Unusual Anthelminthic Oxazoles from a Marine Sponge

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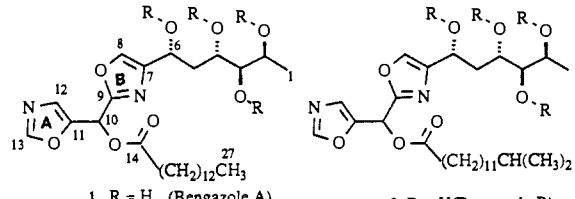
Abstract: Two heterocycles, bengazole A (**1**) and bengazole B (**2**), have been isolated from a Jaspidae Fiji sponge. These compounds contain bis(oxazole) rings, which is an uncommon natural product structural feature. They exhibit anthelminthic activity, and they fragment on standing to lactone **7** and mono(oxazole) **8**, which are devoid of anthelminthic activity but exhibit antimicrobial action. Lactone **7** was converted to dioxolane **9**, and the stereochemistry of the 2(*S**), 3(*R**), 4(*S**), 6-(*R**)-tetrahydroxyhexyl group, attached to the B oxazole ring of bengazoles A and B, was proposed from NOEs measured for **7**, from ^{1}H NMR *J*'s of **7**, from ^{1}H NMR *J*'s of **9** versus those calculated from dihedral angles obtained for energy-minimized structures of model compounds, and from ^{1}H NMR *J* comparisons to chiral carbohydrate models.

We have begun a program to study novel heterocycles from sponges of the Choristida order (=Astrophorida), as this group has received scant attention in the past.[1] We recently described the novel heterocycles bengamide A and bengamide B from an abundant undescribed orange sponge of the Jaspidae family,[2,3] and when additional amounts of these compounds were needed for pharmacological testing, a large re-collection of this sponge was obtained from new locations in the Benga Lagoon, Fiji, during July, 1986. Surprisingly, the methanol extracts of the new collection yielded two very unusual oxazoles, which were accompanied by just trace amounts of bengamides A and B. The chemistry and spectroscopic data in support of the novel oxazole structures are now presented along with their biotoxic properties.

The freshly collected sponge yielded, after being first immersed in CH_2Cl_2 and then CH_3OH, a viscous crude oil (14.07 g) in which bengazoles A and B could be directly seen by ^{13}C NMR. Their



1 R = H (Bengazole A)
3 R = Ac

2 R = H(Bengazole B)
4 R = Ac

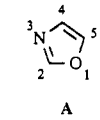
isolation was begun by solvent partitioning of the crude oil (11.9 g; aqueous methanol versus hexane, CCl_4, and then CH_2Cl_2), which concentrated the bengazoles in the CCl_4 (4.27 g) and the CH_2Cl_2 (2.66 g) fractions. These were separately chromatographed (flash column chromatography), and fractions displaying sharp, low-field ^{1}H NMR singlets (between δ 7.0 and 7.9) were further purified by preparative reversed-phase HPLC (10-μm ODS column; 15% aqueous MeOH) and yielded bengazoles A and B as oils.

The nearly identical NMR spectra for bengazoles A (**1**) and B (**2**) indicated they had analogous structural features. Minor, yet significant differences were observed in the upfield ^{1}H NMR region [**1**: δ 0.85 (t, J = 6.3 Hz, 3 H). **2**: δ 0.83 (d, J = 6.6 Hz, 6H)] and in the upfield ^{13}C NMR region [**1**: δ 32.0 (t), 22.7 (t), 14.2 (q). **2**: δ 39.1 (t), 28.0 (d), 22.7 (q), 22.7 (q)]. Structural elucidation was begun first on bengazole A, whose unsaturation number of 7 was obvious from the molecular formula obtained by DCI exact mass spectrometry ($M^+ + H$ = 525.3192 versus 525.3176 required for $C_{27}H_{45}O_8N_2$). The ester linkage was easily observed (^{13}C NMR, δ 172.2 (s), 61.4 (d)) and the intense mass spectral fragment m/z 297 indicated that it was a myristate. A 2,3,4,6-tetrahydroxyhexyl group was unmistakable by ^{1}H-^{1}H COSY NMR ($CDCl_3$) correlations beginning at δ 4.91 (br s, 1 H) and ending at δ 1.10 (d, J = 6.5 Hz, 3 H). Evidence for, respectively, a monosubstituted and disubstituted oxazole ring came from the characteristic NMR shifts and $^1J_{CH}$ values at C-7 (δ 144.2 (s)), C-8/H-8 (δ 136.3 (d, J = 212 Hz), 7.66 (s)), C-9 (δ 158.0 (s)), C-11 (δ 145.9 (s)), C-12/H-12 (δ 127.0 (d, J = 198 Hz), 7.21 (s)), C-13/H-13 (δ 152.3 (d, J = 234 Hz), 7.94 (s)). The preparation of tetracetyl bengazole A (**3**) confirmed that the ester was attached at C-10, and this was also deduced from a ^{13}C-^{1}H COSY (J = 9 Hz, MeOH-d_4, 75/300 MHz) spectrum (Table I) that exhibited correlations both from H-10 and from H-15 to the C=O. Other correlations obtained from this same spectra included from H-8 to C-7 and C-9, from H-10 to C-9, and to C-11, from H-13 to C-11 and to C-12, from H-12 to C-11 and to C-13. A ^{1}H-^{1}H long-range COSY[4] spectrum (MeOH-d_4, 300 MHz) revealed two key long-range correlations including from H-6 to H-8 and from H-10 to H-12.

