Bengazoles C−G from the Sponge *Jaspis* sp. Synthesis of the Side Chain and Determination of Absolute Configuration†

Philip A. Searle,[1] Rowena K. Richter,[2] and Tadeusz F. Molinski*

Department of Chemistry, University of California, Davis, California 95616

Received December 22, 1995[⊗]

Five new antifungal bengazoles (C−G) were isolated and fully characterized from a marine sponge of the genus *Jaspis* sp. Bengazoles C−G, together with the known bengazoles A and B, comprise a homologous series of *n, iso,* and *anteiso* fatty acid esters (C_{13}−C_{16}) of the same heterocyclic bis-(oxazolyl)methanol parent. The complete relative and absolute configurations of the bengazoles were determined by application of the modified Mosher method and interpretation of exciton coupling in the CD spectra of the tetra-*p*-bromobenzoate derivatives of bengazole A and that of a model tetrol synthesized in seven steps from L-fucose.

An increasing number of cytotoxic and antifungal oxazoles have been reported in recent years from marine invertebrates.[3−6] Recent examples include the cytotoxic natural products kabiramide C,[7,8] hennoxazole,[9] phorboxazoles A and B,[10] and theonezolides A−C.[11,12] While the structures of most of these oxazoles have polyketide components, the bengazoles stand out as unique bis-(oxazoles) containing a carbohydrate-like polyol side chain. Bengazole A (**1a**) was first isolated by Crews and co-workers from a Pacific Choristid sponge along with the homolog bengazole B (**1b**), both of which exhibited anthelminthic activity against *Nippostrongylus braziliensis*.[13] In recent work from our laboratory, we showed that **1a**,**b** are also potent ergosterol-dependent antifungal agents; their activity against *Candida albicans* and *Saccharomyces cerevisiae* is comparable with that of amphotericin B.[14] This preliminary report also revealed five additional bengazoles (**1c**−**g**) from a sponge identified as *Jaspis* sp. from the Indo−Pacific region (Figure 1). The new bengazoles are homologous fatty acid esters of a heterocyclic nucleus comprised of a bis(oxazolyl)-methanol further substituted with a hexanetetrol side chain, reminiscent of a carbohydrate analog. Subsequently, two additional reports appeared describing C10 deoxy analogs of **1a**. Bengazoles C_2, C_3, C_4, D_2, D_3, and D_4[15] are antitumor compounds that lack the C10 hydroxyl

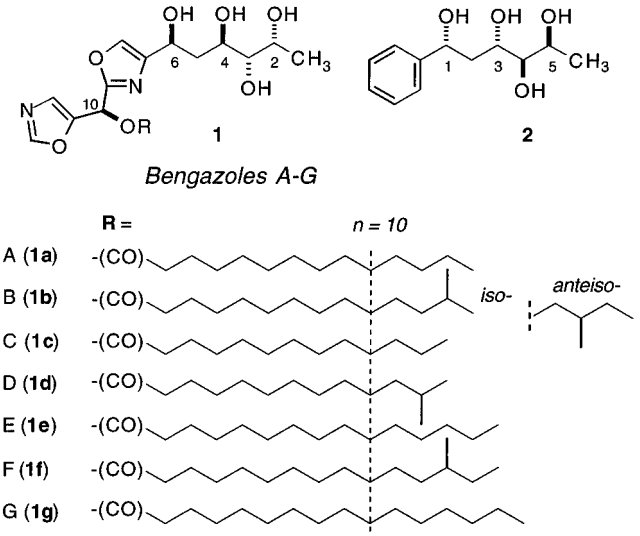


Figure 1. Bengazoles A−G (**1a**−**g**) and model compound **2.** Bengazole B was isolated as an inseparable 5/1 mixture of *iso* and *anteiso* 15:0 fatty acid esters.

of **1a**, but are acylated as myristate (C_{14}) or pentadecanoate esters at one of the side chain hydroxyl groups. Digonazole,[16] another cytotoxic member of the bengazole family, is an homologous *O*-C6 eicosanoate ester (*n*-C_{20}) of bengazoles C_2−D_4. The structures of the bengazole family of alkaloids were solved by a combination of spectroscopic methods and chemical degradation, but there is ambiguity in their stereochemistry.

While the relative stereochemistry of the C1−C6 side chain in **1a** was defined by Crews *et al.*,[13] the configuration at C10 relative to the side chain and the absolute configuration were unassigned leaving the absolute configuration indeterminate among four possible stereoisomers. In order to pursue structure−activity studies related to non-polyene antifungal compounds, we required the absolute configuration of **1a**. In this report we reveal characterization of **1c**−**g**[14] and unambiguous determination of the complete relative and absolute configurations of all stereogenic centers in bengazoles as depicted in **1**. The C10 absolute configuration was elucidated by modified Mosher ester method while the C2−6 absolute stereochemistries were determined by

† This paper is dedicated to Dr. David J. Collins (Monash University) on the occasion of his 65th birthday.

⊗ Abstract published in *Advance ACS Abstracts,* May 15, 1996.

(1) Present address: Harbor Branch Oceanographic Institution, Inc., Division of Biomedical Marine Research, Fort Pierce, FL 34946.
(2) Present address: Shaman Pharmaceuticals, 213 East Grand Ave., South San Franciso, CA 94080.
(3) Lewis, J. R. *Nat. Prod. Rep.* **1994**, *11*, 395−418.
(4) Lewis, J. R. *Nat. Prod. Rep.* **1995**, *12*, 135−163.
(5) Faulkner, D. J. *Nat. Prod. Rep.* **1994**, *11*, 355−395.
(6) Faulkner, D. J. *Nat. Prod. Rep.* **1995**, *12*, 223−269.
(7) Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Koseki, K.; Noma, M. *J. Am. Chem. Soc.* **1986**, *108*, 847−849.
(8) Kernan, M. R.; Molinski, T. F.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 5014−20.
(9) Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Higa, T.; Gravalos, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 3173−3174.
(10) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126−8131.
(11) Kobayashi, J.; Kondo, K.; Ishibashi, M.; Wälchli, M. R.; Nakamura, T. *J. Am. Chem. Soc.* **1993**, *115*, 6661−6665.
(12) Kondo, K.; Ishibashi, M.; Kobayashi, J. *Tetrahedron* **1994**, *50*, 8355−8362.
(13) Adamczeski, M.; Quiñoà, E.; Crews, P. *J. Am. Chem. Soc.* **1988**, *110*, 1598−1602.
(14) Molinski, T. F. *J. Nat. Prod.* **1993**, *56*, 1−8.
(15) Rodriguez, J.; Nieto, R. M.; Crews, P. *J. Nat. Prod.* **1993**, *56*, 2034−2040.
(16) Rudi, A.; Kashman, Y.; Benayahu, Y.; Schleyer, M. *J. Nat. Prod.* **1994**, *57*, 829−832.

S0022-3263(95)02261-4 CCC: $12.00

Table 1. Abundance and HRFABMS Measurements of Bengazoles 1a−g from *Jaspis* sp.

name		formula	% dry weight	*m/z* (MH^+)	Δmmu
bengazole A	**(1a)**	$C_{27}H_{44}N_2O_8$	0.27	525.3176	−2.7
bengazole B	**(1b)**	$C_{28}H_{46}N_2O_8$	0.14	539.3305	2.7
bengazole C	**(1c)**	$C_{26}H_{42}N_2O_8$	0.007	511.3019	0.0
bengazole D	**(1d)**	$C_{27}H_{44}N_2O_8$	0.022	525.3165	1.1
bengazole E	**(1e)**	$C_{28}H_{46}N_2O_8$	0.043	539.3326	0.6
bengazole F	**(1f)**	$C_{29}H_{48}N_2O_8$	0.027	553.3481	0.8
bengazole G	**(1g)**	$C_{29}H_{48}N_2O_8$	0.027	553.3481	0.8

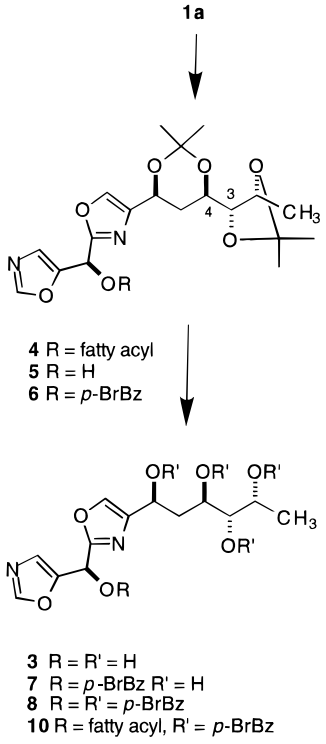
interpretation of the exciton coupling in the circular dichroism (CD) spectra of the tetra-*p*-bromobenzoate esters prepared from **1a** and synthetic model compound **2**, synthesized stereoselectively from L-fucose in seven steps. Knowledge of the correct configuration of **1a** now allows refinement of the structure−activity relationship (SAR) models for the antifungal mechanism of action of bengazoles as well as selection of correct starting materials from the chiral pool for enantioselective total synthesis of **1a**.

