyranoside (**5**) in 65% yield together with a small amount of its α-anomer **6** and β-furanoside **7**. These three products were in equilibrium under the methanolysis conditions, and the ratio of their yields was a function of reaction time. Thus, **7** was formed at the beginning of methanolysis and changed gradually into **5** and **6** over time. The same result was obtained when *c*-HCl, *c*-H_2SO_4, or *p*-TsOH was used instead of Dowex 50W.

The structures of **5**, **6**, and **7** were determined on the basis of the course of methanolysis, their reactivity toward IO_4^-, and ^{1}H NMR. Thus, compound **7**, which reacted with IO_4^- and had a $^3J_{H1,H2}$ = 0 Hz was the initial product in methanolysis and was assigned to be methyl 3-*O*-benzyl-β-D-gulofuranoside. Compound **5**, which did not consume IO_4^- and had a $^3J_{H1,H2}$ = 8.1 Hz, was formed later as the major product in the equilibrium and was assigned to be methyl 3-*O*-benzyl-β-D-gulopyranoside. Compound **6**, which did not react with IO_4^- and had a $^3J_{H1,H2}$ = 4.4 Hz was assigned to be methyl 3-*O*-benzyl-α-D-gulopyranoside.

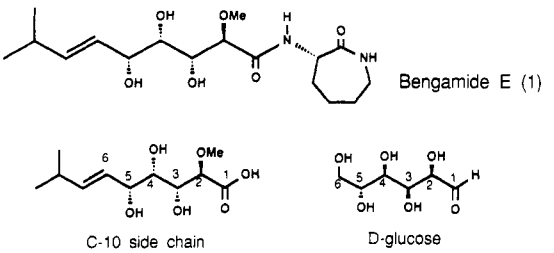

Figure 1.

Compound **5** was converted to its 4,6-*O*-benzylidene derivative **8** and then methylated at O-2 to give methyl 3-*O*-benzyl-4,6-benzylidene-2-*O*-methyl-β-D-gulopyranoside (**9**) in good yield. The reductive ring opening[9] of the 4,6-*O*-benzylidene function of **9** with diisobutyl aluminum hydride (DIBAL) afforded methyl 3,4-di-*O*-benzyl-2-*O*-methyl-β-D-gulopyranoside (**10**) in 75% yield.

The most crucial step was the formation of the terminal *E*-olefin of 1. Swern oxidation[10] of **10** gave aldehyde **11** almost quantitatively. Wittig olefination of **11** with $Me_2CHCH{=}PPh_3$ under various conditions (including the Wittig-Schlosser method,[11] which is known to give predominantly *E*-isomer) gave exclusively *Z*-isomer. Therefore, we next attempted Julia's protocol[12] for stereocontrolled elimination of acetoxy sulfone to yield *E*-olefins. Accordingly, isobutyl phenyl sulfone was condensed with **11** and then acetylated to give a mixture of two diastereomers (**12**). Treatment of the mixture with Na(Hg) gave a mixture of *E*- and *Z*-olefins (**13**) in a ratio of 3:1 (by ^{1}H NMR) in 88% yield. The *E*- and *Z*-isomers could not be separated by any means including $AgNO_3$-coated TLC. Therefore, the two diastereomers (**12**) were first separated by column chromatography, and then we subjected each isomer to Na(Hg) olefination without determining the stereochemistry of the newly formed asymmetric carbons. However, both diastereomers gave almost the same mixture of *E*- and *Z*-olefins (*E*:*Z* = 3:1, by ^{1}H NMR).[13]

Since the *E*- and *Z*-isomers could not be separated at this stage or in the following steps, the following three steps were performed on the mixture. Hydrolysis of the glycosidic linkage of **13** with 50% acetic acid gave an anomeric mixture of reducing sugar **14**, which was oxidized with DMSO-Ac_2O to give lactone **15** (52% from **13**). The δ-lactone **15** was condensed with cyclo-L-lysine (**16**) in THF in the presence of triethylamine to give a mixture of *E*- and *Z*-condensates (**17*E*** and **17*Z***) in good yield. At this stage, **17*E*** and **17*Z*** could be separated by silica gel column chromatography. Birch reduction (Na/NH_3) of **17*E*** afforded bengamide E (1) in 42% yield. The ^{1}H NMR and