Table I. Selected NMR COSY Data for Bengazole A (**1**)

^{13}C-^{1}H (CD_3OD) long range (J = 9 Hz)	^{1}H-^{1}H (CD_3OD) regular	^{1}H-^{1}H (CD_3OD) long range
C-2-H-1	H-1-H-2	H-6-H-8
C-3-H-1	H-2-H-3	H-10-H-12
C-4-H-5′	H-3-H-4	H-12-H-13
C-6-H-5, H-5′	H-4-H-5,5′	
C-7-H-8	H-5,5′-H-6	
C-9-H-8, H-10		
C-11-H-10, H-12, H-13		
C-12-H-13		
C-13-H-12		
C-14-H-10, H-15		
C-16-H-15		
C-25-long chain, H-27		
C-26-long chain, H-27		

It was now clear that the disubstituted oxazole was joined by C-10 to the monosubstituted oxazole, but the nature of the substitution pattern in the oxazole rings was still ambiguous. The possibilities to be reconciled included (a) a monosubstituted substructure A with substituents at position 4 or 5 and (b) a disubstituted substructure A with attachments at positions 2 and 4 or 2 and 5. Examples of both disubstitution patterns can be



A

^{13}C($CDCl_3$) δ = 150.6 (C-2), 125.4 (C-4), 138.1 (C-5)

(1) Examples of heterocyclic natural products from this group are as follows. Jasplakinolide (=Jaspamide) from *Jaspis sp*: (a) Crews, P.; Manes, L. V.; Boehler, M. *Tetrahedron Lett.* **1986**, *27*, 2797. (b) Zabriskie, T. M.; Klocke, J. A.; Ireland, C. M.; Marcus, A. H.; Molinski, T. F.; Faulkner, D. J.; Xu, C.; Clardy, J. *J. Am. Chem. Soc.* **1986**, *108*, 3123. Indole alkaloids from *Geodia baretti*: (c) Lidgren, G.; Bohlin, L.; Bergman J. *Tetrahedron Lett.* **1986**, *28*, 3283. Geodiamolides A and B from *Geodia sp*: (d) Chan, W. R.; Tinto, W. F.; Manchand, P. S.; Todaro, L. *J. Org. Chem.* **1987**, *52*, 3091.

(2) Quiñoà, E.; Adamczeski, M.; Crews, P. *J. Org. Chem.* **1986**, *51*, 4494.

(3) An underwater photograph of this sponge is available from P.C., and a taxonomic description is in ref 2.

(4) Hosur, R. V.; Chary, K. V. R.; Kumar, A.; Govil, G. *J. Magn. Reson.* **1985**, *62*, 123.

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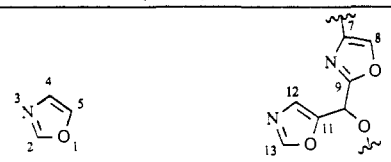
Table II. ^{13}C–^{1}H NMR J's (Hertz)

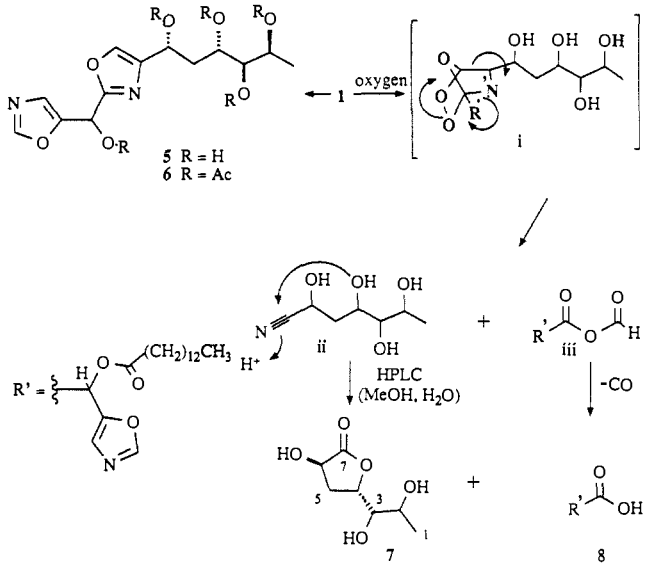


A[a]	1[b]
	$^{1}J_{CH}$
C(2)–H(2) ≈ 230	C(13)–H(13) = 233.6
C(4)–H(4) ≈ 194	C(12)–H(12) = 197.8
C(5)–H(5) ≈ 210	C(8)–H(8) = 211.7
	$^{2}J_{CH}$
C(4)–H(5) ≈ 16	C(7)–H(8) = 15.8
C(5)–H(4) ≈ 18	C(11)–H(12) = 18.4
	$^{3}J_{CH}$
C(2)–H(4) ≈ 11	C(13)–H(12) = 10.5
C(2)–H(5) ≈ 8	C(9)–H(8) = 7.2
C(4)–H(2) ≈ 9	C(12)–H(13) = 7.3
C(5)–H(2) ≈ 4	C(11)–H(13) = 4.4

[a] Reference 10. [b] This work.

