JOC Note
pubs.acs.org/joc

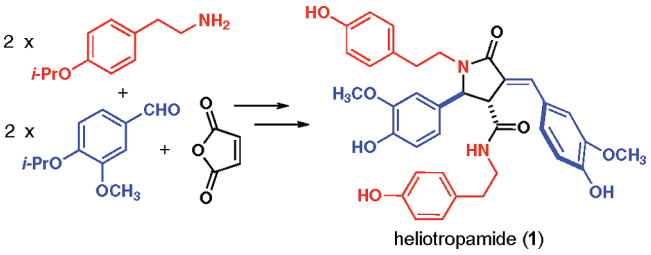
Diastereoselective Synthesis of (±)-Heliotropamide by a One-Pot, Four-Component Reaction

Ashkaan Younai, Gregory F. Chin,[†] and Jared T. Shaw*

Department of Chemistry, One Shields Ave, University of California, Davis, California 95616, United States.
[†]Current address: Department of Chemistry, Columbia University, MC 3178, 3000 Broadway, New York, NY10027 (gfc2109@columbia.edu).

shaw@chem.ucdavis.edu

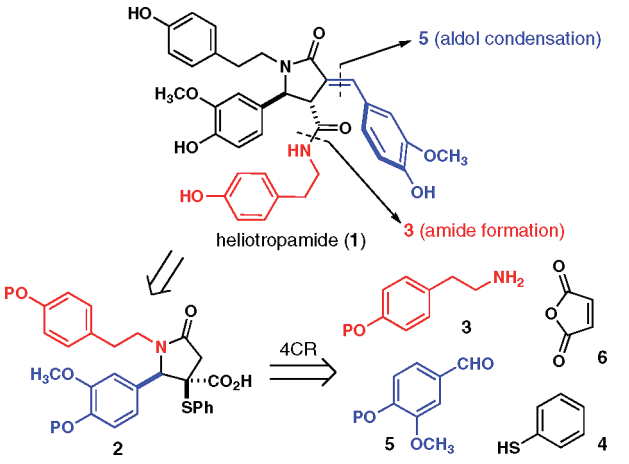
Received September 30, 2010



The first synthesis of heliotropamide is reported. The preparation of this 2-oxopyrrolidine (γ-lactam) natural product relied on a diastereoselective one-pot, four-component reaction (4CR) for the assembly of the core structure. On the basis of chemical shift correlation and NOESY experiments, the previously unknown alkene geometry of heliotropamide is assigned as *E*.

Oxopyrrolidines, or γ-lactams, are important structural motifs in a diverse array of interesting natural products.[1] Heliotropamide is an oxopyrrolidine natural product recently isolated[2] from *Heliotropium ovalifolium* in an effort to identify the cause of "floppy trunk syndrome" in Zimbabwean elephants.[3] Ingestion of *H. ovalifolium* by free-ranging elephants on Fothergill Island of Lake Kariba was initially implicated, prompting an investigation of the secondary metabolites produced by this plant. During the course of these investigations, which failed to elucidate the cause of trunk paralysis, heliotropamide was isolated and its unique structure assigned by spectroscopy. This dehydrodimer of a cinnamic amide (*N*-feruloyltyramine) that forms the γ-lactam core has only recently been observed in one other natural product, namely bis-avenanthramide B.[4] Herein, we report a concise synthesis of heliotropamide using a four-component reaction (4CR) recently reported in our group[5] that confirms the intriguing structure of this compound. This synthesis sets the stage for future efforts directed at biologically important γ-lactam natural products using our 4CR.

SCHEME 1. Retrosynthesis of Heliotropamide (1)



A retrosynthesis of heliotropamide reveals that our recently disclosed 4CR[5a] will assemble the complete core of heliotropamide. Lactam core **2** would be produced by a 4CR between protected tyramine (**3**, Scheme 1), aldehyde **5**, maleic anhydride (**6**), and thiophenol (**4**).

This key intermediate is converted to heliotropamide by desulfurization, amide formation, and aldol condensation with **3** and **5**, respectively. We elected to use a common protecting group for both of these fragments so that a final "global" deprotection would reveal the target.