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(13) In an attempt to obtain better *E*/*Z* ratios, the olefination reaction was tried under various conditions, but without improvement. For example, hydroxy sulfone, rather than acetoxy sulfone **12**, was treated with 5% Na(Hg); however, the reaction was very slow, and the *E*/*Z* ratio of obtained olefin was the same as that when the acetoxy sulfone was used. In addition, acetoxy sulfone **12** was treated with DBU to afford vinyl sulfone, and the vinyl sulfone was treated with 5% Na(Hg) to give a complex mixture.

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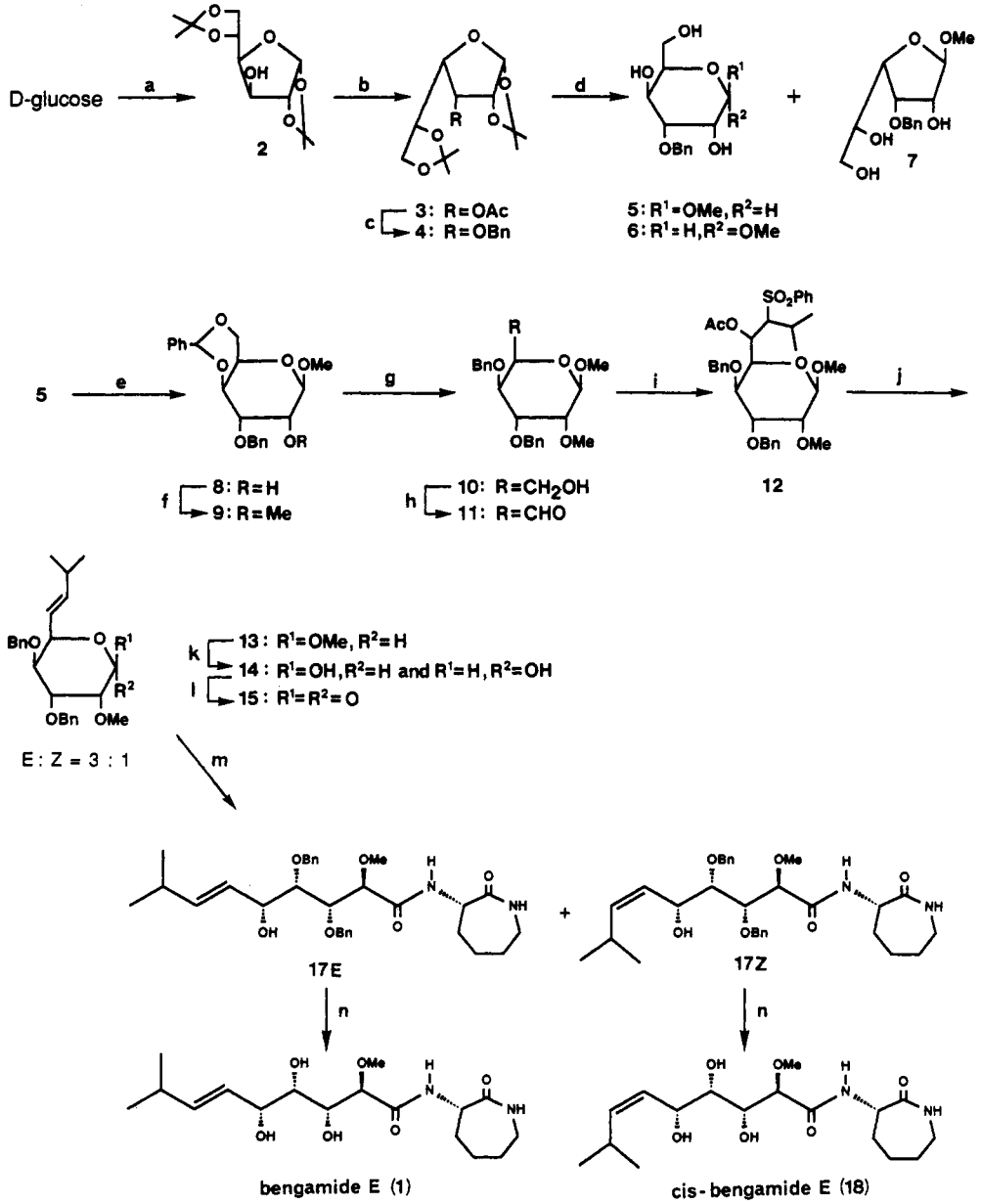
Scheme I[a]