found among known oxazole-containing natural products. For example, virginiamycin M_1,[5] from soil microorganisms, has a 2,4-disubstituted substructure A derived from an acylserine,[6] while kabiramide C, from marine animals, also possesses a 2,4-disubstituted substructure A, which may arise from a polyketide intermediate.[7] Alternatively, annuloline, from plants, has a 2,5-disubstituted substructure A, which may be formed from an amide.[8] A monosubstituted oxazole mold metabolite, conglobatin, has a 5-monosubstituted substructure A.[9] Comparison of the ^{13}C NMR δ's shown with structure A[10] with those of various phenyl- and methyl-substituted 1,3-oxazoles provides a simple way to determine when substituents are present at the C-4 or C-5 sites. A 2-alkyl or 2-aryl substituent imparts a deshielding of 2 ppm or less at C-4 or C-5.[11] Furthermore, the β substituent effect across a C-4···C-5 trisubstituted oxazole double bond results in a small shielding increment at the C(H) position of ≈0–6 ppm for a wide range of substituents,[10] analogous to what happens across a double bond in a benzene ring. Consequently, the ^{13}C shift at the protonated carbon of the C-4···C-5 bond in A bearing a single nonpolar substituent is predicted to occur over a very different range as follows: δ 127–119 at C(H)-4 with C(R)-5; δ 140–132 at C(H)-5 with C(R)-4. The relevant ^{13}C shifts in bengazole A are δ 127.0 (C-12) for the monosubstituted ring, and δ 136.3 (C-8) for the disubstituted ring, and these data require the substitution pattern proposed for the oxazole rings as shown in **1** and **2**.[12] Oxazole ring J_{CH} coupling constants are also diagnostic, as van Leusen[13] has observed that their magnitudes are virtually independent of substituent effects but are dependent on their position and coupling pathway. The patterns shown in Table II for oxazole A are based on data from a series of substituted oxazoles, and the similarities between these and the data for **1**, especially $^{1}J_{CH}$'s at C-8 and C-12, and $^{2}J_{CH}$'s at C-7 and C-11, also support the oxazole substructures proposed above for **1**.

Bengazole B (**2**) displayed NMR data almost identical with that of **1** with the exceptions discussed above. Both the ^{13}C NMR and mass spectral data ($C_{28}H_{46}O_8N_2$, LRCIMS $M^+ + H = 539$) are consistent with **2** differing from **1** by the replacement of the tridecanyl side chain with an isotetradecanyl group. Two additional synthetic transformations were carried out on the bengazoles. Acetylation of **2** gave the corresponding acetate **4**, while hydrolysis of **1** gave pentaol **5**, which was converted to pentacetate **6**.

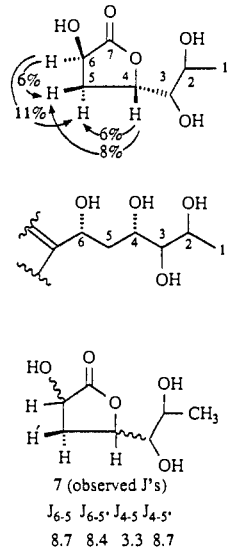


Concurrent with the above structural work were bioassay studies that revealed complete anthelminthic activity for bengazole A at a concentration of 50 μg/mL against *Nippostrongylus braziliensis*. However, reassay against *N. braziliensis* using a sample of bengazole A that had been stored at room temperature for 2 months as a neat oil revealed immensely diminished activity, while completely new antimicrobial activity was observed. Reexamination by ^{1}H NMR showed significant changes such as the δ 1.10 doublet for Me-1 was of reduced intensity, a new multiplet appeared as a shoulder at δ ≈1.14, the intensity of the triplet for H-15,15′ (δ 2.38) was reduced and a new triplet appeared at δ 2.31, and the intensities of the low-field resonances for the oxazole protons and for H-10 were changed. Analysis of this sample by HPLC (ODS, MeOH–H_2O) showed that bengazole A (minor component) was accompanied by two new compounds, a disubstituted aldono-1,4-lactone **7** and a monosubstituted oxazole **8**. Assay of these new compounds revealed that neither were active against *N. braziliensis*, whereas **7** was effective against *Candida albicans* and *Trichophyton mentagrophytes*, while **8** showed potency against *Streptococcus pyrogenes* and *Staphylococcus aureus*. These decomposition products undoubtedly arise from an endoperoxide intermediate by analogy to past observations of oxazole photooxygenations.[14] Such intermediates undergo facile fragmentation, and multiple pathways have been described.[14,15] The route shown here beginning with intermediate i is intended to illustrate one possible fragmentation path, and the products are ii, which lactonizes to **7** by a Pinner type reaction, and iii, which decarbonylates to give **8**.

The relative stereochemistry of the hydroxy substituents within the 2,3,4,6-tetrahydroxyhexyl group attached to the B oxazole ring of bengazoles A and B was assigned based on NOEs and ^{1}H NMR J's measured for **7** and ^{1}H NMR J's of the dioxolane **9**. Investigation of lactone **7** by difference NOE revealed enhancements shown in Chart I of 11% from H-6 to H-5, 6% from H-6