The choice of phenolic protecting group required balancing stability toward many different reaction conditions with lability at the end of the synthesis. Initial studies explored use of TIPS and allyl groups, each of which proved unsuitable at different stages. The TIPS protecting groups were unstable in our 4CR conditions, whereas the allyl groups were cleaved during the subsequent radical desulfurization. We settled on the isopropyl ethers to protect the phenols as they are stable under a variety of conditions and readily cleaved in the presence of mild Lewis acids. *O*-Isopropylvanillin was prepared in high yield using standard alkylation conditions

(1) See, for example, clausenamide: (a) Yang, M.; Chen, Y.; Huang, L. *Phytochemistry* **1988**, *27*, 445–450. Dysidamide: (b) Gebreyesus, T.; Yosief, T.; Carmely, S.; Kashman, Y. *Tetrahedron Lett.* **1988**, *29*, 3863–3864. Lactacystin: (c) Omura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A. *J. Antibiot.* **1991**, *44*, 117–118. anchinopeptolides: (d) Casapullo, A.; Minale, L.; Zollo, F.; Lavayre, J. *J. Nat. Prod.* **1994**, *57*, 1227–1233. Salinosporamide: (e) Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355–357. Berkeleyamides: (f) Stierle, A. A.; Stierle, D. B.; Patacini, B. *J. Nat. Prod.* **2008**, *71*, 856–860.

(2) Guntern, A.; Ioset, J. R.; Queiroz, E. F.; Sandor, P.; Foggin, C. M.; Hostettmann, K. *J. Nat. Prod.* **2003**, *66*, 1550–1553.

(3) Kock, N. D.; Goedegebuure, S. A.; Lane, E. P.; Lucke, V.; Tyrrell, D.; Kock, M. D. *J. Wildl. Dis.* **1994**, *30*, 432–5.

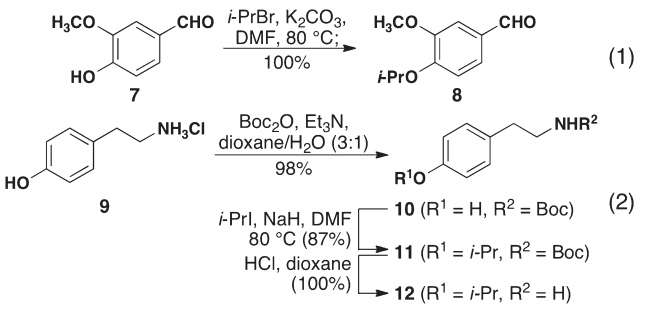
(4) (a) Okazaki, Y.; Ishihara, A.; Nishioka, T.; Iwamura, H. *Tetrahedron* **2004**, *60*, 4765–4771. (b) Okazaki, Y.; Ishizuka, A.; Ishihara, A.; Nishioka, T.; Iwamura, H. *J. Org. Chem.* **2007**, *72*, 3830–3839.

(5) (a) Wei, J.; Shaw, J. T. *Org. Lett.* **2007**, *9*, 4077–4080. (b) González-López, M.; Shaw, J. T. *Chem. Rev.* **2009**, *109*, 164–189.

(6) Use of Bu_3SnH resulted in a slightly higher yield for the desulfurization reaction (91%) on small scale, while TMS_3SiH was used for larger scale work.

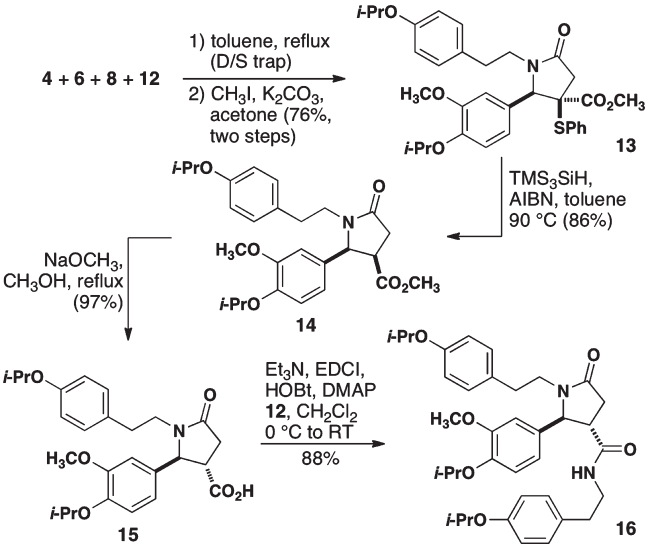
DOI: 10.1021/jo1019317 Published on Web 11/09/2010

(eq 1). The requisite *O*-protected tyramine was prepared similarly from tyramine in a three-step sequence (eq 2).