[a] Key: (a) H_3PO_4, $ZnCl_2$, Me_2CO; (b) (1) RuO_2, KIO_4, (2) Ac_2O, pyridine, (3) H_2, Pd/C; (c) KOH, BnCl; (d) Dowex 50W, MeOH; (e) $PhCH(OMe)_2$, *p*-TsOH; (f) NaH, MeI (g), DIBAL; (h) DMSO, $(COCl)_2$, Et_3N; (i) (1) ^nBuLi, $Me_2CHCH_2SO_2Ph$, (2) Ac_2O, pyridine, DMAP; (j) 5% Na(Hg); (k) 50% AcOH; (l) DMSO, Ac_2O; (m) Et_3N, cyclo-L-lysine (16); (n) Na/NH_3.

^{13}C NMR data, as well as physical properties of the synthetic specimen, were in good agreement with those reported for natural bengamide E.[1] The *Z*-isomer of bengamide E (18) (as a syrup; $[\alpha]_D$ +38.5°) was also prepared for biological evaluation from **17*Z*** by Birch reduction. The present work also serves to confirm the assigned structure and the absolute configuration of bengamide E.

Experimental Section

General Methods. ^1H NMR and ^{13}C NMR spectra were recorded at 21–23 °C in $CDCl_3$ with Me_4Si as an internal standard. $[\alpha]_D$ were measured at 20 °C. Silica gel column chromatography was performed on Merck silica gel (Art. 7734), and analytical TLC was performed on Merck silica gel (Art. 5554). Usual workup refers to dilution with an organic solvent (CH_2Cl_2, Et_2O, or AcOEt), washing with water to neutrality, drying with $MgSO_4$, and evaporating under reduced pressure. When high-resolution mass spectroscopy data were used in lieu of elemental analysis, the full-scale ^1H NMR and/or ^{13}C NMR spectrum of each compound showed satisfactory purity of the compound.

3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (4). A mixture of 3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranoside (3) (50 g, 0.17 mmol) and powdered KOH (250 g, 4.6 mol) in benzyl chloride (420 mL) was vigorously stirred at 140 °C for 2 h. Usual workup (Et_2O) and recrystallization (*n*-hexane–$CHCl_3$) gave 4 (48 g, 83%): mp 128.5–129.5 °C; $[\alpha]_D$ +42.5° (*c* 1.5, $CHCl_3$); ^1H NMR δ 4.49, 4.77 (2 H, ABq, J = 12 Hz, OCH_2Ph). Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.11; H, 7.48. Found: C, 65.44; H, 7.33.

Methyl 3-*O*-Benzyl-β-D-gulopyranoside (5). A mixture of 4 (2 g, 5.7 mmol), Dowex 50W (500 mg), and MeOH (80 mL) was refluxed with stirring for 20 h. The resulting mixture was filtered, and the filtrate was concentrated to give a pale yellow oil, which was purified by column chromatography ($CHCl_3$:MeOH = 100:1) to provide 5 (1.06 g, 65%), 6 (0.15 g, 9%), and 7 (0.42 g, 26%). 5: syrup; R_f = 0.29 ($CHCl_3$:MeOH = 50:1); $[\alpha]_D$ −43.7° (*c* 0.45, $CHCl_3$); ^1H NMR δ 4.56 (1 H, d, $J_{H1,H2}$ = 8.1 Hz, H-1). Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.13; H, 7.09. Found: C, 59.43; H, 7.06. **Methyl 3-*O*-benzyl-α-D-gulopyranoside (6):** syrup; R_f = 0.36; $[\alpha]_D$ +63.0° (*c* 0.07, $CHCl_3$); ^1H NMR δ 4.76 (1 H, d, $J_{H1,H2}$ = 4.4 Hz, H-1); HRMS *m/z* calcd for $C_{14}H_{20}O_6$ 284.1259 (M^+), found

284.1253. **Methyl 3-*O*-benzyl-β-D-gulofuranoside (7)**: syrup; R_f = 0.43; $[\alpha]_D$ −41.9° (*c* 0.82, $CHCl_3$); ^1H NMR δ 4.87 (1 H, s, H-1); HRMS *m/z* calcd for $C_{14}H_{20}O_6$ 284.1259 (M^+), found 284.1245.