(5) For leading references and other examples, see: Myers, A. I.; Lawson, J. P.; Walker, D. G.; Linderman, R. J. *J. Org. Chem.* **1986**, *51*, 5111.
(6) Purvis, M. B.; Kingston, D. G. I.; Fujir, N.; Floss, H. G. *J. Chem. Soc., Chem. Commun.* **1987**, 302.
(7) Ishibashi, M.; Moore, R. E.; Patterson, G. M. L.; Xu, C.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5300.
(8) O'Donovan, D. J.; Horan, H. *J. Chem. Soc.* **1971**, 331.
(9) Wesley, J. M.; Liu, C.-M.; Evans, R. H.; Blount, J. F. *J. Antibiot.* **1979**, *32*, 874.
(10) Maryanoff, C. A. In *The Chemistry of Heterocyclic Compounds*; Turchi, I. J., Ed.; Wiley: New York, 1986; Vol. 45, Chapter 2.
(11) Based on data found in Table 2.3 of ref 10.
(12) The strategy of comparing these expectation ranges of ^{13}C NMR chemical shifts C(4)=C(5) in a 1,3-oxazole to determine the substitution position of a single substitution can be widely applied. For example, the ^{13}C shifts at the oxazole CH position in kabiramide C of 137.1, 136.8, and 135.5 ppm are consistent with the 2,4-disubstitution proposed[20] for each oxazole ring.
(13) Hiemstra, H. Houwing, H. A.; Possel, O.; van Leusen, M. *Can. J. Chem.* **1979**, *57*, 3168.
(14) Lakhan, R.; Ternai, B. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic: New York, 1974; Vol. 17, pp 192–195.
(15) Wasserman, H. H.; McCarthy, K. E.; Prowse, K. S. *Chem. Rev.* **1986**, *86*, 845.

Chart I. Observed NOE's



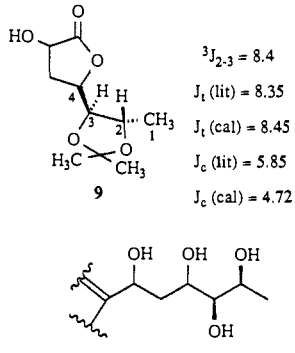
7 (observed J's)

J_{6-5}	$J_{6-5'}$	J_{4-5}	$J_{4-5'}$
8.7	8.4	3.3	8.7

J's from MM2 calculations

TRANS ISOMER				CIS ISOMER			
J_{6-5}	$J_{6-5'}$	J_{4-5}	$J_{4-5'}$	J_{6-5}	$J_{6-5'}$	J_{4-5}	$J_{4-5'}$
8.3	8.5	1.7	8.7	8.2	8.8	11.0	5.4
[30°]	[151°]	[95°]	[24°]	[32°]	[153°]	[158°]	[36°]
E = 13.39 Kcal/mol				E = 13.79 Kcal/mol			

Chart II



$^3J_{2-3}$ = 8.4
J_t (lit) = 8.35
J_t (cal) = 8.45
J_c (lit) = 5.85
J_c (cal) = 4.72

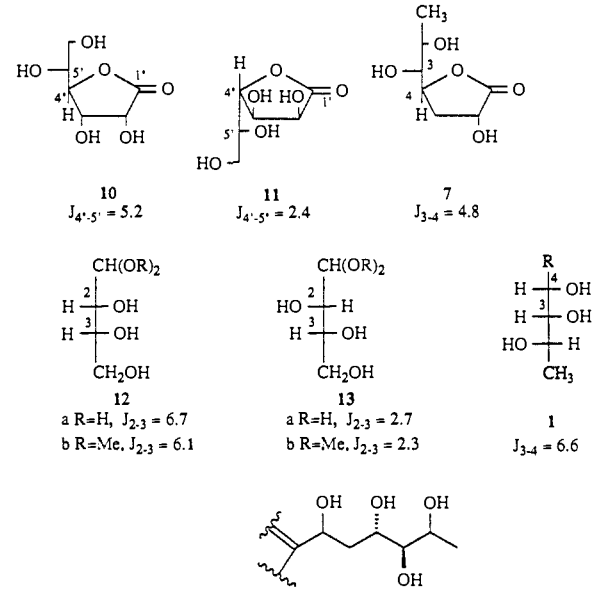
to H-5′, 8% from H-4 to H-5′, and 6% from H-4 to H-5. This suggested their relative 4*S**,6*R** stereochemistry shown for the tetrahydroxyhexyl group. The same relative stereochemistry was predicted by comparing experimental and calculated vicinal ^{1}H NMR couplings. Dihedral angles estimated from the energy-minimized conformations of *cis*- and *trans*-lactones **7** were used to obtain calculated couplings. The ability of PCMODEL[16] MM2 calculations to produce meaningful ^{1}H–^{1}H ^3J's for five-membered lactones was first tested by calculating dihedral angles and J's for several known carbohydrate aldono-1,4-lactones, and the agreement with experimental data was excellent.[17] The J's and dihedral angles predicted on the basis of our calculations are summarized in Chart I, and the couplings from H-4 to H-5,5′ were especially diagnostic of the relative geometry of the C-4 and C-6 substituents. An analogous approach, but focusing on the ^{1}H–^{1}H ^3J's of the dioxolane ring in **9**, supported the relative 2*S**,3*R** stereochemistry shown at C-2 and C-3 in Chart II for the tetrahydroxyhexyl group. The pattern of J's calculated from energy minimization of *cis*- and *trans*-2,2,4,5-tetramethyldioxolanes closely matched those that were actually measured by Anet.[18] Thus, the stereochemical assignment based on the $^3J_{2-3}$ = 8.4 Hz of **9** is unambiguous. Alternatively, it was not possible to directly

(16) Obtained from Serena Software, P.O. Box 3076, Bloomington, IN 47402-3076.

(17) Angelotti, T.; Krisko, M.; O'Connor, T.; Serianni, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 4464.

(18) Anet, F. A. L. *J. Am. Chem. Soc.* **1962**, *84*, 747.