Results and Discussion

An ethanol extract of *Jaspis* sp. from the Great Barrier Reef exhibited potent antifungal activity against *C. albicans* and *S. carlbergensis*. The sponge was exhaustively extracted with methanol, and the antifungal compounds were isolated by solvent partition followed by silica gel flash chromatography and C_{18} reversed phase HPLC (MeOH/H_2O 90:10) to give pure bengazoles A−G (**1a**−**g**, see Table 1). The identities of **1a** and **1b** were established by careful comparison of spectroscopic data (^1H and ^{13}C NMR, FABMS) with published values,[13] and the structures of the new bengazoles were determined by a combination of FABMS and ^1H and ^{13}C NMR spectroscopies. The ^1H NMR spectra of the new bengazoles were identical with each other in the downfield region of δ 3−8. The consistent appearance of the H10 singlet at δ 7.1 showed that C10 was acylated in each compound. Accordingly, we surmised that the compounds differed only in the fatty acid moiety at C10. Indeed, ammoniolysis (NH_3, MeOH) of the mixture of **1a**−**g** gave only one alkaloid, the pentol **3**. Methanolysis of each pure bengazole A−G (HCl, MeOH, 60 °C) gave the corresponding fatty acid methyl ester (FAME) which was analyzed by GCMS with single-ion monitoring of the M − 74 peak (M − $C_3H_6O_2$, McLafferty rearrangment) and comparison of retention times with a commercial standard mixture of bacterial FAMEs. The bengazole FAMEs varied in carbon chain length from C_{12} to C_{18} and belonged to the *n*, *iso*, or *anteiso* series. HRFABMS (see Table 1) and ^1H NMR spectra of pure **1a**−**g** were consistent with FAME analysis.

Crews *et al.* proposed the 2*S**,3*R**,4*S**,6*R** relative configuration for the carbohydrate side chain of **1a** using arguments based on NOE, vicinal ^1H coupling constant analysis of a degradation product, and comparison with simple tetrose models.[13] We were able to verify this by chemical transformations. Treatment of **1a** with 2,2-dimethoxypropane and *p*-toluenesulfonic acid (*p*-TSA) (50 °C) gave **4** as the only acetonide (80%) which was ammoniolyzed (NH_3, MeOH, 87%) to provide alcohol **5**. The ^1H NMR spectrum of **5** was consistent with a chair conformation for the dioxane ring with equatorial substituents at C4 and C6 inferred from axial couplings for H6 (δ 4.97, dd, J = 11.8, 2.1 Hz) and H4 (δ 3.94, ddd, J = 11.4, 7.2, 2.5 Hz). The ^{13}C NMR chemical shifts of the isopropylidene methyl groups (δ 19.3 q, 26.9 q)[17] also supported a *syn* configuration at C4,6 and a *threo* at configuration C2,3. Although the C3,4 relationship could not be confidently assigned on the basis of the vicinal H3,4 coupling alone (J = 7.2 Hz), subsequent ^1H NMR measurements on the model compound **2** (see below) and its diacetonide **18** revealed this to be 3,4-*erythro* in agreement with the assignment of Crews.[13]

The opportunity now presented itself to prepare discrete crystalline *O*-C10 derivatives of **4** and **5** in order to address the stereochemical issue by single-crystal X-ray crystallography. We prepared various derivatives including three characterized *p*-bromobenzoate esters (**6**−**8**), two (−)-(*R*)-(1-naphthylethyl)urethanes, one (1*S*)-(−)-camphanate ester, and a cyclic bis(*p*-bromophenyl)boronate ester (the latter four are not described here), but to no avail; in our hands, these compounds produced crystals of unsuitable dimensions or failed to crystallize at all. We turned instead to chemical and chiroptical correlation.



With **5** in hand, the *absolute* configuration at C10 could be addressed conveniently using Kakisawa's modification of the Mosher method.[18] Separate treatment of **5** with either (*R*)- or (*S*)-MTPA (DCC, CH_2Cl_2, Et_3N) gave the Mosher esters **9a** (65%) and **9b** (46%), respectively. The measured $\Delta\delta = \delta_S - \delta_R$ for ^1H signals in the diastereomeric pair **9a**,**b** (Figure 2) conformed to the configurational model of Kakisawa[18] and revealed the 10*S* configuration.

The Mosher ester method was not appropriate for the C2−6 configurations due to anticipated complexity in interpretation of overlapping ^1H signals in a heavily anisotropic tetra-MTPA derivative. Instead, we converted the mixture **1a**−**g** into the corresponding tetra-

(17) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511−3515.

(18) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

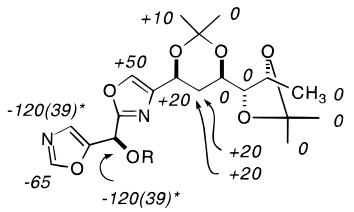
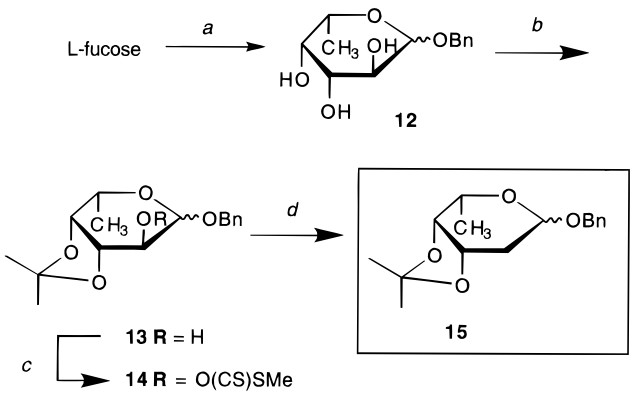


Figure 2. MTPA ester analysis according to the modified Mosher−Kakisawa method (see text). Values are derived from $\Delta\delta = \delta_S - \delta_R$, where δ_S and δ_R denote ^{1}H NMR chemical shifts of *(S)*- and *(R)*-MTPA esters **9a** and **9b**, respectively. Units shown are parts per billion ($\Delta\delta$ ppm × 10^3). Signals shown with an asterisk (*) could not be confidently assigned and so are depicted as interchangeable with the range of possible values from −120 to −139 ppb.

p-bromobenzoate **10** (mixture of fatty acids at C10) and exploited the strongly split Cotton effects in the CD spectrum.[19,20] Nakanishi and co-workers have reported the CD exciton coupling for chromophoric derivatives of a variety of configurationally defined alditols and skipped polyols,[21−24] but CD data for the required models—a hexose with *lyxo* C2,3,4 tri-*p*-bromobenzoate and with both C4,6-*syn* configurations—were not available. In principle, one could predict the expected CD curve of **10** by extrapolating these results, but in order to avoid ambiguity we chose instead to prepare model compound **2** and compare the corresponding tetra-*p*-bromobenzoate **11** with **10**. Two assumptions were made in the choice of the model for CD comparison. First, the replacement of the oxazole, attached to the side chain at C6, with a phenyl group was an acceptable substitution because both alkylbenzenes and 4-alkyloxazoles are chromophores with relatively weak charge-transfer electric transition dipole moments,[20] but it also simplified the synthesis of the model. Second, the perturbation of the tetra-*p*-bromobenzoate manifold in **10** by the second oxazole ring and the fatty ester side chains was expected to be insignificant compared to that of the stronger intra-side chain exciton coupling. Our experience shows that relatively weak split CD effects are found in bis(oxazole)s such as bengazole A (λ 231 nm, $\Delta\epsilon$ −1.55; 202, +3.89) and even the tris(oxazole) kabiramide C.[25] Because the C2−C4 fragment of the bengazole side chain possessed the *lyxo* configuration found in 2-deoxyfucose and related sugars, we selected L-fucose as the starting material for synthesis of **2**.[26]