Methyl 3-*O*-Benzyl-4,6-*O*-benzylidene-β-D-gulopyranoside (8). To a solution of **5** (1 g, 3.52 mmol) in CH_2Cl_2 (20 mL) was added benzaldehyde dimethyl acetal (803 mg, 5.28 mmol) and *p*-TsOH (10 mg). The solution was stirred at rt for 1 h and worked up as usual (CH_2Cl_2) to give a colorless oil, which was purified by column chromatography ($CHCl_3$:Et_2O = 10:1) to give syrupy **8** (1.14 g, 87%): $[\alpha]_D$ −31.4° (*c* 0.8, $CHCl_3$); ^1H NMR δ 5.51 (1 H, s, $PhCH(O-)_2$), 4.64 (1 H, d, $J_{H1,H2}$ = 8.1 Hz, H-1); HRMS *m/z* calcd for $C_{21}H_{24}O_6$ 372.1573 (M^+), found 372.1573.

Methyl 3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-methyl-β-D-gulopyranoside (9). To a solution of **8** (7.68 g, 20 mmol) and NaH (1.65 g, 60% in oil, 41.2 mmol) in dry DMF (160 mL) at 0 °C was added MeI (8.8 g, 62 mmol), and the solution was warmed to rt and then stirred for 5 h. Usual workup (AcOEt) gave a pale yellow oil, which was purified by column chromatography ($CHCl_3$:Et_2O = 50:1) to provide **9** (7.1 g, 89%) as a syrup: $[\alpha]_D$ −31.0° (*c* 1.41, $CHCl_3$); ^1H NMR δ 5.49 (1 H, s, $PhCH(O-_2)$), 4.79 (1 H, d, $J_{H1,H2}$ = 3 Hz, H-1), 3.58 (1 H, s), 3.46 (1 H, s); HRMS *m/z* calcd for $C_{22}H_{26}H_6$ 386.1729 (M^+), found 386.1719.

Methyl 3,4-Di-*O*-benzyl-2-*O*-methyl-β-D-gulopyranoside (10). To a solution of **9** (7.1 g, 18.4 mmol) in CH_2Cl_2 (500 mL) was added DIBALH (25 mL, 1.5 M in toluene, 37.5 mmol) at 0 °C, and the reaction mixture was allowed to warm to room temperature. After 10 h, the mixture was cooled to 0 °C and quenched with MeOH (40 mL) and then with aqueous ammonium chloride (20 mL). Usual workup (CH_2Cl_2 (500 mL) and saturated aqueous sodium potassium tartarate (200 mL)) gave an oil, which was purified by column chromatography (benzene:AcOEt = 5:1) to provide **10** (7.1 g, 75%) as a syrup: $[\alpha]_D$ −36.5° (*c* 1.15, $CHCl_3$); ^1H NMR δ 7.3 (10 H, m), 4.69 (1 H, d, $J_{H1,H2}$ = 7.8 Hz, H-1), 4.74, 4.54 (2 H, ABq, *J* = 12.2 Hz, $PhCH_2-$), 4.52, 4.44 (2 H, ABq, *J* = 12.2 Hz, $PhCH_2-$); HRMS *m/z* calcd for $C_{22}H_{28}O_6$ 386.1884 (M^+), found 386.1884.