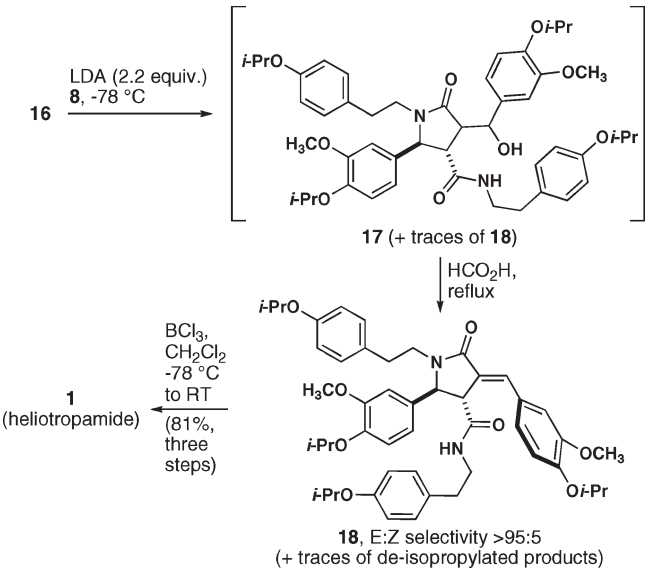
The core of heliotropamide was efficiently assembled using the lactam-forming 4CR under standard conditions (Scheme 2).[5a] Maleic anhydride, thiophenol, **8**, and **12** were heated to reflux in toluene with azeotropic removal of water using a Dean–Stark trap for 24 h. Conversion of the resultant acid to the methyl ester allowed isolation of intermediate **13** in 76% yield. Desulfurization was achieved with TMS_3SiH with AIBN added as a radical initiator.[6] Epimerization of the resultant *cis*-lactam was effected with $NaOCH_3$, which also resulted in complete saponification to acid **15**. This intermediate was coupled with **12** using EDCI/HOBt/DMAP to provide **16**, the completed core of heliotropamide.

SCHEME 2. Assembly of the Lactam Core of Heliotropamide



Conversion of **16** to heliotropamide required aldol condensation with **8**. This transformation was effected in two steps, beginning with aldol addition of the doubly anionic lithium enolate of **16** to **8**. This aldol reaction proceeded in high yield to provide alcohol **17** as a mixture of diastereomers along with traces of dehydration product **18**. Complete dehydration of the unpurified mixture was achieved using refluxing formic acid to provide **18** as a single alkene isomer.[7] The formation of compound **18** was accompanied with traces of products in which one to four of the isopropyl groups had been cleaved. After purifying and characterizing the major

SCHEME 3. Completion of Heliotropamide Synthesis



product (**18**), the mixture was treated with BCl_3 to cleave all of the isopropyl ethers to yield heliotropamide (Scheme 3).

After completing exploratory studies, the entire three-step sequence from **16** to **1** was completed in 81% yield without purification of the intermediates. Synthetic heliotropamide exhibited spectral data (^{1}H NMR, ^{13}C NMR) identical to those reported in the original isolation,[8] confirming the connectivity and relative stereochemical configuration of this compound.[9]

The only remaining ambiguity in the structure of heliotropamide is in the configuration of the trisubstituted double bond, which was depicted as Z in the original report but not assigned. Several papers note a trend in alkylidene lactones and lactams for the alkene proton, specifically that this signal appears at 7.5–7.7 ppm for *E*, whereas the signal for the *Z* isomer appears upfield by 0.5–0.6 ppm (Figure 1).[10] The related natural product bisavenanthramide B is assigned as *E* by NOESY correlation and exhibits a chemical shift of 7.69 ppm.[4a]

The close chemical shifts of heliotropamide and bisavenanthramide B to each other and to the related lactone **20** reported by Taylor, for which there is an accompanying X-ray crystal structure, support the assignment of heliotropamide as *E*. Further support comes from other compounds reported in the literature, including the benzylidene lactones *E*- and *Z*-**19**, which exhibit chemical shifts of 7.60 and 6.99,

(7) Okazaki, Y. I., A.; Ishihara, A.; Nishioka, T.; Iwamura, H. *J. Org. Chem.* **2007**, *27*, 3830–3839.