Chart III



resolve the problem of the relative erythro or threo stereochemistry across C-3···C-4 in **1** or **2**, but comparisons of our experimental ^{1}H J's with those of erythro and threo carbohydrate models support our assignment as erythro. The J_{3-4} = 4.8 Hz (D_2O) of **7** can be compared with that at the erythro or threo vicinal protons H-4′/H-5′ of, respectively, the allono (**10**; J = 5.2 Hz (D_2O)) and the talono (**11**; J = 2.4 Hz (D_2O)) diastereomers[17] shown in Chart III. Likewise, the J_{3-4} = 6.6 Hz (MeOH-d_4) of **1** can be compared with that of the epimeric pair erythrose (**12**; J = 6.7 or 6.1 Hz (D_2O)) and the threose (**13**; J = 2.7 or 2.3 Hz (D_2O)) of Chart III.[19] Accordingly, the very close agreement between the erythro chiral models and our compounds supports the assignment of the relative stereochemistry of the 2,3,4,6-tetrahydroxyhexyl as 2*S**,3*R**,4*S**,6*R**.

The bengazoles are among the first oxazole-containing metabolites to be isolated from a marine sponge,[20d] and the geminal arrangement of the two oxazole groups and the carbohydrate appendage in **1** and **2** are unprecedented natural product structural features. The bis(oxazole) array is in contrast to the three contiguous oxazole rings that are a part of a macrocyclic ring in ulapualides A and B obtained from *Hexabranchus sanguineus* egg masses,[20a] kabiramide C isolated from unidentified egg masses[20b] and the sponge *Halichondria sp.*,[20c] and halichondramide from the sponge *Halichondria sp.*.[20c]

Experimental Section

The NMR spectra were recorded on a JEOL FX-100 PFT spectrometer (99.5 MHz for ^{1}H, 25.0 MHz for ^{13}C) or on a GN-300 spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C). Multiplicities of ^{13}C NMR peaks were determined from APT or DEPT data, and COSY experiments were done on the GN-300. Electron impact mass spectrometry data were obtained on a Finnigan 4000 (6000 LS7 computer system). High-resolution mass spectral data were obtained from the UC Berkeley MS laboratory on a Kratos MS-50 spectrometer. High-performance liquid chromatography (HPLC) was done on a Waters ALC-201, using columns that include a Waters μ-Porasil, Whatman Partisil, Rainin Microsorb C-18, or a Regis 10-μm ODS. All solvents were distilled and dried for HPLC use and were spectral grade for spectroscopy. Rotations were measured on a Perkin-Elmer 141 polarimeter.

Two-Dimensional NMR Procedures. Standard pulse sequences[21] were used for the homo COSY (ref 21b, Figure 37) and the hetero COSY (ref 21b, Figure 35) experiments.

(19) Serianni, A. S.; Barker, R. *J. Org. Chem.* **1984**, *49*, 3292.

(20) (a) Roesener, J. A.; Scheuer, P. J. *J. Am. Chem. Soc.* **1986**, *108*, 846. (b) Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Koeski, K.; Noma, M. *J. Am. Chem. Soc.* **1986**, *108*, 847. (c) Kernan, M. R.; Faulkner, D. J. *Tetrahedron Lett.* **1987**, *28*, 2809. (d) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Fujita, S.; Furuya, T. *J. Am. Chem. Soc.* **1986**, *108*, 2780.

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Isolation Procedures. The fresh Jaspidae sponge (13.7-kg wet weight) was cut into small pieces and soaked with CH_2Cl_2 for 24 h. The solvent was decanted and the oil concentrated. Next, the sponge was soaked with MeOH for 24 h. Similarly, the solvent was decanted and the oil concentrated to yield 14.07 g of crude viscous oil. Bengazoles A (**1**) and B (**2**) were the major components in the extract as detected by ^{13}C NMR. A portion of the crude oil (11.88 g) was then successively partitioned between equal volumes (500 mL of aqueous MeOH, percent adjusted to produce a biphase solution) and a solvent series of hexanes (5.3 g), CCl_4, (4.27 g), and CH_2Cl_2 (2.66 g). Both the CCl_4 and the CH_2Cl_2 partition fractions were then separately chromatographed (normal-phase flash column chromatography) with MeOH–CH_2Cl_2 in a ratio of 5:95 with successive increases in MeOH until pure MeOH was attained. The fractions containing compounds of similar polarity were monitored by TLC and NMR. The fractions that displayed sharp, low-field signals in the ^1H NMR spectra were combined and further purified via preparative reversed-phase HPLC (10-μm ODS column; solvent, MeOH–H_2O, 85:15) to yield (percents based on the crude oil) bengazoles A (**1**; 1.3%; of shorter retention time) and B (**2**; 1.1%).