L-Fucose was converted (Scheme 1) into benzyl fucopyranoside **12** (BnOH, HCl, 0 °C, mixture of anomers, 80%) followed by protection of the 3,4-dihydroxyl group as the acetonide **13** (2,2-dimethoxypropane, *p*-TSA, 97%). Compound **13**, as a 5/1 mixture of β/α anomers, was carried through to the xanthate ester **14** (NaH, CS_2, MeI, 98%) followed by Barton deoxygenation using hypophosphorous acid in the presence of triethylamine[27] to afford the differentially protected L-2-deoxyfucose derviative **15** (74%). Samples of the product anomers **15**α and **15**β were separated and characterized, but it was more convenient to carry through the mixture. Removal of the *O*-benzyl group from **15** ($Pd(OH)_2$, H_2, 1 atm, 77%) gave 3,4-isopropylidene-2-deoxy-L-fucose (**16**). Treatment of **16** with phenyllithium (5 equiv, THF, −78 °C, Scheme 2) gave a 2.4/1 mixture of two epimeric diol acetonides **17a**,**b** (86%) which was separated by preparative HPLC (silica, 1:1 *n*-hexane/EtOAc). As expected, the H1 signal of the major C1 epimer **17a** (δ 4.90, dd, J = 8.5, 4.5 Hz, 1H) differed only slightly from that of **17b** (δ 4.98, dd, J = 9, 3.2 Hz, 1H). Nevertheless, we were able to show that the relative configuration of the newly created stereogenic center C1 in **17a** was the same as that of C6 in bengazole A as follows. Deprotection of acetonide (−)-**17a** (Dowex 50-X8, THF/H_2O, 85%) provided tetrol **2** with vicinal ^{1}H coupling constants (CD_3OD) similar to those of **1a**. Further transformation of **2** to diacetonide **18** (2,2-dimethoxypropane, *p*-TSA, acetone, 74%) locked the C1 phenyl susbstituent to the 1,3-dioxane ring in an equatorial position, allowing direct comparison of **5** and **18** (Table 2). Interpretation of the COSY and the decoupled spectra of **18** allowed the assignment of respective vicinal ^{1}H coupling constants which were identical with those of **5**. Note that the H3,4 vicinal coupling observed in L-fucose-derived **18** ($J_{3,4}$ = 7.0 Hz) independently supports the 3,4-*erythro* configuration (bengazole numbering) assigned to **1a**[13] ($J_{3,4}$ = 7.2 Hz). The trend for larger couplings in *erythro* derivatives (J = 6.5−7.1 Hz) compared to their *threo* isomers (J = 3.6−4.7 Hz) has been well established in closely related acyclic polyol derivatives.[22] Because the configuration of the other centers in **17a** are conserved from the starting material, it is proven that the *relative* stereochemistries in model tetrol **2** and bengazole (**1a**) are identical; however, the absolute configurations are antipodal as demonstrated below.

Scheme 1

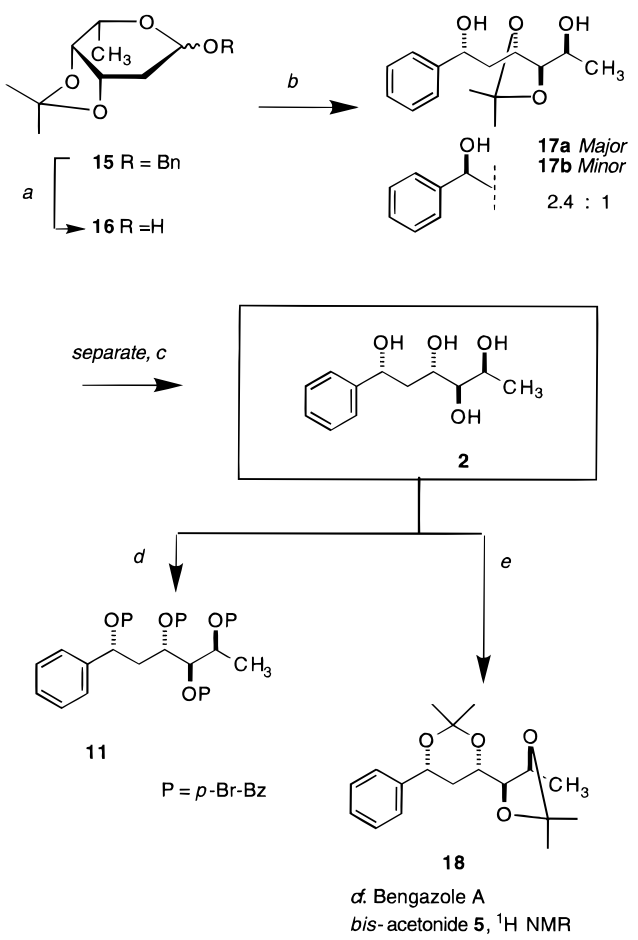


[a] a, BnOH, HCl, 80%; b, $Me_2C(OMe)_2$, *p*-TSA, acetone, 97%; c, NaH, CS_2, MeI, THF, 98% d, H_3PO_2, Et_3N, AlBN, dioxane, reflux, 74%.

The bengazole mixture **1a**−**g** and pure **2** were smoothly converted (*p*-bromobenzoyl chloride, DMAP, pyridine, 25 °C) to the tetra-*p*-bromobenzoate derivatives **10** and **11** (25 and 91%, respectively). The circular dichroism spectrum of bengazole A derivative **10** showed, as expected, complex split Cotton effects due to exciton coupling among the four *p*-bromobenzoate groups (Figure

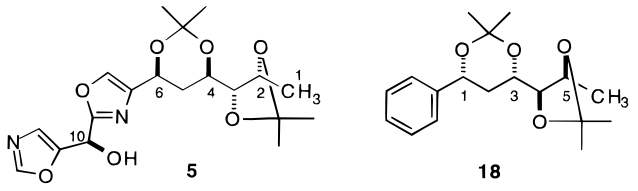
(19) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy: Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983; p 460.
(20) *Circular Dichroism: Principles and Applications*; Nakanishi, K., Berova N., Woody, R. W., Eds.; VCH: New York, 1994; p 570.
(21) Wiesler, W. T.; Nakanishi, K. *J. Am. Chem. Soc.* **1989**, *111*, 3446−3447.
(22) Wiesler, W. T.; Nakanishi, K. *J. Am. Chem. Soc.* **1990**, *112*, 5574−5583.
(23) Zhao, P.; Zhao, N.; Rele, D. N.; Berova, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1993**, *115*, 9313−9314.
(24) Zhou, P.; Berova, N.; Wiesler, W. T.; Nakanishi, K. *Tetrahedron* **1993**, *49*, 9343−9352.
(25) Molinski, T. F. Unpublished results.
(26) The choice of L- or D-fucose was arbitrary at this point; however, L-fucose was the less expensive enantiomer.
(27) Barton, D. H.; Jang, D. O.; Jaszberenyi, J. C. *J. Org. Chem.* **1993**, *58*, 6838−6842.

Scheme 2



[a] a, $Pd(OH)_2$, H_2, 1 atm, EtOH; b, PhLi, THF, −78° to 0 °C, 86%; c, Dowex 50-X8, THF, H_2O, 90%; d, *p*-BrBzCl, py, DMAP, 91%; e, $Me_2C(OMe)_2$, acetone, *p*-TSA, 74%.