(8) We were unable to contact Prof. Hostettmann (ref 2) to obtain an authentic sample for direct comparison.

(9) In the isolation paper (ref 2), the configuration of the aromatic and carboxamide substituents on the core lactam are described as "cis", though they are depicted as trans (anti). We assumed this to be a typographical error. Our synthesis, which relies on methods to prepare the anticonfigured lactam (previuosly demonstrated by X-ray crystallography, see ref 5a), established that the configuration is anti. Attempts to crystallize **21**, heliotropamide and several derivatives thereof were unsuccessful.

(10) The ^{1}H NMR shifts of the vinylic proton in related alkylidene γ-lactams and lactones is generally 0.4–0.6 ppm higher upfield for the *Z* isomer when compared to the *E* isomer. See: (a) Lewis, F. D.; Oxman, J. D.; Gibson, L. L.; Hampsch, H. L.; Quillen, S. L. *J. Am. Chem. Soc.* **1986**, *108*, 3005–3015. (b) Ezquerra, J. P., C.; Yruretagoyena, B.; Rubio, A.; Carreno, M. C.; Escribano, A.; Ruano, J. L. G. *J. Org. Chem.* **1995**, *60*, 2925–2930. (c) Kang, J.-H. C., H.-E.; Kim, S. Y.; Kim, Y.; Lee, J.; Lewin, N. E.; Pearce, L. V.; Blumberg, P. B.; Marquez, V. E. *Bioorg. Med. Chem.* **2003**, *11*, 2529–2539. (d) Cohen, J. L.; C., A. R. *J. Org. Chem.* **2007**, *72*, 9240–9247.

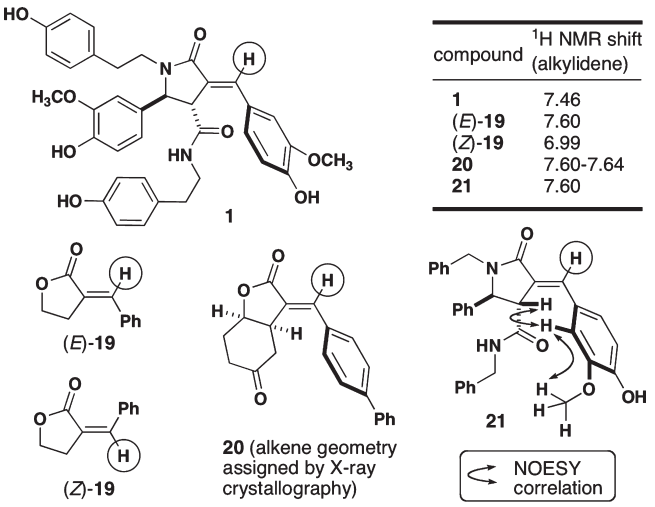


FIGURE 1. Chemical shift correlation and NOESY assignments for the alkene configuration of heliotropamide. The ^{1}H NMR spectra were recorded in CD_3OD (**1**) or $CDCl_3$ (**19**−**21**) at room temperature.

respectively. Although chemical shift overlap prevents accurate NOESY correlation of heliotropamide, model compound **21** exhibited NOESY correlation and a chemical shift of the arylidene proton consistent with the assignment of *E* geometry about the trisubstituted alkene.

In summary, we have demonstrated the utility of our recently discovered 4CR in the efficient synthesis of heliotropamide in an overall yield of 41% over 11 steps. In so doing, we have confirmed the identity of this structurally distinct natural product. We are currently applying similar strategies to related natural products, the syntheses of which will be reported in due course.