Acetoxy Sulfone (12). To a cooled (−78 °C) mixture of oxalyl chloride (982 mg, 7.73 mmol) and DMSO (804 mg, 10.3 mmol) in CH_2Cl_2 (20 mL) under N_2 was added **10** (2 g, 5.15 mmol) in CH_2Cl_2 (15 mL). After the mixture was stirred at −70 °C for 30 min, triethylamine (1.56 g, 15.5 mmol) was added, and the solution was allowed to warm to rt. Usual workup (CH_2Cl_2) gave a very unstable aldehyde **11**, which was used immediately in the next step. To a cooled (0 °C) mixture of isobutyl phenyl sulfone (2.04 g, 10.3 mmol) and *n*-BuLi (6.28 mL, 1.64 M in *n*-hexane, 10.3 mmol) in dry THF was added a solution of **11** in dry THF (20 mL). After the mixture was kept at 0 °C for 30 min, it was quenched by the addition of saturated aqueous ammonium chloride. Usual workup (AcOEt) gave a syrup, which was dissolved in pyridine (15 mL). To the pyridine solution was added Ac_2O (3 mL) and DMAP (catalytic amount), and the mixture was kept for 12 h at rt. Usual workup (AcOEt) gave a syrup, which was purified by column chromatography (benzene:AcOEt = 20:1) to give **12** (1.6 g, 50% from **10**) as a mixture of diastereomers: IR ($CHCl_3$) 1745 cm^{-1}; ^1H NMR δ 7.28 (15 H, m, Ph × 3), 3.59 (1.5 H, s, C_1-OMe), 3.48 (1.5 H, s, C_2-OMe), 3.31 (1.5 H, s, C_2-OMe), 3.29 (1.5 H, s, C_2-OMe), 2.14 (3 H, s, OCOMe), 2.09 (1.5 H, s, OCOMe), 1.52 (1.5 H, d, *J* = 7.0 Hz, MeCMe), 1.42 (1.5 H, d, *J* = 7 Hz, MeCMe), 0.97 (1.5 H, d, *J* = 6.8 Hz, MeCMe), 0.96 (1.5 H, d, *J* = 6.8 Hz, MeCMe); HRMS *m/z* calcd for $C_{34}H_{42}O_9S$ 626.2547 (M^+), found 626.2545.

***E* and *Z* Mixture of Methyl 3,4-Di-*O*-benzyl-6,7-didehydro-6,7-dideoxy-7-*C*-isopropyl-2-*O*-methyl-β-D-gulo-heptopyranoside (13).** To a mixture of **12** (100 mg, 0.16 mmol) and Na_2HPO_4 (100 mg, 0.7 mmol) was added 5% Na(Hg) (400 mg) at 0 °C. The mixture was stirred at 0 °C for 4 h and quenched with H_2O (5 mL). Usual workup (AcOEt) gave a syrup, which was purified by column chromatography (benzene:AcOEt = 20:1) to provide **13** (60 mg, 88%, *E*:*Z* = 3:1 by ^1H NMR) as a syrup: ^1H NMR δ 5.69 (0.75 H, dd, *J* = 6, 4, 15.9 Hz, *E*-olefinic proton), 5.51 (0.75 H, ddd, *J* = 1.2, 6.6, 15.9 Hz, *E*-olefinic proton), 5.52 (0.25 H, ddd, *J* = 0.7, 8.11, 11.0 Hz, *Z*-olefinic proton), 5.34 (0.25 H, ddd, *J* = 1.09, 8.11, 11.0 Hz, *Z*-olefinic proton); HRMS *m/z* calcd for $C_{26}H_{34}O_5$ 426.2483 (M^+), found 426.2479.

3,4-Di-*O*-benzyl-6,7-didehydro-6,7-dideoxy-7-*C*-isopropyl-2-*O*-methyl-β-D-gulono-1,5-lactone (15). A solution of **13** (50 mg, 0.12 mmol) in 50% acetic acid (1 mL) was heated for 20 h at 110 °C. Usual workup (AcOEt) gave a pale yellow syrup, which was used without purification in the next step. A mixture of the syrup, DMSO (0.2 mL), and Ac_2O (0.15 mL) was stirred for 24 h at rt. Usual workup (AcOEt) and purification by column chromatography (benzene:AcOEt = 20:1) gave **15** (25 mg, 52% from **13**) as a syrup: IR ($CHCl_3$) 1745 cm^{-1}; HRMS *m/z* calcd for $C_{25}H_{30}O_5$ 410.2092 (M^+), found 410.2089.