Table 2. Comparison of Vicinal Constants (*J*) for Bengazole A Derivative 5 and Model Compound 18 (Note: order of numbering is different for 5 and 18)



compound **5** ($CDCl_3$)				compound **18** (d_6-acetone)			
no.	δ	mult	*J* (Hz)	no.	δ	mult	*J* (Hz)
1	1.34	d	6.1	6	1.28	d	6.0
2	4.00	dq	7.6, 6.1	5	3.99	dq	7.7, 6.0
3	3.44	dd	7.6, 7.2	4	3.37	dd	7.7, 7.0
4	3.94	ddd	11.4, 7.2, 2.5	3	4.08	ddd	11.5, 7.0, 2.5
5α	2.10	ddd	13.0, 2.5, 2.1	2α	1.96	ddd	12.9, 2.5, 2.5
5β	1.69	ddd	13.0, 11.8, 11.4	2β	1.45	ddd	12.9, 11.5, 11.5
6	4.97	dd	11.8, 2.1	1	5.04	dd	11.5, 2.5

3). The CD of **10** showed a strong negative Cotton effect at λ 252 nm (Δε −14.8) followed by two positive Cotton effects at λ 235 (+17.3) and 208 (+12.5) nm and a smaller negative Cotton effect at λ 196 (−10) nm. The CD spectrum of model compound **11** (λ 252 (Δε +6.5), 234 (−19.5), 207 (−9.8), 197 (+2.5) nm) was essentially the same in magnitude but opposite sign as that of **10**. In order to reconcile concerns about the influence of background dichroism from the remainder of the molecule, the CD spectrum of pure penta-*p*-bromobenzoate **8**

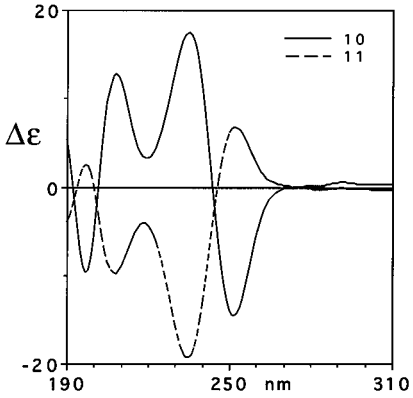


Figure 3. Circular dichroism spectra of tetra-*p*-bromobenzoates **10** and **11** in MeCN.

($C_{48}H_{33}N_2O_{12}Br_5$, HRFABMS found 1224.8029 (MH^+), Δmmu 1.9) was also measured. We were reassured to find the CD spectrum of **8** had essentially the same form as that of **10**, albeit with diminished magnitudes for the Cotton effects (λ 252 (Δε −2.7), 236 (+10.2), 208 (+8.7), 198 (−0.2) nm). The bengazole side chain is, thus, stereochemically related to D-fucose, and the complete absolute configuration of **1a** is now revealed as 2*R*,3*S*,4*R*,6*S*,10*S*. Given that the homologs **1b**−**g** produce only one bis(oxazole), the pentol **3,** upon ammoniolysis of the fatty acid side chains, the C2−6 configurations in all bengazoles A−G (**1a**−**g**) must be identical.[28]

Biological Activity. Bengazoles **1c**−**g** were approximately equipotent with **1a** and **1b** in agar disk diffusion antifungal assay against *C. albicans*. All gave zones of inhibition of 9−10.5 mm at 0.5 μg/disk. In broth dilution assays, bengazole E (**1e**) gave minimum inhibitory concentrations (MICs) of 1 μg/mL against *C. albicans* (c.f. amphotericin B, 0.3 μg/mL) and >100 μg/mL against *S. carlsbergensis*. The ergosterol-dependent activity of **1a,b** has already been described[14] and suggests a mode of action for bengazoles that is shared with amphotericin B. What remains is identification of the minimum pharmacophore of the bengazole structure that accounts for antifungal activity, although clearly the fatty acid side chain is important.[29]

Conclusion

The notable biological activity of alkaloids in the bengazole family and the need for sufficient quantities for SAR and *in vivo* studies makes these natural products important targets for total synthesis. The absolute configuration of C10 in **1a** is *S*, and the side chain configuration is 2*R*,3*S*,4*R*,6*S* by excition coupling of *p*-bromobenzoate derivatives. The latter approach now makes it a simple matter to confirm the side chain configuration of digonazole[16] and other bengazoles.[15] Synthesis of **17a** and **2** models a side chain synthesis of **1a**, with stereoselective control at C6, and presages our approach to the total synthesis of bengazole A based on oxazole C4 anion addition to the protected side chain precursor **16**.[30] We have embarked upon the completion

(28) We cannot, of course, rule out the very unlikely possibility of a partial racemate containing *ent*-**3** and, therefore, heterochirality in **1a**−**g**.

(29) Loss of the fatty acid side chain, e.g. **3**, renders deacyl bengazoles inactive against *C. albicans*.

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

of the synthesis of **1a** and will report our findings in due course.

Experimental Section

General. Unless otherwise stated all new compounds were purified to >95% as determined by NMR spectroscopy and HPLC or TLC. Optical rotations were measured on a digital spectropolarimeter. NMR spectra were recorded at 300 MHz for ^{1}H and 75.4 MHz for ^{13}C. ^{1}H and ^{13}C NMR spectra are referenced to residual CD_3OD signals at 3.30 and 49.00 ppm, $CDCl_3$ at 7.26 and 77.00 ppm, or $(CD_3)_2CO$ at 2.04 and 29.8 ppm, respectively. Mulitiplicities of ^{13}C spectra were assigned by DEPT experiments, and proton δ and J assignments were aided by interpretation of COSY experiments. Standard pulse sequences were employed for DEPT and magnitude COSY experiments. IR spectra were recorded on a Fourier transform instrument at 2 cm^{-1} resolution, and circular dichroism (CD) measurements were made on a recording spectropolarimeter interfaced to a microcomputer. UV spectra were recorded using a diode array spectrophotomer or an analytical HPLC with a diode array detector. Mass spectra were provided by the University of Minnesota, Chemistry Department Mass Spectrometry Service Laboratory. TLC was carried out on 0.2 mm silica gel plates impregnated with a fluorescent indicator and visualized under a UV lamp or with 1% vanillin/EtOH/H_2SO_4. All solvents were distilled in glass before use.

Collection and Extraction. The sponge *Jaspis* sp. (90-09-080) was collected in 1990 by hand using SCUBA at a depth of 10 m on the Great Barrier Reef, Australia, and frozen at −20 °C until required. Lyophilized animals (59.8 g) were extracted with MeOH (350 mL), homogenized in MeOH (2 × 500 mL), and filtered. The extracts were combined, concentrated to approximately 150 mL, and successively extracted as follows. The water content (% v/v) of the MeOH extract was adjusted prior to sequential partitioning against *n*-hexane (10% v/v H_2O), CCl_4 (20% v/v H_2O), and $CHCl_3$ (40% v/v H_2O). Both the CCl_4 (59.6 mg) and $CHCl_3$ (111.3 mg) extracts inhibited the growth of *C. albicans* and were combined. This material was purified by flash chromatography (silica gel, stepwise gradient elution $CHCl_3$/MeOH 99:1 to 1:1). After the elution of bengamides A and B,[31] fractions eluting with $CHCl_3$/MeOH 90:10 and 80:20 were found to be antifungal and exhibited sharp singlets due to oxazole and H10 protons in their ^{1}H NMR spectra at δ 7.0−9.0 suggestive of bengazoles. These combined fractions were purified on reversed phase cartridges (C_{18}, MeOH/H_2O 90:10) followed by HPLC (reversed phase, C_{18}, 5 μm, 300 × 10 mm, MeOH/H_2O 90:10, 3 mL/min) to afford the seven bengazoles A−G (**1a**−**g**, see Table 1).

Bengazole A (**1a**): UV (MeOH/H_2O 9:1) λ_{max} 217 nm; CD (MeOH) 202 nm ($\Delta\epsilon$ +3.89), 217 (0), 231 (−1.55); ^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) identical with reported values;[13] FABMS *m*/*z* 547 (M + Na^+, 15%), 525 (MH^+, 100); HRFABMS found 525.3149 (MH^+), $C_{27}H_{45}N_2O_8$ requires 525.3176.

Bengazole B (**1b**): UV (MeOH/H_2O 9:1) λ_{max} 217 nm; ^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) identical with reported values;[13] FABMS *m*/*z* 561 (M + Na^+, 15%), 539 (MH^+, 100); HRFABMS found 539.3305 (MH^+), $C_{28}H_{47}N_2O_8$ requires 539.3332. This sample of bengazole B was obtained as an inseparable 5/1 mixture of the *iso* and *anteiso* 15:0 fatty acid esters as shown by GCMS.