Experimental Section

***tert*-Butyl 4-Isopropoxyphenethylcarbamate (11).** To a solution of **10** (847 mg, 3.57 mmol) and sodium hydride (257 mg, 10.71 mmol) in DMF (35.7 mL, 0.1 M) was added isopropyl iodide (1.21 mL, 10.71 mmol), and the solution was stirred at 80 °C overnight. The solution was diluted in water (10 mL), extracted with $CHCl_3$ (3 × 10 mL), and dried over $MgSO_4$. Concentration in vacuo and purification by flash chromatography (33:67 EtOAc/hexanes) afforded a pale yellow solid (871 mg, 87%): mp 42−45 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 4.54−4.46 (m, 2H), 3.33 (d, J = 6.3 Hz, 2H), 2.71 (t, J = 6.9 Hz, 2H), 1.43 (s, 9H), 1.32 (d, J = 6.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 156.1, 131.0, 130.0, 116.2, 79.4, 70.1, 42.2, 35.5, 28.6, 22.3; IR (neat) 1691, 3376 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{26}NO_3$ $(M + H)^+$ 280.1913, found 280.1914.

2-(4-Isopropoxyphenyl)ethanamine (12). To a solution of **11** (4.203 g, 15.04 mmol) in dioxane (50.0 mL, 0.3 M) was added concentrated hydrochloric acid (25.0 mL), and the solution was stirred at room temperature for 2 h. The mixture was basified with 10% NaOH, extracted with CH_2Cl_2, and dried over $MgSO_4$. Concentration in vacuo afforded a yellow oil (2.669 g, 100%) which was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, J = 8.5 Hz, 2H), 6.76 (d, J = 8.6 Hz, 2H), 4.43 (sep, J = 6.1 Hz, 1H), 2.85 (t, J = 6.9 Hz, 2H), 2.61 (t, J = 6.9 Hz, 2H), 1.48 (s, 2H), 1.25 (d, J = 6.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 131.8, 129.9, 116.1, 70.0, 43.8, 39.2, 22.3; IR (neat) 3357 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_{18}NO$ $(M + H)^+$ 180.1388, found 180.1390.

***syn*-Methyl 2-(4-Isopropoxy-3-methoxyphenyl)-1-(4-isopropoxyphenethyl)-5-oxo-3-(phenylthio)pyrrolidine-3-carboxylate (13).** A solution of **8** (530.9 mg, 2.74 mmol), **12** (490.7 mg, 2.74 mmol), maleic anhydride (268.0 mg, 2.74 mmol), and thiophenol (0.28 mL, 2.74 mmol) in toluene (41 mL, 0.07 M) was stirred at reflux with a Dean−Stark trap for 24 h. After being cooled to room temperature, the mixture was concentrated in vacuo. The residue was then dissolved in acetone (55 mL, 0.05 M), to this mixture were added K_2CO_3 (1.511 g, 10.92 mmol) and CH_3I (0.68 mL, 10.92 mmol), and the resulting mixture was stirred at room temperature overnight. The solution was concentrated in vacuo, diluted in water (20 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were then washed with brine (60 mL) and dried over $MgSO_4$. Concentration in vacuo and purification by flash chromatography (0:100−50:50 EtOAc/hexanes) afforded an orange oil (990.7 mg, 76%, 86:14 dr). A small sample of the major diastereomer was purified by HPLC for characterization: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35−7.31 (m, 1H), 7.25 (s, 1H), 7.24 (d, J = 2.0 Hz, 1H), 7.22 (d, J = 1.2 Hz, 1H), 7.21 (t, J = 1.7 Hz, 1H), 6.99 (s, 1H), 6.97 (s, 1H), 6.90 (d, J = 8.3 Hz, 1H), 6.78−6.74 (m, 3H), 6.71 (s, 1H), 5.02 (s, 1H), 4.58 (sep, J = 6.1 Hz, 1H), 4.48 (sep, J = 6.1 Hz, 1H), 4.02−3.95 (m, 1H), 3.87 (s, 3H), 3.55 (s, 3H), 3.17 (d, J = 17.1 Hz, 1H), 2.86 (d, J = 17.0 Hz, 1H), 2.82 (dd, J = 7.1, 13.7 Hz, 1H), 2.74−2.69 (m, 1H), 2.67−2.61 (m, 1H), 1.405 (d, J = 6.1 Hz, 3H), 1.400 (d, J = 6.1 Hz, 3H), 1.30 (d, J = 6.1 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.2, 172.1, 156.7, 150.3, 148.3, 136.3, 136.2, 130.4, 130.3, 130.0, 129.9, 129.8, 129.5, 129.1, 126.6, 116.1, 114.7, 71.4, 70.1, 68.3, 59.1, 56.4, 53.2, 42.6, 41.1, 32.7, 22.33, 22.30, 22.29, 22.25; IR (neat) 1695, 1728 cm^{-1}; HRMS (ESI) m/z calcd for $C_{33}H_{40}NO_6S$ $(M + H)^+$ 578.2576, found 578.2587.