6,7-Di-*O*-benzylbengamide E (17*E*) and *cis*-6,7-Di-*O*-benzylbengamide E (17*Z*). A mixture of **15** (100 mg, 0.24 mmol), cyclo-L-lysine (47 mg, 0.37 mmol), and triethylamine (37 mg, 0.37 mmol) in dioxane (5 mL) was stirred for 3 d. After filtration, the reaction mixture was concentrated to give a syrup which was purified by column chromatography ($CHCl_3$:MeOH = 100:1) to provide **17*E*** (93 mg, 71%) and **17*Z*** (34 mg, 26%). **17*E***: syrup; $[\alpha]_D$ +56.6° (*c* 0.48, $CHCl_3$); IR ($CHCl_3$) 1650, 1670 cm^{-1}; ^1H NMR δ 8.12 (1 H, bd, *J* = 5.9 Hz, NH), 7.29 (10 H, m), 6.49 (1 H, bs, OH), 3.43 (3 H, s, OMe), 0.99 (6 H, d, *J* = 6.8 Hz, MeCMe); HRMS *m/z* calcd for $C_{31}H_{42}N_2O_6$ 538.3043 (M^+), found 538.3035. **17*Z***: syrup; $[\alpha]_D$ +19.9° (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) 1650, 1670 cm^{-1}; ^1H NMR δ 8.07 (1 H, bd, *J* = 6.1 Hz, NH), 7.28 (10 H, m), 6.09 (1 H, bs, OH), 3.46 (3 H, s, OMe), 0.95 (3 H, d, *J* = 6.6 Hz, MeCMe), 0.91 (3 H, d, *J* = 6.6 Hz, MeCMe); HRMS *m/z* calcd for $C_{31}H_{42}N_2O_6$ 538.3043 (M^+), found 538.3043.

Bengamide E (1). To a solution of **17*E*** (50 mg, 0.14 mmol) in a mixture of THF (3 mL) and liquid ammonia (15 mL) at −78 °C was added sodium metal until the blue color persisted. After 30 min, the mixture was worked up as usual (AcOEt) to give a syrup. The syrup was purified by column chromatography ($CHCl_3$:MeOH = 20:1) to afford **1** (14 mg, 42%): $[\alpha]_D$ +33.7° (*c* 0.61, MeOH) (lit.[1] $[\alpha]^{29}_D$ +37° (*c* 0.043, MeOH), lit.[3] $[\alpha]^{20}_D$ +25° (*c* 0.29, MeOH)); ^1H NMR δ 5.79 (1 H, dd, *J* = 6.4, 15.6 Hz), 5.45 (1 H, dd, *J* = 7.1, 15.6 Hz); ^{13}C NMR δ 174.8, 172.0, 141.8, 125.3, 81.0, 74.3, 72.7, 59.9, 51.9, 42.1, 31.0, 30.8, 28.8, 27.9, 22.2, 22.1; HRMS *m/z* calcd for $C_{17}H_{30}N_2O_6$ 358.2173 (M^+), found 358.2173.

cis*-Bengamide E (18).** Treatment of **17*Z (20 mg, 0.037 mmol) by the procedure similar to that described for **1** gave **18** (5 mg, 38%) as a syrup: $[\alpha]_D$ +38.5° (*c* 0.51, $CHCl_3$); ^1H NMR δ 5.46 (1 H, t, *J* = 11.0 Hz), 5.29 (1 H, dd, *J* = 9.0, 11.0 Hz); ^{13}C NMR δ 174.7, 172.1, 142.6, 125.2, 81.1, 72.9, 72.2, 69.1, 60.0, 52.0, 42.1, 31.0, 28.8, 27.9, 27.2, 23.2, 22.9; HRMS *m/z* calcd for $C_{17}H_{30}N_2O_6$ (M^+ + 1) 358.2173, found 358.2180.

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Supplementary Material Available: ^1H and/or ^{13}C NMR spectra for compounds **1**, **6–10**, **12**, **13**, **15**, **17*E***, **17*Z***, and **18** (14 pages). This material is contained in many 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.