First Total Synthesis of Bengazole A†

Roger J. Mulder, Cynthia M. Shafer, and Tadeusz F. Molinski*

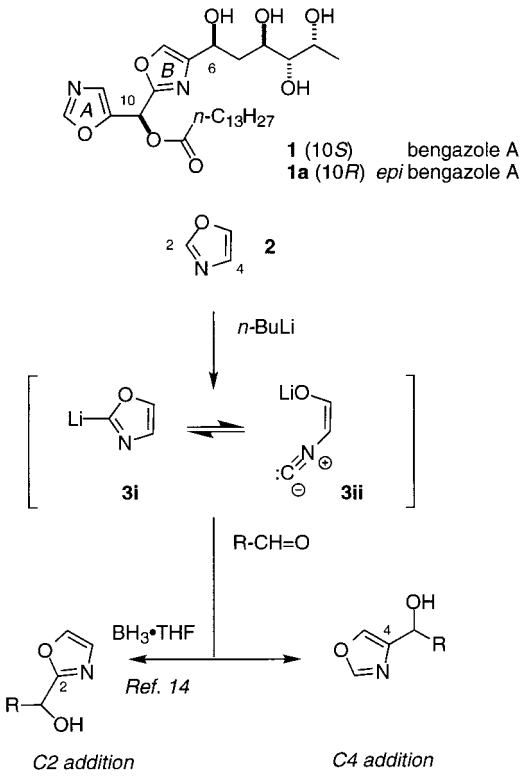
Department of Chemistry, University of California, 1 Shields Avenue, Davis, California 95616

Received April 14, 1999

Bengazole A (**1**) and related homologues,[1] isolated from marine sponges of the genus *Jaspis*, are representative members of a small family of bis-oxazole natural products. Other members include hennoxazole from the sponge *Polyfibrospongia* sp.[2] and diazonamide from the ascidian *Diazona chinensis*.[3] Bengazole A (**1**) exhibits potent in vitro antifungal activity against *Candida albicans*[1b,4] and fluconazole-resistant *Candida* strains,[5] comparable to that of the clinical agent amphotericin B. Ring B of **1** displays the common biogenic 2,4-disubstituted oxazole motif, but ring A is a rare 5-monosubstituted oxazole, previously seen only in members of the oxazolomycin family (e.g., oxazolomycin,[6] produced by the actinomycete *Streptomyces albus* strain JA 3453), and more recently in phthoxazolins[7] and inthomycins.[8]

The complete configuration of **1** was established by NMR and chiroptical studies.[1b] Despite the potent bioactivity of **1,** no stereoselective synthesis of this compound or any other member of the bengazole family has appeared.[9] The central ring B in **1** (Scheme 1) suggests a conventional biomimetic 2,4-disubstituted oxazole synthesis from an appropriate *N*-acylserine amide via the corresponding oxazoline,[10] but the density of functionality on the oxazole ring substituents detracts from this approach in this instance. We recognized that a conceptually simpler approach to 2,4-disubstituted oxazoles lies

Scheme 1



in two consecutive regiocontrolled metalation−addition reactions on the parent heterocycle, oxazole (**2**), at C4 and C2, respectively.[11] Oxazole is metalated at C2 with *n*-BuLi to give the ambident nucleophile 2-lithiooxazole (**3i**), but subsequent reaction with an electrophile can occur at either C2 or C4 via a ring-opened valence bond isomer **3ii**, followed by ring closure (Scheme 1).[12] The regioselectivity of electrophilic addition to **3i** is dependent upon the nature of the electrophile and reaction conditions. Our approach to **1** exploits a regiocontrolled metalation−addition protocol that was inspired by two independent sets of observations: Hodges' report[13] of reaction of 2-lithiooxazole at C4 with aldehydes and Vedejs' borane-mediated lithiooxazole addition to aldehydes[14] that constrains reaction to C2. Thus, reaction of oxazole with aldehydes can be fine-tuned to provide, in two contiguous steps, an initially formed C4 monosubstituted oxazole and then a 2,4-disubstituted oxazole. Here we report the first total synthesis of bengazole A by this sequential "grafting" of side chains to oxazole. This work also demonstrates that addition of 2-lithiooxazole to a β-alkoxy aldehyde precursor proceeds with good chelation-controlled stereoselectivity.

The requisite aldehyde **4** (Scheme 2) was obtained from D-galactose in nine steps (26%) as reported elsewhere.[15,16] Addition of 2-lithiooxazole (10 equiv, generated from **2**,[17]

† Presented in part at the 4th U.S.−Japan Symposium on Bioorganic Marine Chemistry, Santa Cruz, CA, Dec 14−18, 1998.

* Author for correspondence. Tel.: (530) 752-6358. Fax: (530) 752-8995. E-mail: tfmolinski@ucdavis.edu.