***syn*-Methyl 2-(4-Isopropoxy-3-methoxyphenyl)-1-(4-isopropoxyphenethyl)-5-oxopyrrolidine-3-carboxylate (14).** A solution of **13** (50 mg, 0.09 mmol), AIBN (10 mg, 0.06 mmol), and tributyl tin hydride (0.10 mL, 0.49 mmol) in toluene (3.4 mL, 0.02 M) was stirred at 90 °C for 8 h. The reaction was cooled and concentrated in vacuo, and purification by flash chromatography (60:40 to 100:0 EtOAc/hexanes) afforded a colorless oil (38 mg, 91%, 81:19 dr).

14: Alternate Procedure for Larger Scale Reactions. A solution of **13** (622.1 mg, 1.08 mmol), tris(trimethylsilyl)silane (freshly distilled, 1.16 mL, 3.77 mmol), and AIBN (63.2 mg, 0.38 mmol) in toluene (43.0 mL, 0.025 M) was stirred at 90 °C for 24 h. The reaction was cooled, concentrated in vacuo, and purified by flash chromatography (50:50 EtOAc/hexanes) to afford a colorless oil (433.4 mg, 86%, 93:7 dr). Major diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.95 (d, J = 8.1 Hz, 2H), 6.73 (m, 3H), 6.48 (d, J = 7.4 Hz, 1H), 6.41 (s, 1H), 4.48 (d, J = 9.1 Hz, 1H), 4.45−4.39 (m, 2H), 3.89−3.83 (m, 1H), 3.71 (s, 3H), 3.38 (q, J = 9.3 Hz, 1H), 3.19 (d, J = 0.8 Hz, 3H), 2.97 (dd, J = 9.9, 17.2 Hz, 1H), 2.74−2.68 (m, 2H), 2.63−2.57 (m, 1H), 2.41 (dd, J = 9.3, 17.2 Hz, 1H), 1.26 (d, J = 6.0 Hz, 6H), 1.242 (d, J = 6.1 Hz, 3H), 1.240 (d, J = 6.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.8, 170.2, 156.2, 150.1, 147.2, 130.3, 129.3, 128.37, 119.5, 115.8, 115.2, 110.7, 71.0, 69.5, 63.2, 55.7, 51.3, 42.9, 42.3, 32.5, 31.5, 21.8, 21.73, 21.72, 21.71. Visible peaks for minor diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.89 (d, J = 8.1 Hz, 2H), 6.77 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 8.0 Hz, 2H), 6.60 (d, J = 8.2 Hz, 1H), 6.54 (s, 1H), 4.47 (d, J = 6.0 Hz, 1H), 3.74 (s, 3H), 3.60 (s, 3H), 1.28 (d, J = 6.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.2, 171.9, 129.4, 45.8, 33.4; IR (neat) 1689, 1740 cm^{-1}; HRMS (ESI) m/z calcd for $C_{27}H_{36}NO_6$ $(M + H)^+$ 470.2543, found 470.2546.