Bengazole A (1). Viscous oil. $[\alpha]^{20}D$ +5.0° (*c* 0.107, MeOH). IR (neat): 3600–3100, 1750, 1500 cm^{-1}. UV, λ_{max} (MeOH): 209 nm (ϵ 1400). NMR shifts (δ) from Me_4Si, assignments based on assessing the number of attached protons and the COSY data in Table I [[atom number], ^{13}C δ's at 75 MHz, 7.2, δ's at 300 MHz, (*J*'s (hertz) at 300 MHz)]: (MeOH-d_4) [1] 19.9, 1.13 (d, *J* = 6.6, Me); [2] 67.7, 3.90 (dq, *J* = 6.6, 3.6); [3] 78.8, 3.16 (dd, *J* = 6.6, 3.3); [4] 71.7, 3.65 (ddd, *J* = 6.6, 6.0, 2.4); [5] 40.4, 2.22 (ddd, *J* = 14.1, 7.2, 2.7), 1.88 (ddd = 14.1, 10.1, 6.0); [6] 66.2, 4.88 (dd, *J* = 10.1, 7.2); [7] 145.6; [8] 138.0, 7.84 (s); [9] 159.6; [10] 62.8, 7.10 (s); [11] 147.6; [12] 127.5, 7.30 (s); [13] 154.4, 8.24 (s); [14] 173.3; [15] 34.4, 2.41 (t, *J* = 7.2, 2 H); [16] 25.8, 1.61 (t, *J* = 6.3, 2 H); [17–24] 30.8–30.0, 1.2–1.4 (m, 16 H); [25] 33.1, ≈1.3 (m, 2 H); [26] 23.8, ≈1.3 (m, 2 H); [27] 14.5, 0.87 (t, *J* = 6.3, Me); ($CDCl_3$) [1] 19.4, 1.10 (d, *J* = 6.5, Me); [2] 66.8, 3.91 (br s); [3] 77.2, 3.28 (br s); [4] 72.2, 3.91 (br s); [5] 38.4, 2.05 (m), 1.95 (m); [6] 66.4, 4.91 (br s); [7] 144.2; [8] 136.3, 7.66 (s); [9] 158.0; [10] 61.4, 7.04 (s); [11] 145.9; [12] 127.0, 7.21 (s); [13] 152.3, 7.94 (s); [14] 172.2; [15] 33.8, 2.38 (t, *J* = 7.2, 2 H); [16] 24.7, 1.60 (p, *J* = 6.6, 2 H); [17–24] 29.9–29.0, 1.3–1.2 (m, 16 H); [25] 32.0, ≈1.3 (m, 2 H); [26] 22.7, ≈1.3 (m, 2 H); [27] 14.2, 0.85 (t, *J* = 6.3, Me). LRCIMS (CH_4) *m/z* (rel intens): 553 [M^+ + 29 (5)], 525 [M^+ + H) (23)], 524 [M^+ (3)], 507 [M^+ + H – H_2O (9)], 489 [507 – H_2O (3)], 473 [M^+ – $2H_2O$ – CH_3 (8)], 449 (M^+ – $C_3H_7O_2$ (1)], 325 [M^+ + H – $C_{13}H_{27}$ – OH (28)], 307 [325 – H_2O (50)], 297 [M^+ + H – $C_{14}H_{28}O_2$ (100)], 279 (297 – H_2O (65)], 261 [279 – H_2O (30)], 229 [$C_{14}H_{28}O_2$ + H (40), myristic acid]; LREIMS *m/z* (rel intens) 524 [M^+ (5)], 507 [M^+ + H – H_2O (9)], 473 [M^+ – $2H_2O$ – CH_3 (7)], 449 [M^+ – $C_3H_7O_2$ (15)], 431 (449 – H_2O (5)], 406 [M^+ + H – $C_5H_{11}O_3$ (12)], 324 [M^+ H – $C_{13}H_{27}$ – H_2O (50)], 307 [324 – OH (68)], 297 [M^+ – $C_{14}H_{28}O_2$ (100)], 279 [297 – H_2O (90)].

Bengazole B (2). Viscous oil. $[\alpha]^{20}D$ = +4.7° (*c* 0.024, MeOH). IR (neat): 3600–3100, 1750, 1550 cm^{-1}. UV (MeOH): 209 nm (ϵ 1400). NMR shifts (δ) from TMS, assignments as described above (see Table I) [[atom number], ^{13}C δ's at 75 MHz, ^1H δ's at 300 MHz (*J*'s (hertz) at 300 MHz)]: ($CDCl_3$) [1] 19.5, 1.10 (d, *J* = 6.5, Me); [2] 66.8, 3.95 (br s); [3] 76.9, 3.30 (br s); [4] 72.5, 3.95 (br s); [5] 36.7, 1.22 (m, 2 H); [6] 66.6, 4.92 (br s); [7] 144.2; [8] 136.2, 7.66 (s); [9] 158.0; [10] 61.4, 7.04 (s); [11] 145.8 ; [12] 127.0, 7.20 (s); [13] 152.2, 7.93 (s); [14] 172.1; [15] 33.8, 2.38 (t, *J* = 7.5, 2 H); [16] 24.7, 1.60 (p, *J* = 6.6, 2 H); [17–23] 29.9–29.0, 1.4–1.1 (m, 14 H); [24] 27.4, ≈1.3 (m, 2 H); [25] 39.1, ≈1.3 (m, 2 H); [26] 28.0, ≈1.3 (m, 1 H); [27], 22.7, 0.83 (d, *J* = 6.6, Me); [28] 22.7, 0.83, (d, *J* = 6.6, Me). LRCIMS (CH_4) *m/z* (rel intens): 567 [M^+ + 29 (3)], 539 [M^+ + H (5)], 538 [M^+ (1)], 521 [M^+ + H – H_2O (4)], 487 [M^+ – 2 H_2O – CH_3 (2)], 325 [M^+ + H – $C_{14}H_{29}$ – OH (9)], 307 [325 – H_2O (20)], 297 [M^+ + H – $C_{15}H_{30}O_2$ (100)], 279 [297 – H_2O (63)], 243 [$C_{15}H_{30}O_2$ + H (30)]; LREIMS *m/z* (rel intens) 538 [M^+ (2)], 521 [M^+ + H – H_2O (3)], 487 [M^+ – $2H_2O$ – CH_3 (1)], 463 [M^+ – $C_3H_7O_2$ (3)], 420 (M^+ + H – $C_5H_{11}O_3$ (4)], 324 [M^+ + H – $C_{14}H_{29}$ – H_2O (20)], 307 [324 – OH (26)], 297 [M^+ + H – $C_{15}H_{30}O_2$ (100)], 279 [297 – H_2O (95)].