(1) (a) Adamczeski, M.; Quiñoà, E.; Crews, P. *J. Am. Chem. Soc.* **1988**, *110*, 1598−1602. (b) Searle, P. A.; Richter, R. K.; Molinski, T. F. *J. Org. Chem.* **1996**, *61*, 4073−4079. (c) Rodríguez, J.; Nieto, R. M.; Crews, P. *J. Nat. Prod.* **1993**, *56*, 2034−2040. (d) Rudi, A.; Kashman, Y.; Benayahu, Y.; Schleyer, M. *J. Nat. Prod.* **1994**, *57*, 829−832.

(2) Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Higa, T.; Gravalos, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 3173−3174.

(3) Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303−2304.

(4) Antonio, J.; Molinski, T. F. *J. Nat. Prod.* **1993**, *56*, 54−61.

(5) Molinski, T. F. Unpublished results.

(6) Mori, T.; Takakashi, M.; Kashiwabara, M.; Uemura, D.; Katayama, C.; Iwadare, S.; Shizuri, Y.; Mitomo, R.; Nakano, F.; Matsuzaki, A. *Tetrahedron Lett.* **1985**, *26*, 1073−1133.

(7) Shiomi, K.; Arai, N.; Shinose, M.; Takahashi, Y.; Yoshida, H.; Iwabuchi, J.; Tanaka, Y.; Omura, S. *J. Antibiot.* **1995**, *48*, 714−719.

(8) Henkel, T.; Zeeck, A. *Liebigs Ann. Chem.* **1991**, 367−373.

(9) A patent for a racemic, nonstereospecific synthesis of **1** has been claimed. Crews, P.; Matthews, T. R.; Cabana, E. Q.; Adamczeski, M. U.S. Patent 4,785,012, 1988.

(10) Recent examples include total syntheses of phorboxazole ((a) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597−5598), calyculin A ((b) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434−9453), calyculin C ((c) Ogawa, A. K.; Armstrong, R. A. *J. Am. Chem. Soc.* **1998**, *120*, 12435−12442), hennoxazole ((d) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558−559. (e) Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157−167), rhizoxin ((f) Nakada, M.; Kobayashi, S.; Iwasaki, S.; Ohno, M. *Tetrahedron Lett.* **1993**, *34*, 1035−1038. (g) Nakada, M.; Kobayashi, S.; Shibasaki, M.; Iwasaki, S.; Ohno, M. *Tetrahedron Lett.* **1993**, *34*, 1039−1042. (h) Williams, D. R.; Werner, K. M.; Feng, B. N. *Tetrahedron Lett.* **1997**, *38*, 6825−6828), and the trisoxazole segment of the halichondramide macrolide family ((j) Knight, D. W.; Pattenden, G.; Rippon, D. E. *Synlett* **1990**, *1*, 36).

(11) 1,3-Oxazole numbering will be used throughout unless otherwise specified. All new compounds were >95% pure by ^{1}H NMR and/or HPLC and gave satisfactory ^{1}H, ^{13}C NMR spectral data and elemental analysis or HRMS.

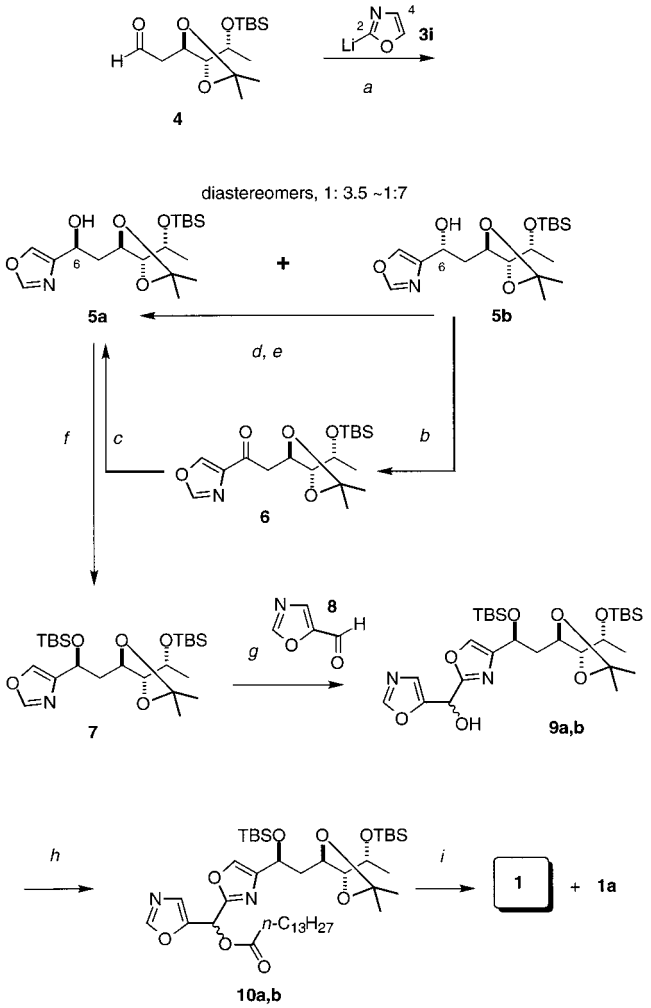
(12) Iddon, B. *Heterocycles* **1994**, *37*, 1321−1346.