Bengazole C (**1c**): UV (MeOH/H_2O 9:1) λ_{max} 217 nm; IR (film) ν_{max} 3600−3100, 2955, 2925, 2855, 1750, 1110 cm^{-1}; ^{1}H NMR (CD_3OD) δ 0.89 (t, J = 7.0 Hz, 3H), 1.28 (m, 18H), all other signals identical to those for bengazole A; FABMS *m*/*z* 533 (M + Na^+, 6%), 511 (MH^+, 18); HRFABMS found 511.3019 (MH^+), $C_{26}H_{43}N_2O_8$ requires 511.3019.

Bengazole D (**1d**): UV (MeOH/H_2O 9:1) λ_{max} 217 nm; IR (film) ν_{max} 3600−3100, 2950, 2920, 2850, 1750, 1115 cm^{-1}; ^{1}H NMR (CD_3OD) δ 0.87 (d, J = 6.6 Hz, 3H), 1.28 (m, 16H), all other signals identical to those for bengazole B; FABMS *m*/*z* 547 (M + Na^+, 6%), 525 (MH^+, 38); HRFABMS found 525.3165 (MH^+), $C_{27}H_{45}N_2O_8$ requires 525.3176.

Bengazole E (**1e**): UV (MeOH/H_2O 9:1) λ_{max} 217 nm; IR (film) ν_{max} 3600−3100, 2955, 2920, 2860, 1750, 1110 cm^{-1}; ^{1}H NMR (CD_3OD) δ 0.89 (t, J = 7.0 Hz, 3H), 1.28 (m, 22H), all other signals identical to those for bengazole A; ^{13}C NMR (CD_3OD) δ 14.4, 19.9, 23.7, 25.8, 30.0, 30.3, 30.5, 30.6, 30.7, 30.8 (4 × CH_2), 33.1, 34.5, 40.4, 62.8, 66.2, 67.7, 71.2, 78.8, 127.5, 138.0, 145.6, 147.7, 154.4, 159.6, 173.3; FABMS *m*/*z* 561 (M + Na^+, 25%), 539 (MH^+, 100); HRFABMS found 539.3326 (MH^+), $C_{28}H_{47}N_2O_8$ requires 539.3332.

Bengazole F (**1f**): UV (MeOH/H_2O 9:1) λ_{max} 217 nm; IR (film) ν_{max} 3600−3100, 2955, 2925, 2855, 1750, 1110 cm^{-1}; ^{1}H NMR (CD_3OD) δ 0.88 (m, 6H), 1.28 (br s, 23H), all other signals identical to those for bengazole A; FABMS *m*/*z* 575 (M + Na^+, 8%), 553 (MH^+, 72); HRFABMS found 553.3481 (MH^+), $C_{29}H_{49}N_2O_8$ requires 553.3489.

Bengazole G (**1g**): UV (MeOH/H_2O 9:1) λ_{max} 217 nm; IR (film) ν_{max} 3600−3100, 2955, 2915, 2855, 1750, 1110 cm^{-1}; ^{1}H NMR (CD_3OD) δ 0.89 (t, J = 7.0 Hz, 3H), 1.28 (m, 24H), all other signals identical to those for bengazole A; FABMS *m*/*z* 575 (M + Na^+, 11%), 553 (MH^+, 68); HRFABMS found 553.3481 (MH^+), $C_{29}H_{49}N_2O_8$ requires 553.3489.

Methanolysis of Bengazoles. Samples (*ca*. 25 μg) of each of **1a**−**g** were dissolved in 5% HCl in MeOH (0.2 mL) and heated at 50 °C for 2 h and treated as follows. The solution was cooled, diluted with MeOH (1 mL), and extracted with $NaHCO_3$ (aqueous 7%) followed by *n*-hexane (3 × 1 mL). The combined *n*-hexane extracts containing fatty acid methyl esters (FAMEs) were dried (Na_2SO_4), and each sample was directly analyzed by GCMS (0.25 mm × 25 m capillary, 150 °C, 5 min; 150−250 °C at 4 °C/ min, He carrier, quadrupole EIMS detection). Eluted FAMEs were identified by single-ion monitoring of the prominent McLafferty rearrangement fragment peak (M − 74) and matching of retention times with a standard mixture of bacterial FAMEs (Supelco).

Bengazole Pentol (**3**). A solution of mixed bengazoles A−G (**1a**−**g**, 21.1 mg, obtained prior to HPLC, see isolation procedure, above) in methanol (2.0 mL) was treated with a saturated solution of ammonia in methanol (2.0 mL) and stirred at 25 °C under a nitrogen atmosphere for 1.5 h. Solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, $CHCl_3$/MeOH 4:1) to afford the pentol **3** as a colorless glass (12.1 mg, *ca*. 60%): $[\alpha]_D$ +2.0° (*c* 0.76, MeOH); UV (MeOH) λ_{max} 216 nm (ϵ 9960); IR (film) ν_{max} 3600−3100, 1105, 1065 cm^{-1}; ^{1}H NMR (CD_3OD) δ 1.15 (d, J = 6.5 Hz, 3H), 1.90 (ddd, J = 14.0, 9.6, 6.9 Hz, 1H), 2.25 (ddd, J = 14.0, 7.0, 2.7 Hz, 1H), 3.17 (dd, J = 6.9, 3.2 Hz, 1H), 3.64 (ddd, J = 9.6, 6.9, 2.7 Hz, 1H), 3.89 (qd, J = 6.5, 3.2 Hz, 1H), 4.91 (dd, 7.0, 6.9 Hz, 1H), 5.98 (s, 1H), 7.17 (s, 1H), 7.82 (d, J = 8.7 Hz, 2H), 8.20 (s, 1H); ^{13}C NMR (CD_3OD) δ 19.9 (q), 40.6 (t), 62.9 (d), 66.3 (d), 67.7 (d), 71.2 (d), 78.7 (d), 125.1 (d), 137.5 (d), 145.2 (s), 151.7 (s), 153.7 (d), 163.3 (s); HRFABMS found 315.1196 (MH^+), $C_{13}H_{19}N_2O_7$ requires 315.1192.

Bengazole A 2,3:4,6-Diacetonide (**4**). Bengazole A (**1a**, 15.7 mg) was treated with 2,2-dimethoxypropane (2.0 mL) and *p*-TSA (*ca*. 0.1 mg), and the solution was heated to 60 °C under a nitrogen atmosphere for 1 h. Evaporation under reduced pressure gave a yellow oil which was purified by column chromatography (silica gel, $CHCl_3$/MeOH 99:1) to afford the diacetonide **4** as a colorless oil (14.5 mg, 80%): IR (film) ν_{max} 1755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.0 Hz, 3H), 1.24 (m, 20H), 1.33 (d, J = 6.2 Hz, 3H), 1.36 (s, 3H), 1.40 (s, 3H), 1.43 (s, 3H), 1.52 (s, 3H), 1.60 (m, 3H), 2.12 (dt, J = 13.0, 2.5 Hz, 1H), 2.40 (t, J = 7.6 Hz, 2H), 3.44 (t, J = 7.3 Hz, 1H), 3.93 (ddd, J = 11.4, 7.2, 2.4 Hz, 1H), 4.00 (dq, J = 7.3, 6.2 Hz, 1H), 4.98 (dd, J = 11.8, 2.3 Hz, 1H), 7.07 (s, 1H), 7.23 (s, 1H), 7.61 (s, 3H), 7.89 (s, 1H); FABMS 605 (MH^+, 32%), 589 ($M^+ - CH_3$, 18), 547 (63), 531 (28); HRFABMS found 605.3817 (MH^+), $C_{33}H_{53}N_2O_8$ requires 605.3802.