Acetylation of Bengazole A (1). A solution of **1** (19 mg) in dry pyridine (0.5 mL) and acetic anhydride (0.5 mL) at room temperature was placed in the dark under nitrogen for 48 h. The reaction mixture was concentrated in vacuo, and the residue was chromatographed via reversed-phase HPLC (MeOH–H_2O, 95:5) to afford tetracetate **3** in 85% yield. NMR ($CDCl_3$) shifts (δ) from TMS (see Table I) [[atom number], ^1H δ's at 300 MHz (*J*'s (hertz) at 300 MHz)]: [1] 1.11 (d, *J* = 6.3, Me); [2] 5.07 (m), [3] 4.84 (m); [4] 5.07 (m); [5] 2.24 (m); [6] 5.75 (dd, *J* = 9.0, 5.4); [8] 7.65 (s); [10] 7.07 (s); [12] 7.26 (s); [13] 7.91 (s); [15] 2.41 (t, *J* = 7.5); [16] 1.64 (p, *J* = 6.9); [17–24] 1.2–1.4 (m, 16 H); [25] ≈1.3 (m, 2 H); [26] ≈ 1.3 (m, 2 H); [27] 0.87 (t, *J* = 6.3, Me); [OAc] 2.11 (s, Me), 2.05 (s, Me), 2.00 (s, Me), 1.98 (s, Me). LRCIMS (CH_4) *m/z* (rel intens): 721 [M^+ + 29 (2)], 693 [M^+ + H (4)], 633 [M^+ + H – AcOH (20)], 465 [693 – $C_{14}H_{28}O_2$ (78)], 422 [465 – Ac (20)], 405 [465 – AcOH (15)], 363 [422 – AcOH+H (26)], 345 [405 – AcOH (4)], 302 [363 – AcOH – H (15)], 285 [345 – AcOH (4)], 243 [302 – AcOH+H (30)], 229 [$C_{14}H_{28}O_2$ + H (100)]. LREIMS *m/z* (rel intens) 692 [M^+ (4)], 633 [M^+ + H – AcOH (3)], 590 [633 – Ac (3)], 572 [633 – AcOH – H (5)], 512 [572 – AcOH (2)], 482 [M^+ + H – $C_{14}H_{27}O$ (5)], 465 [M^+ + H – $C_{14}H_{28}O_2$ (25)], 422 [482 – AcOH (50)], 406 [465 – AcOH + H (24)], 362 [422 – AcOH (50)], 346 [406 – AcOH (8)], 302 [362 – AcOH (50)], 242 [302 – AcOH (100)].

Acetylation of Bengazole B (2). In the same manner as above, a solution of **2** (10 mg) was acetylated to afford tetracetate **4** in 87% yield. NMR shifts (δ) from TMS (see COSY data in Table I) [[atom number], ^1H δ's at 300 MHz, (*J*'s (hertz) at 300 MHz)]: $CDCl_3$ [1] 1.11 (d, *J* = 6.6, Me); [2] 5.08 (m), [3] 4.84 (m); [4] 5.08 (m); [5] 2.22 (m); [6] 5.75 (dd, *J* = 9.0, 5.4); [8] 7.66 (s); [10] 7.08 (s); [12] 7.25 (s); [13] 7.91 (s); [15] 2.41 (t, *J* = 7.8); [16] 1.64 (m); [17–24] 1.2 – 1.4 (m, 16 H); [25] ≈1.3 (m, 2 H); [26] ≈1.3 (m, 1 H); [27] 0.85 (d, *J* = 6.6, Me); [28] 0.85 (d, *J* = 6.6 Me); [OAc] 2.11 (s, Me), 2.05 (s, Me), 2.00 (s, Me), 1.98 (s, Me). $C_{36}H_{54}O_{12}N_2$ LRCIMS (CH_4) *m/z* (rel intens): 707 [M^+ + H (1)].

Hydrolysis of Bengazole A (1). A solution of **1** (15 mg) in 1% MeOH–KOH (1 mL) was placed in the dark, under nitrogen for 48 h. After being neutralized with a 1% solution of HCl, the mixture was partitioned between H_2O (5 mL) and CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated to dryness to obtain myristic acid (identified by its characteristic ^1H NMR, IR, MS), identical with those of an authentic sample. The aqueous extract was concentrated in vacuo and the residue extracted with a 50% mixture of MeOH and CH_3CN to yield after filtration and concentration an 82% yield of the pure hydrolyzed product **5**. NMR (50% CD_3OD–CD_3CN) shifts (δ) from Me_4Si [[atom number], ^1H δ's at 300 MHz (*J*'s (hertz) at 300 MHz)]: [1] 1.09 (d, *J* = 6.6, 3 H); [2] 3.86 (dq, *J* = 6.3, 3.3); [3] 3.12 (dd, *J* = 6.6, 2.7); [4] 3.64 (ddd, *J* = 9.0, 7.2, 3.0), [5] 2.12 (ddd, *J* = 15.6, 5.7, 3.3), 1.82 (ddd, *J* = 14.1, 9.0, 5.7); [6] 4.85 (dd, *J* = 5.7, 5.7; [8] 7.80 (s); [10] 6.00 (s); [12] 7.28 (br s); [13] 8.34 (br s). $C_{13}H_{18}O_7N_2$ LREIMS *m/z* (rel intens): 314 [M^+ (9)], 296 [M^+ – H_2O (2)], 278 [296 – H_2O (2)], 269 [M^+ – C_2H_5O (3)], 251 [269 – H_2O (7)], 239 [M^+ – $C_3H_7O_2$ (100)], 221 [239 – H_2O (11)], 209 [M^+ – $C_4H_9O_3$ (26)], 196 [M^+ – $C_5H_{11}O_3$ + H (49)], 100 [$C_4H_6O_2N$ (40)].