(13) Hodges, J. C.; Patt, W. C.; Connolly, C. J. *J. Org. Chem.* **1991**, *56*, 449−452.

(14) Vedejs, E.; Monahan, S. D. *J. Org. Chem.* **1996**, *61*, 5192−5193.

10.1021/jo9906328 CCC: $18.00
Published on Web 06/06/1999

Scheme 2[a]



[a] Key: (a) *n*-BuLi, THF/hexanes, −78 °C, **2** (10 equiv of each) then **4**, 57%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 80%; (c) $NaBH_4$, CF_3CH_2OH, −20 °C, 94%; (d) DEAD, Ph_3P, C_6H_6, *p*-$NO_2C_6H_4COOH$, 70%; (e) K_2CO_3, MeOH, 96%; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 25 °C, 99%; (g) BH_3·THF, 25 °C, 30 min, THF, cool −78 °C, *n*-BuLi, then add **8**, 40%; (h) *n*-$C_{13}H_{27}COCl$, DMAP, Et_3N, CH_2Cl_2, 84%; (i) HF aq, CH_3CN, 94%.

n-BuLi, THF, −78 °C, 1:20 v/v THF/hexanes, 30 min) to **4** gave coupled products **5a** and **5b**[15b] in 57% yield and 1:7 diastereoselectivity (>95% reaction at C4). The configuration of the newly created stereocenter in **5a** was correlated with that of **1** as described previously,[1b,15b,18] and the ratio of epimers was determined by integration of isopropylidene ^{1}H NMR signals. Addition of **3i** to the carbonyl group of aldehyde **4** appears to be chelation-controlled by coordination to the *β*-oxygen of **4**. Inclusion of additional Li (LiBr, 10 equiv) did not change the ratio of **5a** to **5b** (Table 1), but replacement of the solvent (hexanes/THF) with hexanes/Et_2O/TMEDA prevented product formation. The ratio and yield of **5a**:**5b** were also

Table 1. Diastereoselectivity of Addition of 2-Lithiooxazole to 4: Effect of Solvents and LiBr

yield of **5a,b** (%)	additive	**5a**:**5b**	hex/THF (v/v)
52		1:3	1:10
33		1:3.5	1:11
7		1:3	1:3.7
49		1:4	1:14
57		1:7	1:20
62	DMPU (9 equiv)	1:3.4	1:4.3
~57%	LiBr (10 equiv)	1:7	1:20
25%		1:1	1:2.5

[a] Reaction performed at 0.1 M concentration of **4**.

dependent upon the solvent composition. When the reaction was run in 1:2.5−1:4.3 hexane/THF (four replicates) the yield decreased (25−49%) and the ratio of **5a**:**5b** diminished (1:1−1:1.4). Addition of DMPU (9 equiv, 1:7 hexanes/THF) accelerated the reaction (~0.3−1 h) and increased the yield slightly (62%), but without improvement of diastereoselectivity (1:3.4). When the reaction was carried out in the presence of either $ZnCl_2$ or $MgBr{\cdot}Et_2O$ (1.1 equiv) no product was obtained.

Although the formation of **5** under the above conditions favored the wrong epimer for bengazole A synthesis, inversion of C6 to the naturally occurring 6*S* configuration in **1** (bengazole numbering) was achieved by either of two methods. Oxidation of secondary alcohol **5a**,**b** without separation (Swern conditions, 80%) gave ketone **6**, which was reduced ($NaBH_4$, −20 °C, CF_3CH_2OH, 94%) to provide **5a**,**b** (3.3:1). More conveniently, Mitsunobu inversion of the 1:7 mixture of **5a**,**b** (DEAD, PPh_3, benzene, *p*-$NO_2C_6H_4COOH$, 25 °C, 70%) followed by methanolysis (K_2CO_3, MeOH, 96%) gave **5a** (>86% ds).[19] Separation of epimers[20] and protection of **5a** (TBSOTf, 2,6-lutidine, CH_2Cl_2, 25 °C, 99%) as the silyl ether **7** set the stage for the second oxazole addition.

Initial attempts at the Vedejs borane-modified metalation−addition[14] of lithiated-**7** to 5-oxazolecarboxaldehyde (**8**)[21] returned only starting material. After considerable experimentation, an optimized modification of the Vedejs method was applied as follows. A solution of **7** was treated at 25 °C with BH_3·THF (1.05 equiv, 1 M in THF),[22] stirred for 30 min, and then cooled to −78 °C before addition of *t*-BuLi (1.7 M, pentanes, 2.05 equiv). After 30 min, the mixture was treated with aldehyde **8**

(15) (a) Shafer, C. M.; Molinski, T. F. *Carbohydr. Res.* **1998**, *310*, 223−228. (b) Shafer, C. M.; Molinski, T. F. *Tetrahedron Lett.* **1998**, *39*, 2903−2906.