***anti*-2-(4-Isopropoxy-3-methoxyphenyl)-1-(4-isopropoxyphenethyl)-5-oxopyrrolidine-3-carboxylic Acid (15).** To a solution of **14** (2.771 g, 5.90 mmol) in methanol (60.0 mL, 0.1 M) was added sodium methoxide (3.188 g, 59.00 mmol) and the mixture stirred

at 60 °C overnight. The reaction was cooled, acidified with 10% HCl, extracted with dichloromethane, and concentrated in vacuo to afford a white solid (2.609 g, 97%) which was used without further purification: mp 149−152 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.38 (bs, 1H), 6.97 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.2 Hz, 1H), 6.76 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.2 Hz, 1H), 6.64 (s, 1H), 4.70 (d, J = 5.8 Hz, 1H), 4.53 (sep, J = 6.1 Hz, 1H), 4.48 (sep, J = 6.0 Hz, 1H), 3.87−3.80 (m, 4H), 3.10−3.06 (m, 1H), 2.92−2.87 (m, 1H), 2.84− 2.72 (m, 3H), 2.66−2.59 (m, 1H), 1.372 (d, J = 6.0 Hz, 3H), 1.369 (d, J = 6.0 Hz, 3H), 1.29 (d, J = 5.6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.1, 173.4, 156.7, 151.0, 147.9, 131.5, 130.5, 129.89, 119.7, 116.3, 115.6, 110.3, 71.6, 70.2, 65.0, 56.3, 46.3, 43.0, 33.9, 32.6, 22.27, 22.24; IR (neat) 1646, 1727 cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{34}NO_6$ (M + H)$^+$ 456.2386, found 456.2390.

***anti*-2-(4-Isopropoxy-3-methoxyphenyl)-*N*,1-bis(4-isopropoxyphenethyl)-5-oxopyrrolidine-3-carboxamide (16).** A solution of **12** (775.0 mg, 1.70 mmol), EDC hydrochloride (652.4 mg, 3.40 mmol), HOBt (459.8 mg, 3.40 mmol), and DMAP (41.5 mg, 0.34 mmol) in CH_2Cl_2 (113.5 mL, 0.015 M) was stirred at 0 °C for 1 h. Et_3N (0.48 mL, 3.40 mmol) was added followed by amine **12** (339.6 mg, 1.89 mmol). The reaction was allowed to warm to rt and stirred overnight. The reaction was then quenched with satd NH_4Cl and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were then dried over $MgSO_4$. Concentration in vacuo and purification by flash chromatography (30:70 EtOAc/CH_2Cl_2) afforded an amorphous white solid (920.6 mg, 88%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.95 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 7.8 Hz, 1H), 6.77 (d, J = 2.9 Hz, 2H), 6.76 (d, J = 2.9 Hz, 2H), 6.64 (d, J = 8.1 Hz, 2H), 5.41 (t, J = 5.8 Hz, 1H), 4.58 (d, J = 7.6 Hz, 1H), 4.56−4.52 (m, 1H), 4.51−4.46 (m, 2H), 3.83−3.77 (m, 4H), 3.55−3.50 (m, 1H), 3.34−3.28 (m, 1H), 2.84 (dd, J = 9.4, 16.5 Hz, 1H), 2.75−2.66 (m, 4H), 2.62−2.57 (m, 3H), 1.391 (d, J = 6.0 Hz, 3H), 1.385 (d, J = 6.0 Hz, 3H), 1.31 (d, J = 6.1 Hz, 6H), 1.30 (d, J = 6.1 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.3, 171.1, 156.8, 156.7, 151.1, 147.9, 131.6, 130.7, 130.4, 129.9, 129.8, 120.2, 116.20, 116.17, 115.4, 110.2, 71.6, 70.07, 70.06, 65.7, 56.3, 49.3, 42.8, 41.2, 34.9, 34.7, 32.5, 29.9, 22.31, 22.28, 22.27, 22.25; IR (neat) 1666, 1681, 3367 cm^{-1}; HRMS (ESI) m/z calcd for $C_{37}H_{49}N_2O_6$ (M + H)$^+$ 617.3591, found 617.3589.