10-Desacylbengazole 2,3:4,6-Diacetonide (5). A solution of the diacetonide **4** (14.3 mg) in methanol (1.0 mL) was treated with a saturated solution of ammonia in methanol (1.0 mL) and stirred at 25 °C under a nitrogen atmosphere for 3 h. Solvent was removed under reduced pressure, and the residue

(31) Quiñoà, E.; Adamczeski, M.; Crews, P.; Bakus, G. J. *J. Org. Chem*. **1986**, *51*, 4494−4497.

was purified by column chromatography (silica gel, $CHCl_3$/MeOH 99:1) to afford the C10 alcohol **5** as a colorless oil (8.1 mg, 87%): IR (film) ν_{max} 3500−3100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (d, J = 6.1 Hz, 3H), 1.36 (s, 3H), 1.40 (s, 3H), 1.43 (s, 3H), 1.54 (s, 3H), 1.69 (ddd, J = 13.0, 11.8, 11.4 Hz, 1H), 2.10 (ddd, J = 13.0, 2.5, 2.1 Hz, 1H), 3.44 (dd, J = 7.6, 7.2 Hz, 1H), 3.86 (br d, J = 5.8 Hz, 1H), 3.94 (ddd, J = 11.4, 7.2, 2.5 Hz, 1H), 4.00 (dq, J = 7.6, 6.1 Hz, 1H), 4.97 (dd, J = 11.8, 2.1 Hz, 1H), 5.98 (d, J = 5.8 Hz, 1H), 7.13 (s, 1H), 7.60 (s, 1H), 7.88 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.3 (q), 19.7 (q), 26.9 (q), 27.4 (q), 29.8 (q), 33.6 (t), 62.3 (d), 65.1 (d), 71.0 (d), 76.3 (d), 84.1 (d), 99.1 (s), 108.7 (s), 125.1 (d), 136.1 (d), 142.3 (s), 149.0 (s), 151.5 (d), 161.2 (s); FABMS m/z 395 (MH^+, 58%), 379 ($M^+ - CH_3$, 10), 337 (45), 279 (100), 261 (30); HRFABMS found 395.1800 (MH^+), $C_{19}H_{27}N_2O_7$ requires 395.1818.

Bengazole Acetonide 10-*O*-*p*-Bromobenzoate (6). A solution of **5** (7.9 mg) in pyridine (1.5 mL) was treated with *p*-bromobenzoyl chloride (100 μL) and DMAP (*ca*. 0.1 mg), and the solution was heated at 50 °C for 2 h. Pyridine was removed under high vacuum, and the residue was purified by preparative TLC (silica gel, 1 mm, $CHCl_3$/MeOH 96.5:3.5) to afford the *p*-bromobenzoyl derivative **6** as a colorless solid (8.2 mg, 71%): IR (film) ν_{max} 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (d, J = 6.0 Hz, 3H), 1.36 (s, 3H), 1.40 (s, 3H), 1.43 (s, 3H), 1.53 (s, 3H), 1.65 (ddd, J = 13.0, 11.4, 11.3 Hz, 1H), 2.13 (dt, J = 13.0, 2.5 Hz, 1H), 3.44 (t, J = 7.4 Hz, 1H), 3.94 (ddd, J = 11.4, 7.1, 2.5 Hz, 1H), 4.00 (dq, 7.4, 6.0 Hz, 1H), 4.99 (dd, J = 11.3, 2.5 Hz, 1H), 7.30 (s, 1H), 7.32 (s, 1H), 7.60 (d, J = 8.7 Hz, 2H), 7.65 (s, 1H), 7.93 (d, J = 8.7 Hz, 2H), 7.93 (s, 1H); FABMS m/z 579 (MH^+ + 2, 14%), 577 (MH^+, 13), 521 (18), 519 (20), 463 (30), 461 (32), 185 (95), 183 (100); HRFABMS found 577.1188 (MH^+), $C_{26}H_{30}N_2O_8Br$ requires 577.1186.

Bengazole Tetrol 10-*O*-*p*-Bromobenzoate (7). A solution of **6** in THF (1.0 mL) was treated with 50% aqueous acetic acid (1.6 mL) and heated to 60 °C under a nitrogen atmosphere for 19 h. The solution was evaporated to dryness under reduced pressure, and the residue was purified by column chromatography (silica gel, $CHCl_3$/MeOH 9:1) to afford the *p*-bromobenzoyl derivative **7** as a colorless solid (3.6 mg, 69%): IR (film) ν_{max} 3600−3100, 1730 cm^{-1}; ^1H NMR (CD_3OD) δ 1.11 (d, J = 6.6 Hz, 3H), 1.90 (ddd, J = 14.0, 9.7, 6.8 Hz, 1H), 2.23 (ddd, J = 14.0, 7.2, 2.7 Hz, 1H), 3.16 (dd, J = 6.7, 3.4 Hz, 1H), 3.65 (ddd, J = 9.7, 6.7, 2.7 Hz, 1H), 3.89 (qd, J = 6.6, 3.4 Hz, 1H), 4.92 (dd, 7.2, 6.8 Hz, 1H), 7.35 (s, 1H), 7.41 (s, 1H), 7.69 (d, J = 8.7 Hz, 2H), 7.88 (s, 1H), 7.95 (d, J = 8.7 Hz, 2H), 8.29 (s, 1H); FABMS m/z 499 (MH^+ + 2, 41%), 497 (MH^+, 42); HRFABMS found 497.0560 (MH^+), $C_{20}H_{22}N_2O_8Br$ requires 497.0559.

Bengazole Penta-*p*-bromobenzoate (8). A solution of **3** (5.3 mg) in pyridine (2.0 mL) was treated with *p*-bromobenzoyl chloride (*ca*. 16 mg) and DMAP (*ca*. 0.1 mg), and the solution was heated at 55 °C for 20 h. Excess *p*-bromobenzoyl chloride was quenched by the addition of 3-(*N*,*N*-dimethylamino)-propylamine (50 μL), and the reaction mixture was stirred for an additional 1 h. Pyridine was removed under high vacuum, and the residue was purified by column chromatography (silica gel, $CHCl_3$/MeOH 0.5%) to afford the penta-*p*-bromobenzoate **8** as a colorless solid (18.5 mg, 89%): CD (CH_3CN) 252 nm ($\Delta\epsilon$ −2.7), 246 (0), 236 (+10.2), 208 (+8.7), 200 (0), 198 (−0.2); IR (film) ν_{max} 1710, 1580, 1245, 1075, 1065, 1005, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (d, J = 6.4 Hz, 3H), 2.75 (m, 2H), 5.45 (m, 1H), 5.50 (qd, J = 6.4, 6.2 Hz, 1H), 5.63 (dd, J = 6.2, 4.2 Hz, 1H), 6.13 (dd, J = 7.8, 6.1 Hz, 1H), 7.25 (s, 1H), 7.32 (s, 1H), 7.44 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 8.6 Hz, 2H), 7.49 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 7.65 (d, J = 8.6 Hz, 2H), 7.68 (s, 1H), 7.72 (d, J = 8.6 Hz, 2H), 7.78 (d, J = 8.6 Hz, 2H), 7.82 (d, J = 8.6 Hz, 2H), 7.91 (d, J = 8.6 Hz, 2H); FABMS m/z 1224.8 (MH^+, 5%) 1024.8 ($M^+ - C_7H_4BrO_2$, 77%); HRFABMS found 1224.8010 (MH^+), $C_{48}H_{34}N_2O_{12}Br_5$ requires 1224.8029.

***(R)*- and *(S)*-MTPA Mosher Esters 9a and 9b**. Samples of alcohol **6** (*ca*. 1−2 mg) were acylated, separately, with (*R*)- and (*S*)-MTPA in the presence of DCC and DMAP in CH_2Cl_2 as described previously.[32] Purification of each crude product by chromatography (basic alumina, 1:5 to 1:1 EtOAc/*n*-hexane) gave (*R*)-MTPA ester **9a** (65%) and (*S*)-MTPA ester **9b** (46%, see Figure 2 for ^1H NMR $\Delta\delta$[18]). **Ester 9a:** HRFABMS found (MH^+) 611.2214, calculated for $C_{29}H_{33}N_2O_9F_3$ 611.2216. **Ester 9b**: HRFABMS found (MH^+) 611.2229, calculated for $C_{29}H_{33}N_2O_9F_3$ 611.2216.