(16) Shafer, C. M. Ph.D. Thesis, University of California, Davis, 1998.

(17) Oxazole (**2**) is no longer commercially available. In our hands, the most expedient preparation of **2** was saponification of ethyl oxazole-4-carboxylate, prepared from ethyl isocyanoacetate according to Schöllkopf (Henneke, K.-W.; Schöllkopf, U.; Neudecker, T. *Liebigs Ann. Chem.* **1979**, 1370−1387), followed by decarboxylation-distillation from hot quinoline−CuO (Cornforth, J. W.; Cornforth, R. H. *J. Chem. Soc.* **1947**, 96−102). Our overall yield of **2** from the isocyanide was 54%.

(18) Briefly, epimer **5a** was deprotected ((i) TBAF, THF, 50 °C, (ii) Dowex (H^+), MeOH, 23 °C, 2 h) and the product converted to the bis-acetonide **iii** (DMP, acetone, *p*-TsOH). Comparative analysis of the ^{1}H NMR spectra (500 MHz) of **iii** and the bis-acetonide prepared from bengazole A **iv**,[1b] in particular the vicinal coupling constants, showed the two to have identical stereochemistry at C2−C4 and C6.[15b]

(19) Evidently, there is some S_N1 participation in the Mitsunobu nucleophilic displacement of benzylic alcohol **5b**,which gives ~8% retention of configuration.

(20) Routine separation of **5a,b** was achieved by preparative HPLC (21.4 × 250 mm, Rainin Dynamax, silica, 2:3 EtOAc, hexane, 13 mL/min). The unwanted epimer **5b** could be recycled by either of the two methods for inversion (see text).

(21) (a) Kende, A. S.; Kawamura, K.; DeVita, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4070−4072. (b) Schöllkopf, U.; Schröder, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 333.

(22) It was essential to use a *freshly opened* bottle of borane (Aldrich). The use of aged borane resulted in return of starting material or reduction of the aldehyde.

(4.1 equiv), stirred for 4 h, and worked up to give the desired product **9a**,**b** as a 1:1 mixture of diastereomers (40%).[23] In contrast to the formation of **5a**,**b**, which proceeded by regioselective addition to C4 of oxazole, aldehyde **8** reacts with lithiated **7** at C2 (>95% regioselective, ^{1}H NMR). It is notable that the basic nitrogen in **8** does not appear to interfere with the reactivity of lithiated-**7** complexed with borane.

The synthesis of bengazole A was completed as follows. Esterification of epimeric alcohols **9a**,**b** (myristoyl chloride, DMAP, Et_3N, CH_2Cl_2, 84%) gave a mixture of esters **10a**,**b** that was deprotected (HF (aq), CH_3CN, 94%) to deliver bengazole A (**1**) and *epi*-bengazole A (**1a**) (ESI MS *m*/*z* 525, MH^+). The mixture of epimers **1** and **1a** was inseparable on HPLC (reversed phase or Chiracel OD), but coeluted with authentic **1**. The ^{1}H and ^{13}C NMR signals of authentic **1** were superimposable with those of synthetic **1**.[24] In other respects, the synthetic **1**/**1a** mixture was identical to the natural product we isolated from *Jaspis* sp.[1b] In particular, we found the biological activity of the mixture of **1**/**1a** was the same as that of an authentic sample of natural bengazole A. Both natural **1** and synthetic **1**/**1a** inhibited the growth of *C. albicans* ATCC 14503 and fluconazole-resistant *Candida krusei* and *Candida glabrata* with a range of minimum inhibitory concentrations (MIC) of 3−10 μg/mL. Assuming no synergistic effect, these results suggest that **1** and **1a** have comparable antifungal potency. It is noteworthy that intermediate **9a**,**b** was not active.

In summary, we have completed the first synthesis of bengazole A (**1**) and 10-*epi*-bengazole A (**1a**) by sequential two-stage grafting of side chains to the central oxazole ring with tight control of regioselectivity. The synthesis was carried out in 14 steps and an overall yield of 2.9% for **1**/**1a**. We have demonstrated that oxazole-metalation and aldehyde **4** addition of the side chain to C4 of **2** occurs with chelation-controlled stereoselection to give a product that subsequently undergoes metalation−addition at C2 by a modified Vedejs borane-mediated lithiation−aldehyde addition. This "grafting approach" to 2,4-disubstituted oxazoles, illustrated here by the first application toward natural products synthesis, offers new opportunities for stereocontrolled oxazole synthesis. This method complements cyclodehydration−oxidation of *N*-acylserines, which has been employed almost uniformly in modern syntheses of 2,4-disubstituted oxazole natural products.[10]