***anti*-(*E*)-4-(3-Isopropoxy-2-methoxybenzylidene)-2-(4-isopropoxy-3-methoxyphenyl)-*N*,1-bis(4-isopropoxyphenethyl)-5-oxopyrrolidine-3-carboxamide (18).** To a cooled (0 °C) solution of diisopropylamine (freshly distilled over KOH, 0.04 mL, 0.28 mmol) in anhydrous THF (2.0 mL) at 0 °C was added 0.15 mL of *n*-butyllithium (1.59 M in THF, 0.24 mmol). The mixture was stirred at 0 °C for 30 min, and then a solution of **16** (51.6 mg, 0.08 mmol) in anhydrous THF (1.0 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and then cooled to −78 °C. A −78 °C solution of **8** (23.8 mg, 0.12 mmol) in THF (1.0 mL) was then added by cannulation. After the addition was complete, the reaction was allowed to warm to rt and stirred for 12 h. The reaction was then quenched with satd NH_4Cl and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were then dried over $MgSO_4$. Concentration in vacuo afforded a mixture of aldol addition product **17** (inseparable diastereomeric mixture) and aldol condensation product **18** (> 95:5 E/Z selectivity) by MS and ^{1}H NMR. The crude mixture of **17** and **18** was dissolved in formic acid (2.0 mL) and heated to reflux for 90 min. The solution was cooled to rt, diluted in water (20 mL), extracted with EtOAc (3 × 25 mL), and dried over $MgSO_4$. Concentration in vacuo afforded a mixture of aldol condensation product **18** and its partially deisopropylated isomers (by MS and ^{1}H NMR). A small amount of **18** was purified by flash chromatography (15:85 EtOAc/CH_2Cl_2) for characterization. The rest of the crude mixture was taken into the next step: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, J = 1.8 Hz, 1H), 7.01 (d, J = 8.4 Hz, 2H), 6.98 (dd, J = 1.8, 8.4 Hz, 1H), 6.91 (d, J = 1.7 Hz, 1H), 6.85−6.79 (m, 4H), 6.75 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 6.64−6.62 (m, 2H), 5.80 (t, J = 5.8, 1H), 4.60−4.52 (m, 2H), 4.50−4.40 (m, 3H), 4.11−4.03 (m, 1H), 3.83 (d, J = 6.9 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.51−3.45 (m, 1H), 3.17−3.12 (m, 1H), 2.95−2.91 (m, 1H), 2.80−2.76 (m, 1H), 2.68−2.64 (m, 1H), 2.58−2.53 (m, 1H), 2.42−2.39 (m, 1H), 1.35−1.32 (m, 12H), 1.29−1.25 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 168.8, 156.90, 156.88, 151.3, 150.6, 149.4, 147.9, 135.6, 133.2, 130.5, 130.4, 129.9, 129.8, 127.1, 125.6, 124.3, 118.8, 116.4, 116.3, 116.2, 115.0, 113.5, 110.2, 71.8, 71.7, 70.23, 70.20, 64.8, 56.45, 56.44, 54.3, 42.8, 41.4, 34.9, 32.9, 22.43, 22.42, 22.40, 22.38, 22.32, 22.29; IR (neat) 3317, 1671 cm^{-1}; HRMS (ESI) m/z calcd for $C_{48}H_{61}N_2O_8$ (M + H)$^+$ 793.4428, found 793.4451.

Heliotropamide (1). To a −78 °C solution of **18** and its deisopropylated isomers in 0.8 mL of CH_2Cl_2 was added BCl_3 (1.0 mL of a 1.0 M solution CH_2Cl_2, 1.00 mmol). The reaction was kept at −78 °C for 8 h, warmed to rt, and stirred for an additional 1 h. (Reaction progress was tracked by MS.) Upon completion, the reaction was slowly quenched with 10% HCl, whereupon a brown amorphous solid crashed out. The residue was washed with CH_2Cl_2 followed by 10% HCl and then the solid collected by dissolution in methanol. Concentration in vacuo and purification by flash chromatography (3:97 to 5:95 MeOH/CH_2Cl_2) afforded an amorphous yellow solid (44.6 mg, 81% over three steps from **13**). ^{1}H and ^{13}C NMR comparison of synthetically obtained compound **1** with reported natural product[2] can be found in the Supporting Information: IR (neat) 3293, 1648 cm^{-1}; HRMS (ESI) m/z calcd for $C_{36}H_{37}N_2O_8$ (M + H)$^+$ 625.2550, found 625.2556.

Acknowledgment. This research was supported by startup funds from UC Davis and the NSF in the form of a CAREER award to J.T.S. G.F.C. thanks the R. Bryan Miller Memorial Fund (UC Davis), Chevron, and Schering Plough for undergraduate research support. Dr. Marcos González-López is acknowledged for helpful discussions.

Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C NMR and IR spectral data, HRMS, and additional information on key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.