Bengazole Tetra-*p*-bromobenzoate (10). The mixture of bengazoles A−G (1a−g, 2.0 mg) was converted to their corresponding tetra-*O*-*p*-bromobenzoates as described above for 8. Purification of the crude product by chromatography (silica gel, 75:25 *n*-hexane/EtOAc) gave tetra-*O*-*p*-bromobenzoate 10 as a mixture of fatty acid esters at *O*-C10 (1.2 mg, ∼25%) and as a colorless glass: CD (MeCN) 252 ($\Delta\epsilon$ −14.6), 246 (0), 235 (+17.4), 219 (+3.2), 208 (12.8), 200 (0), 197 (−9.8).

(1*R*,3*S*,4*R*,5*R*)1-Phenylhexane-1,3,4,5-tetrol Tetra-*O*-*p*-bromobenzoate (11). A solution of the tetrol **2** (5.0 mg, 0.022 mmol) in pyridine (3 mL) was treated with *p*-bromobenzoyl chloride (80 mg, 0.36 mmol) and 4-(*N*,*N*-dimethylamino)-pyridine (*ca*. 0.1 mg). After 18 h of stirring at 25 °C, 3-(*N*,*N*-dimethylamino)propylamine (800 μL) was added and stirring continued for a further 30 min. Pyridine was removed under high vacuum, and the residue was chromatographed on silica gel (hexane/EtOAc 9:1) to afford the tetra-*p*-bromobenzoate **11** as a colorless glass (19.2 mg, 91%): UV (MeCN) λ_{max} 244 nm (ϵ 70100); CD (MeCN) λ 252 ($\Delta\epsilon$ +6.5), 244 (0), 234 (−19.5), 207 (−9.8), 200 (0), 197 (+2.5); IR (film) ν_{max} 1710, 1590, 1266, 1099, 1011, 753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (d, J = 6.5 Hz, 3H), 2.42 (ddd, J = 14.6, 7.4, 2.6 Hz, 1H), 2.71 (ddd, J = 14.6, 9.6, 6.4 Hz, 1H), 5.43 (m, 2H), 5.62 (dd, J = 5.3, 4.8 Hz, 1H), 6.09 (dd, J = 7.4, 6.4 Hz, 1H), 7.24−7.34 (m, 5H), 7.46 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2H), 7.79 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 8.5 Hz, 2H); HRFABMS found 954.8815 (MH^+), $C_{40}H_{31}O_8Br_4$ requires 954.8752.

Benzyl L-Fucopyranoside (12) and Benzyl 3,4-Isopropylidene-L-fucopyranoside (13). A stirred suspension of L-fucose (2.00 g, 12.2 mmol) in benzyl alcohol (10 mL) was saturated with dry HCl gas (∼10 min), stirred for 3 h at 25 °C, and then allowed to stand at 4 °C for 16 h. The volatiles were removed under vacuum, and the residue was purified by column chromatography (silica gel, MeOH/$CHCl_3$ 1:19 to 1:9) to provide pure 1-*O*-benzyl-L-fucose (**12**, 2.48 g, 80%) as a viscous oil (5/1 mixture of β/α anomers, by ^1H NMR) which was used directly in the next step. Benzyl glycoside **12** was suspended in acetone (20 mL) and 2,2-dimethoxypropane (30 mL) and stirred with a catalytic amount of *p*-TSA. The mixture produced a homogeneous solution after 15 min. After 1.5 h, the mixture was concentrated and the residue was purified by chromatography (silica gel, ethyl acetate/hexane 1:1) to give 1-*O*-benzyl acetonide **13** as a viscous colorless oil (2.78, 97%) that was used directly in the next step.

Benzyl 2-Deoxy-3,4-isopropylidene-L-fucopyranoside (15). (i) A solution of the fucose derivative **13** (2.90 g, 9.85 mmol) in THF (20 mL) was added to a dispension of sodium hydride (0.59 g, 80% dispersion, 19.7 mmol) in THF (10 mL). Imidazole (20 mg) was added, and the mixture was stirred at 25 °C under nitrogen. After 30 min, carbon disulfide (4.5 mL, 75 mmol) was added and stirring continued (1 h). Methyl iodide (1.5 mL, 24 mmol) was then added, and after a further 15 min of stirring, the reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined, dried ($MgSO_4$) extracts were evaporated under reduced pressure to give the crude xanthate **14** (3.72 g, 98%), which was used directly in the next step.

(ii) The xanthate **14** (3.72 g, 9.69 mmol) was dissolved in dioxane (40 mL), triethylamine (14.9 mL, 107 mmol), and 50% aqueous hypophosphorous acid (5.0 mL, 48 mmol) under nitrogen. A 1 mL aliquot of a solution of AIBN (0.79 g, 4.84 mmol, in 5 mL dioxane) was added, and the reaction mixture was heated to reflux. Further 1 mL aliquots of AIBN solution were added until the reaction was complete by TLC (2.5 h).

(32) Searle, P. A.; Molinski, T. F. *Tetrahedron* **1994**, *50*, 9893−9908.

The reaction mixture was poured into water and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil. Purification by column chromatography on silica gel (hexane/EtOAc 9:1 to 7:3) gave the 2-deoxy compound **15** as a mixture of anomers (1.99 g, 74%), together with recovered starting material **14** (20%). A portion of the product was separated by preparative HPLC (Microsorb silica gel, hexane/EtOAc 8:2) to afford pure anomers, in order of elution, **15**β and **15**α.

(+)-1α-Benzyl-2-deoxy-3,4-isopropylidene-L-fucopyranose (15*β*): glass, $[\alpha]_D$ +46.3° (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 2984, 2937, 2871, 1380, 1368, 1244, 1218, 1085, 1027 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (d, J = 6.5 Hz, 1H), 1.34 (s, 3H), 1.49 (s, 3H), 1.80 (ddd, J = 14.9, 6.3, 3.9 Hz, 1H), 2.22 (ddd, J = 14.9, 5.1, 5.1 Hz, 1H), 3.92 (qd, J = 6.5, 2.0 Hz, 1H), 3.99 (dd, J = 7.1, 2.0 Hz), 4.48 (m, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.78 (d, J = 12.0 Hz, 1H), 5.03 (dd, J = 6.3, 5.1 Hz, 1H), 7.25−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.0 (q), 25.4 (q), 26.8 (q), 30.7 (t), 64.7 (d), 69.1 (t), 70.8 (d), 75.4 (d), 95.9 (d), 108.7 (s), 127.4 (d), 127.7 (2 × d), 128.3 (2 × d), 138.5 (s); HRCIMS found 279.1586 (MH^+), $C_{16}H_{23}O_4$ requires 279.1596.

(−)-1*β*-*O*-Benzyl-2-deoxy-3,4-isopropylidene-L-fucopyranose (15α): solid, $[\alpha]_D$ −80.3° (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 2983, 2935, 2902, 1379, 1360, 1215, 1124, 1063, 1041, 1027, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.45 (d, J = 6.6 Hz, 3H), 1.52 (s, 3H), 1.70 (ddd, J = 12.8, 9.8, 9.8 Hz, 1H), 2.09 (ddd, J = 12.9, 7.0, 2.0 Hz, 1H), 3.75 (qd, J = 6.6, 2.1 Hz, 1H), 3.83 (dd, J = 5.1, 2.1 Hz, 1H), 4.22 (ddd, J = 9.8, 7.0, 5.2 Hz, 1H), 4.39 (dd, J = 9.8, 2.0 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.91 (d, J = 12.0 Hz, 1H), 7.25−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.9 (q), 26.4 (q), 28.3 (q), 35.5 (t), 69.1 (d), 70.0 (t), 72.6 (d), 74.3 (d), 98.3 (d), 109.2 (s), 127.6 (d), 128.0 (2 × d), 128.3 (2 × d), 137.9 (s); HRCIMS found 279.1586 (MH^+), $C_{16}H_{23}O_4$ requires 279.1596.

2-Deoxy-3,4-isopropylidene-L-fucose (16). A solution of benzyl glycoside **15** (1.76 g, 6.32 mmol) in absolute EtOH (25 mL) was treated with Pearlman's catalyst (1.0 g) and stirred under a hydrogen atmosphere for 2 days. The suspension was then filtered through a short pad of diatomaceous earth, the pad was washed with EtOH, and the combined EtOH solutions were evaporated to give a yellow oil. Purification by column chromatography on silica gel ($CHCl_3$/MeOH 95:5) afforded the debenzylated product **16** as a mixture of anomers (0.92g, 77%) that was used immediately in the next step.