Experimental Section

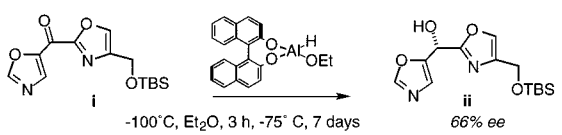
General Methods. All solvents were distilled from glass. THF was distilled from sodium benzophenone ketyl prior to use. DMSO, Et_3N, and CH_2Cl_2 were distilled from CaH_2 prior to use. All reactions were performed under an atmosphere of nitrogen in dried glassware. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra of all compounds were recorded at 300 and 75 MHz, respectively, or at 600 and 151 MHz, respectively, in the case of synthetic **1**/**1a** in deuterated solvents as noted. ^{1}H shifts are referenced to the residual protonated solvent signal (δ 7.26 for $CDCl_3$ or δ 3.30 for CD_3OD), and ^{13}C shifts are referenced to the deuterated solvent signal (δ 77.03 for $CDCl_3$ or δ 49.00 for CD_3OD). ^{13}C multiplicities were deduced from DEPT experiments. Infrared spectra were recorded as thin films on an FTIR spectrophotometer at 2 cm^{-1} resolution. Mass spectra were provided by the University of California, Riverside, Mass Spectroscopy Facility.

Oxazole Adduct 5a,b. *n*-Butyllithium (3.73 mL, 9.33 mmol, Aldrich, 2.5 M in hexanes) was added to oxazole (**2**, 657 mg, 9.52 mmol) in THF (50 mL) at −78 °C (1:14 hexane/THF). After 30 min, aldehyde **4** (576 mg, 1.90 mmol, prepared from D-galactose[15]) in THF (20 mL) was added dropwise. After the mixture was stirred at −78 °C for 1.5 h, saturated aqueous $NaHCO_3$ solution (20 mL) was added and the mixture warmed to ambient temperature and extracted with dichloromethane (3 × 100 mL). The organic extracts were combined, dried (Na_2SO_4), and evaporated under reduced pressure. Flash chromatography (silica, 2:3 ethyl acetate/hexane) gave **5a,b** as a colorless oil (404 mg, 57%) as a 1:7 mixture of epimers at C6 by ^{1}H NMR spectroscopy. HPLC (silica, 21.4 × 250 mm, 2:3 ethyl acetate/hexane, 13 mL/min) gave epimers **5a** (50 mg, 7%) and **5b** (347 mg, 49%), identified by comparison with published spectral data.[15b] See also Table 1.

Ketone 6.[25] Dimethyl sulfoxide (80 μL, 259 μmol) was added to oxalyl chloride (22 μL, 119 μmol) in dichloromethane (0.5 mL) at −78 °C. After 10 min, alcohol **5b** (40.2 mg, 0.108 μmol) in dichloromethane (0.3 mL) was added. After a further 15 min, triethylamine (75 μL, 540 μmol) was added, the cooling bath was removed, and after a further 5 min, saturated $NaHCO_3$ solution (0.5 mL) was added. After the mixture was stirred for 10 min, the organic layer was separated, the aqueous layer was extracted with dichloromethane (5 mL), and the combined organic layers were dried (Na_2SO_4) and evaporated in vacuo. HPLC purification of the residue (silica, 21.4 × 250 mm, 2:3 ethyl acetate/hexane, 13 mL/min) gave **6** as an orange oil (32 mg, 80%): $[\alpha]^{24}_D$ +39.9° (*c* 1.22, $CHCl_3$); IR (NaCl, neat) ν 1696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 1.20 (d, 3H, *J* = 6.3 Hz), 1.31 (s, 3H), 1.45 (s, 3H), 3.08 (dd, 1H, *J* = 15.6, 4.2 Hz), 3.28 (dd, 1H, *J* = 15.6, 9.3 Hz), 3.87 (p, 1H, *J* = 6.3 Hz), 3.98−4.02 (m, 1H), 4.72−4.78 (m, 1H), 7.88 (s, 1H), 8.25 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.5 (CH_3), −4.4 (CH_3), 18.3 (C), 20.3 (CH_3), 25.7 (CH_3), 25.9 (CH_3), 27.8 (CH_3), 40.9 (CH_2), 67.6 (CH), 73.0 (CH), 81.6 (CH), 108.5 (C), 140.3 (C), 142.4 (CH), 150.8 (CH), 192.9 (C); HRCIMS (NH_3) found *m*/*z* 370.2050 ($[MH]^+$), $C_{18}H_{32}NO_5Si$ requires 370.2050.

Inversion[26] of Alcohol 5b (Mitsunobu Reaction). Triphenylphosphine (210 mg, 800 μmol), 4-nitrobenzoic acid (119 mg, 712 μmol), and diethyl azodicarboxylate (126 μL, 798 μmol) were added sequentially to alcohol **5b** (59.0 mg, 159 μmol) in benzene (5.0 mL) at ambient temperature. The mixture was stirred for 2 h, diluted with ethyl acetate (75 mL), and washed with water (20 mL) and brine (20 mL). The aqueous layers were combined and extracted with ethyl acetate (30 mL), and the organic layers were combined, dried (Na_2SO_4), and evaporated in vacuo. Flash chromatography (silica, 1:4 ethyl acetate/hexane) of the residue gave the corresponding 2-nitrobenzoate ester (58.4 mg, 70%) as an orange solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.16 (d, *J* = 5.1 Hz), 1.27 (s, 3H), 1.49 (s, 3H), 2.25 (ddd, *J* = 12.5, 11.8, 5.2 Hz, 1H), 2.41 (ddd, 12.5, 10.3, 2.2 Hz, 1H), 3.75−3.94 (m, 3H), 6.29, (dd, *J* = 10.3, 5.2 Hz), 7.83

(23) As expected, the stereocenter at C10 (bengazole numbering) is too remote to afford any stereocontrol in the addition of **7** to **8**. Shioiri has reported an enantioselective reduction of a (5′-oxazolyl)(4″-oxazolyl)ketone **i** to afford alcohol **ii** in 78% yield with modest enantioselectivity [(*R*)-(+)-BINAL-H, −100 °C, 3 h, −75 °C, 7 days, 66% ee]. Chittari, P.; Hamada, Y.; Shioiri, T. *Synlett* **1998** (9), 1022−1024. We are pursuing diastereoselective addition of **7** to **8** by employing a chiral auxiliary that may preorganize reaction components during metalation−addition, but it will not solve the lack of separation of the C10 epimers **9a**,**b**.



(24) Interestingly, the ^{13}C NMR spectrum of the mixture of **1** and **1a** (Bruker DRX, 150.1 MHz) gave a single set of discrete peaks corresponding to authentic **1** with doubling only for C6 (bengazole numbering, ^{13}C NMR, 150 MHz, CD_3OD, δ 66.21 and 66.18 d). The ^{1}H NMR spectrum of the synthetic product was identical to that of natural **1**, plus new signals due to **1a** were assigned as follows (order for **1**/**1a**, respectively): δ 2.43 (t, 2H) *J* = 7.5 Hz/2.25 (t, 2H) *J* = 7.7 Hz (α-myristate CH_2); 1.13 (d, 3H, *J* 6.6 Hz)/1.14 (d, 3H, *J* = 6.6 Hz) (CH_3). The remainder of the ^{1}H NMR spectrum of **1**/**1a** was identical to natural **1**, in particular, H10 and the three oxazole singlets (δ 7.30, s; 7.85, s; 8.25, s).

(25) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651−1660.
(26) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1997**, *62*, 5672−5673.

(s, 1H), 7.89 (s, 1H), 8.20 (d, J = 8.8 Hz, 2H), 8.26 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.6 (CH_3),. −4.5 (CH_3), 18.3 (C), 20.3 (CH_3), 25.8 (3 × CH_3), 25.9 (CH_3), 28.3 (CH_3), 32.9 (CH_2), 67.2 (CH), 67.4 (CH), 73.5 (CH), 82.2 (CH), 108.6 (C), 123.4 (2 × CH), 130.9 (2 × CH), 135.6 (C), 137.0 (C), 138.3 (CH), 150.5 (C), 151.5 (CH), 163.8 (C). Potassium carbonate (24 mg, 167 mmol) was added to a solution of the ester (58.4 mg, 111 mmol) in methanol (6 mL) and dichloromethane (0.6 mL). After being stirred for 16 h, the solution was diluted with ethyl acetate (50 mL) and washed with water (30 mL) and brine (30 mL). The aqueous layers were combined and extracted with ethyl acetate (40 mL), and the organic layers were combined, dried, and evaporated in vacuo. Flash chromatography (silica, 2:3 ethyl acetate/hexane) gave alcohol **5a** (39.2 mg, 96%, 67% from **5b**) as an orange oil (>85% ds) that was repurified by HPLC as described above (**5a**, ds >95%).

Reduction of Ketone 6 (Method A). Sodium borohydride (9.4 mg, 0.25 mmol) was added to ketone **6** (18.3 mg, 50 μmol) in 2,2,2-trifluoroethanol (2 mL) at −45 °C. The solution was allowed to warm to −20 °C, and after it was stirred at −20 °C for 20 min, saturated $NaHCO_3$ solution (0.2 mL) was added. After the solution was stirred for 5 min, the solvent was evaporated and the residue triturated with dichloromethane (6 × 50 mL). The combined extracts were dried (Na_2SO_4) and evaporated in vacuo to give the epimeric alcohols **5a**:**5b** (17.2 mg, 94%) in a ratio of ca. 10:3.