(1*R*,3*S*,4*R*,5*R*)-1-Phenyl-3,4-*O*-isopropylidenehexane-1,3,4,5-tetrol (17a) and (1*S*,3*S*,4*R*,5*R*) Isomer (17b). Phenyllithium (1.8 M solution in cyclohexane/diethyl ether, 6.0 mL, 10.8 mmol) was added slowly to a stirred solution of the sugar derivative **16** (406 mg, 2.16 mmol) in THF (10 mL) at −78 °C under nitrogen. The reaction mixture was stirred for 1 h at −78 °C and then at 0 °C for 2 h. A saturated ammonium chloride solution (10 mL) was added, and the reaction mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil. Purification by flash chromatography on silica gel (hexane/EtOAc 1:1) afforded a mixture of acetonides **17a** and **17b** as a colorless glass (496 mg, 86%). The ^1H NMR spectrum indicated a 2.4:1 ratio of **17a**:**17b**. An analytically pure sample of the major diastereomer was obtained by preparative HPLC (Microsorb silica gel, hexane/EtOAc 1:1), while the minor compound **17b** could only be obtained as an enriched mixture with **17a** (~60% purity).

Major diastereomer (17a): $[\alpha]_D$ −45.0° (*c* 1.0, MeOH); UV (MeOH) λ_{max} 207 nm (ϵ 8310); IR (film) ν_{max} 3450 (br), 2984, 1380, 1371, 1238, 1219, 1060, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (d, J = 6.2 Hz, 3H), 1.38 (s, 3H), 1.56 (s, 3H), 1.75 (ddd, J = 13.9, 4.5, 2.4 Hz, 1H), 2.12 (ddd, J = 13.9, 11.3, 8.5 Hz, 1H), 3.75 (qd, J = 6.2, 6.2 Hz, 1H), 3.85 (dd, J = 6.2, 6.0 Hz, 1H), 4.23 (ddd, J = 11.3, 6.0, 2.4 Hz, 1H), 4.90 (dd, J = 8.5, 4.5 Hz, 1H), 7.23−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.7 (q), 25.4 (q), 27.8 (q), 39.0 (t), 65.4 (d), 73.8 (d), 76.6 (d), 81.7 (d), 108.7 (s), 125.9 (2 × d), 127.6 (d), 128.4 (2 × d), 143.8 (s); HRCIMS found 284.1875 ($M + NH_4^+$), $C_{15}H_{26}NO_4$ requires 284.1862. **Minor diastereomer (17b):** ^1H NMR ($CDCl_3$) δ 1.15 (d, J= 6.2 Hz, 3H), 1.38 (s, 3H), 1.53 (s, 3H), 3.77 (m, 1H), 3.86 (m, 1H), 4.42 (ddd, J = 11.3, 6.0, 2.4 Hz, 1H), 4.98 (dd, J = 9.0, 3.2, Hz, 1H), 7.23−7.40 (m, 5H).

(1*R*,3*S*,4*R*,5*R*)-1-Phenylhexan-1,3,4,5-tetrol (2). A solution of the acetonide **17a** (28.6 mg, 0.107 mmol) in 50% aqueous THF (8 mL) was stirred with Dowex 50-X8 (H^+) ion-exchange resin. After 18 h, the resin was removed by filtration and washed with THF (5 mL) and water (1 mL). The combined filtrates were evaporated under reduced pressure, and the residue was chromatographed on a short column of silica gel (EtOAc) to afford the tetrol **2** as a colorless amorphous solid (20.6 mg, 85%), mp 85−87 °C (benzene): $[\alpha]_D$ +3.2° (*c* 1.0, MeOH); UV (MeOH) λ_{max} 207 nm (ϵ 8500); IR (film) ν_{max} 3500−3100 (br), 1062, 1005, 990, 698 cm^{-1}; ^1H NMR (CD_3OD) δ 1.10 (d, J = 6.5 Hz, 3H), 1.90 (ddd, J = 14.0, 9.7, 7.2 Hz, 1H), 2.06 (ddd, J = 14.0, 6.9, 2.6 Hz, 1H), 3.13 (dd, J = 6.9, 6.2 Hz, 1H), 3.57 (ddd, J = 9.7, 6.9, 2.6 Hz, 1H), 3.90 (qd, J = 6.5, 3.2 Hz, 1H), 4.90 (dd, J = 7.2, 6.9 Hz, 1H), 7.20−7.40 (m, 5H); ^{13}C NMR (CD_3OD) δ 19.8 (q), 43.2 (t), 67.6 (d), 71.6 (d), 74.1 (d), 78.8 (d), 127.4 (2 × d), 128.4 (d), 129.3 (2 × d), 146.0 (s); HRCIMS found 244.1554 ($M + NH_4^+$), $C_{12}H_{22}NO_4$ requires 244.1549. Anal. Calcd for $C_{12}H_{18}O_2$: C, 63.70; H 8.02. Found: C, 63.55; H, 7.99.

(1*R*,3*S*,4*R*,5*R*)-1-Phenyl-1,3:4,5-*O*-diisopropylidenehexane-1,3,4,5-tetrol (18). A solution of the tetrol **2** (4.9 mg, 0.022 mmol) in acetone (1 mL) was treated with 2,2-dimethoxypropane (1 mL) and *p*-TSA (*ca*. 0.1 mg). After 3 h of stirring at 25 °C, the reaction mixture was evaporated to dryness and the residue purified by flash chromatography (silica gel, hexane/EtOAc 1:1) to afford the diacetonide **18** as a colorless glass (4.9 mg, 74%): $[\alpha]_D$ +3.0° (*c* 0.33, MeOH); UV (MeOH) λ_{max} 207 nm (ϵ 8500); IR (film) ν_{max} 2989, 1379, 1200, 1168, 1103, 1066, 854, 699 cm^{-1}; ^1H NMR (acetone-d_6) δ 1.28 (d, J = 6.0 Hz, 3H), 1.29 (s, 3H), 1.30 (s, 3H), 1.40 (s, 3H), 1.45 (ddd, J = 12.9, 11.5, 11.5 Hz, 1H, H2β), 1.56 (s, 3H), 1.96 (ddd, J = 12.9, 2.5, 2.5 Hz, 1H, H2α), 3.37 (dd, J = 7.7, 7.0 Hz, 1H, H4), 3.99 (dq, J = 7.7, 6.0 Hz, 1H, H5), 4.08 (ddd, J = 11.5, 7.0, 2.5 Hz, 1H, H3), 5.04 (dd, J = 11.5, 2.5 Hz, 1H, H1), 7.21−7.42 (m, 5H); ^{13}C NMR (acetone-d_6) δ 19.5 (q), 20.1 (q), 27.2 (q), 27.7 (q), 30.4 (q), 37.5 (t), 71.4 (d), 71.9 (d), 76.7 (d), 85.1 (d), 99.4 (s), 108.9 (s), 126.6 (2 × d), 128.0 (d), 129.0 (2 × d), 143.8 (s); HRCIMS (NH_3) found 249.1486 ($MH^+ - C_3H_60$), $C_{18}H_{26}O_4$ requires 249.1491.

Acknowledgment. This research was supported by the NIH (AI-31660) and the UC Davis Committee on Research. We thank Dr. Dan Jones (University of California, Davis, Facility for Advanced Instrumentation) for assistance with the GCMS analysis, Mary Kay Harper (Scripps Institution of Oceanography) for taxonomic identification of the sponge, Dr. Ed Larka (University of Minnesota) for the high-resolution mass spectra, and Professor Barry Trost (Stanford) for useful comments regarding determination of C10 configuration in **1a**. T.F.M. gratefully acknowledges the receipt of an American Cyanamid Faculty Award.

Supporting Information Available: ^1H NMR spectra of **1**−**11**, **15** (α and β epimers), **17a**−**b** and **18**, ^{13}C NMR spectra of **1e**, **3**, and **17a,** and CD spectra of **1a** and **8** (29 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO952261A