Reduction of Ketone 6 (Method B). Sodium borohydride (1.9 mg, 56 μmol) was added to ketone **6** (2.1 mg, 5.6 μmol) in methanol (0.5 mL) at 0 °C. After the solution was stirred at 0 °C for 20 min, saturated $NaHCO_3$ solution (0.1 mL) was added. After the solution was stirred for 5 min, the solvent was evaporated and the residue triturated with dichloromethane (6 × 10 mL). The combined extracts were dried (Na_2SO_4) and evaporated in vacuo to give the epimeric alcohols (1.9 mg, 90%) in a ratio of ca. 5:2 **5a**:**5b**.

Silyl Ether 7.[27] 2,6-Lutidine (42 μL, 0.34 mmol) was added to alcohol **5a** (50.0 mg, 0.135 mmol) in dichloromethane (0.5 mL). *tert*-Butyldimethylsilyl trifluoromethanesulfonate (50 μL, 0.20 mmol) was added and the mixture stirred at ambient temperature for 1 h. Dichloromethane (10 mL) and saturated $NaHCO_3$ solution (0.1 mL) were added, and the mixture was stirred for 2 min, dried (Na_2SO_4), and evaporated in vacuo. Flash chromatography (silica, 1:9 ethyl acetate/hexane) gave silyl ether **7** (64.5 mg, 99%) as a colorless oil: IR (NaCl, neat) ν 1514, 1096, 1061, 1006 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.03 (s, 3H), 0.06 (s, 6H), 0.07 (s, 3H), 0.86 (s, 18H), 1.04 (d, 3H, J = 6.0 Hz), 1.27 (s, 3H), 1.44 (s, 3H), 1.93−2.01 (m, 2H), 3.76−3.86 (m, 3H), 4.94 (dd, 1H, J = 9.0, 4.5 Hz), 7.57 (s, 1H), 7.84 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.8 (CH_3), −4.7 (CH_3), −4.6 (CH_3), −4.5 (CH_3), 18.2 (CH_3), 18.3 (CH_3), 20.3 (CH_3), 25.8 (CH_3), 25.9 (CH_3), 26.0 (CH_3), 28.5 (CH_3), 38.1 (CH_2), 65.4 (CH), 67.3 (CH), 73.7 (CH), 82.2 (CH), 108.2 (C), 135.5 (CH), 143.1 (C), 151.0 (CH); HRCIMS (NH_3) found m/z 486.3065 (MH^+), $C_{24}H_{48}NO_5Si_2$ requires 486.3071.

Oxazole-5-carboxaldehyde (8).[28] Amberlyst-15 (0.48 g) was added to a vigorously stirring solution of oxazole-5-carboxaldehyde diethyl acetal[21] (0.50 g, 2.9 mmol) and water (0.17 mL, 9.5 mmol) in acetone (12 mL). After 1 h, the resin was removed by filtration and washed with acetone (20 mL), and the filtrate and washing were evaporated in vacuo. Flash chromatography (silica, 1:1 diethyl ether/pentane) gave aldehyde **8** (0.19 g, 69%) as colorless crystals: mp 29−33 °C (sublimes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 8.11 (s, 1H), 9.85 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0 (CH), 148.2 (C), 154.3 (CH), 176.8 (C).

Borane-Mediated Addition of 2-Lithioxazole[14] Bis(oxazole) 9a,b. BH_3·THF (140 μL, 140 μmol, 1.0 M in THF) was added dropwise to silyl ether **7** (64.5 mg, 133 μmol) in THF (1 mL) at ambient temperature. After 30 min, the solution was cooled to −78 °C and *tert*-butyllithium (161 μL, 273 μmol, 1.7 M in pentane) added dropwise. After a further 30 min, aldehyde **8** (54 mg, 546 μmol) in THF (0.5 mL) was added dropwise. After a further 4 h, methanol (2 mL) was added, and the solution was allowed to warm to ambient temperature and stirred for 1 h. The solvent was evaporated in vacuo, and the residue was dissolved in methanol (2 mL) and stirred a further 30 min. The solvent was again removed and the residue partitioned between dichloromethane (15 mL) and saturated $NaHCO_3$ solution (1 mL). The organic layer was separated, the aqueous layer was extracted with dichloromethane (3 × 15 mL), and the organic layers were combined, dried (Na_2SO_4), and evaporated in vacuo. Flash chromatography (silica, 2:3 ethyl acetate/hexane) gave the bis(oxazole) **9a**,**b** (30.5 mg, 40%) as a colorless gum as a 1:1 mixture of epimers at C10 (bengazole numbering): IR (NaCl, neat) ν 3205, 1103, 1068 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.03 (s, 3H), 0.06 (s, 3H), 0.07 (s, 6H), 0.86 (s, 9H), 0.87 (s, 9H), 1.05 (d, 3H, J = 6.0 Hz), 1.27 (s, 3H), 1.44 (s, 3H), 1.93−2.01 (m, 2H), 3.77−3.87 (m, 3H), 4.93 (dd, 1H, J = 9.1, 4.5 Hz), 5.98 (s, 0.5H), 6.00 (s, 0.5H), 7.08 (s, 0.5H), 7.07 (s, 0.5H), 7.56 (bs, 1H), 7.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.8 (CH_3), −4.8 (CH_3), −4.6 (CH_3), −4.5 (CH_3), 18.1 (C), 18.3 (C), 20.2 (CH_3), 25.8 (3 × CH_3), 25.8 (CH_3), 25.9 (3 × CH_3), 28.4 (CH_3), 37.8 (CH_2), 62.1 (CH), 65.3 (CH), 67.3 (CH), 73.5 (CH), 82.1 (CH), 108.2 (C), 124.8 (CH), 136.3 (CH), 143.5, 143.6 (C), 149.4 (C), 151.5 (CH), 161.3, 161.6 (C); HRCIMS (NH_3) found m/z 583.3243 (MH^+), $C_{28}H_{51}N_2O_7Si_2$ requires 583.3235.

Myristate Ester 10a,b. Myristic acid (7.9 mg, 34.6 μmol), oxalyl chloride (0.1 mL), *N*,*N*-dimethylformamide (20 μL), and dichloromethane (0.5 mL) were stirred at ambient temperature for 2 h and then evaporated in vacuo. Dichloromethane (1 mL) was added and evaporated in vacuo, and this step was repeated. The myristoyl chloride was dissolved in dichloromethane (0.2 mL) and triethylamine (0.1 mL), and alcohol **9a**,**b** (15.5 mg, 26.6 μmol) in dichloromethane (0.5 mL) was added. The volume was reduced with a stream of nitrogen to ca. 0.2 mL, 4-(dimethylamino)pyridine (1 mg) added, and the solution stirred at ambient temperature for 21 h. Saturated $NaHCO_3$ solution (1 mL) was added and the biphasic mixture stirred rapidly for 30 min. Dichloromethane (5 mL) and water (2 mL) were added, the organic layer was separated, and the aqueous layer was extracted with dichloromethane (5 mL). The organic layers were combined, dried (Na_2SO_4), and evaporated in vacuo. Flash chromatography (silica, 1:9 ethyl acetate/hexane) gave ester **10a,b** (17.7 mg, 84%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.11 (s, 3H), 0.06 (s, 9H), 0.79−0.94 (m, 3H), 0.87 (s, 18H), 1.17−1.38 (m, 15H), 1.42 (d, J = 2.4 Hz, 3H), 1.58−1.67 (m, 2H), 1.96−2.00 (m, 2H), 2.31−2.43 (m, 2H), 3.77−3.90 (m, 3H), 4.91 (t, J = 5.4 Hz, 1H), 7.04 (s, 1H), 7.20 (bs, 1H), 7.57 (s, 1H), 7.88 (s, 1H).

Bengazole A (1) and 10-*epi*-Bengazole A (1a). Ester **10a**,**b** (17.7 mg, 22.3 μmol) was dissolved in a mixture of 40% aqueous hydrofluoric acid (0.3 mL) and acetonitrile (0.7 mL) and then stirred at ambient temperature for 90 min. Chloroform (10 mL) and 50% saturated $NaHCO_3$ solution (2 mL) were added, the organic layer separated, and the aqueous layer extracted with chloroform (3 × 10 mL). The organic extracts were combined, dried (Na_2SO_4), and evaporated in vacuo to leave **1** (bengazole A) and **1a** as a yellow oil (11.1 mg, 94%). HPLC of **1**/**1a** gave a single peak (C18 3 μm Microsorb 4.8 × 100 mm, 9:1 MeOH/H_2O, rt 5.5 min) identical with that of natural **1**. UV identical with **1**. ^{1}H NMR (600 MHz, CD_3OD) and ^{13}C NMR (150 MHz, CD_3OD) data for the mixture of **1** and **1a** were identical to those of the natural product,[1b] with the exception of signal doubling for C6 (^{13}C NMR, δ 66.21, d, 66.18, d) and the following ^{1}H NMR signals (assigned for **1**/**1a**, respectively): δ 2.43 (t, 2H) J = 7.5 Hz/2.25 (t, 2H) J = 7.5 Hz (α-myristate CH_2); 1.14 (d, 3H, J = 6.6 Hz)/ 1.13 (d, 3H, J = 6.6 Hz) (CH_3); ESIMS m/z 525 (MH^+, 100), 312 (63).

Acknowledgment. We are grateful to Scott Stanley (Equine Analytical Chemistry Laboratory, UC Davis) for ESI MS spectra of **1/1a** and Gillian Nicholas for assistance with antifungal assays. Financial support for this work was provided by the National Institutes of Health (AI 39887). The Bruker DRX 600 MHz NMR spectrometer was partially funded through NIH RR 11973.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **6**, **7**, **9a**,**b**, **10a**,**b**, and synthetic **1**/**1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9906328

(27) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455−3458.

(28) Coppola, G. M. *Synthesis* **1984**, 1021−1023.