Acetylation of 5. In the same manner as above, a solution of **5** (5 mg) was acetylated to afford the pentacetate **6** in a yield of 78%. NMR (CD_3OD) shifts (δ) from Me_4Si [[atom number], ^1H δ's at 300 MHz (*J*'s (hertz) at 300 MHz)]: [1] 1.11 (d, *J* = 6.3, 3 H); [2] 5.06 (m); [3] 4.86 (under solvent peak); [4] 5.06 (m); [5] 2.31 (m), 2.21 (m); [6] 5.76 (dd, *J* = 8.5, 5.6); [8] 7.92 (s); [10] 7.10 (s); [12] 7.32 (s); [13] 8.27 (s); [OAc] 2.14 (s, Me) 2.09 (s, Me), 2.02 (s, Me), 1.96 (s, Me), 1.94 (s, Me). $C_{23}H_{28}O_{12}N_2$ LRCIMS (CH_4) *m/z* (rel intens) 553 [M^+ + 29 (4)], 525 [M^+ + H (3)].

Fragmentation Products. After 2 months of being stored as a neat oil, bengazole A was chromatographed via reversed-phase HPLC (10-μm ODS column; solvent, MeOH–H_2O, 80:20) to afford bengazole A (12% of the original weight) along with two new compounds, identified as **7**, as disubstituted lactone, and **8**, a monosubstituted oxazole. A parallel study of a sample of bengazole B showed that it also had undergone a similar process.

Disubstituted Lactone 7. $[\alpha]^{20}D$ –5.2° (*c* 0.039, MeOH). IR (neat): 3600–3200, 1770 cm^{-1}. NMR (CD_3OD) shifts (δ) from Me_4Si [[atom number], ^1H δ's at 300 MHz (*J*'s (hertz) at 300 MHz)]: [1] 19.9, 1.19 (d, *J* = 6.6, 3 H); [2] 68.4 (*), 3.75 (dq, *J* = 4.5, 6.3); [3] 79.9, 3.48 (dd, *J* = 4.2, 4.5); [4] 76.7, 4.65 (ddd, *J* = 3.3, 4.2, 8.7); [5] 32.9, 2.68 (ddd, *J* = 3.3, 8.7, 14.8), 2.13 (ddd, *J* = 8.4, 8.7, 14.8); [6] 68.3 (*), 4.54 (dd, *J* = 8.4, 8.7); [7] 179.6 [(*) interchangeable]. $C_7H_{12}O_5$ LRCIMS (CH_4) *m/z* (rel intens): 177 [M^+ + H (22)], 159 [177 – H_2O (9)], 141 [159 – H_2O (18)], 131 [159 – CO (74)], 114 [131 – OH (100)].

Monosubstituted Oxazole 8. NMR (CD_3OD) shifts (δ) from Me_4Si [atom number], ^{13}C δ's at 75 MHz, ^1H δ's at 300 MHz (*J*'s (hertz) at 300 MHz)]: [9] 171.7; [10] 68.4, 6.01 (s); [11] 149.9; [12] 126.0, 7.15 (s); [13] 153.3, 8.15 (s); [14] 174.1; [15] 34.5, 2.43 (m), 2.37 (m); [16] 25.6, 1.61 (t, *J* = 6.3, 2 H); [17–24] 30.6–29.9, 1.2–1.4 (m, 16 H); [25] 32.8, ≈1.3 (m, 2 H); [26] 23.5, ≈1.3 (m, 2 H); [27] 14.2, 0.87 (t, *J* = 6.3, 3 H). $C_{19}H_{31}O_5N$ LRCIMS (CH_4) *m/z* (rel intens) 382 [M^+ + 29 (1)], 354 [M^+ + H (6)], 353 [M^+ (2)], 310 [M^+ + H – CO_2 (3)], 229 [$C_{14}H_{28}O_2$ + H (35)], 211 [$C_{14}H_{27}O$ (32)], 144 [M^+ – $C_{14}H_{27}O$ + 2H (40)], 126 [M^+ – $C_{14}H_{27}O_2$ (75)], 59 [$C_2H_3O_2$ (100)]; LREIMS 353 [M^+ (4)], 335 [M^+ – H_2O (3)], 309 [M^+ – CO_2 (5)], 229 [$C_{14}H_{28}O_2$ + H (18)], 211 [$C_{14}H_{27}O$ (25)], 143 [M^+ – $C_{14}H_{27}O$ + H (100)], 127 [M^+ – $C_{14}H_{27}O_2$ + H (40)].

Preparation of Dioxolane 9. The lactone **7** (25 mg) with 2 equiv of 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid in dry *N*,*N*-dimethylformamide (2 mL) was allowed to stand under a nitrogen atmosphere at room temperature for 48 h. After the mixture was neutralized with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 5 mL), the combined organic layers were concentrated to dryness (temperature below 40 °C) in vacuo and chromatographed (reversed-phase HPLC; 10-μm ODS column; solvent, MeOH–H_2O, 45:55), 24% of the starting material **7** and 41% of the ketal **9** were afforded. $[\alpha]^{20}D$ = −5.5° (*c* 0.0061, MeOH). IR (neat): 3600–3200, 1770 cm^{-1}. NMR ($CDCl_3$) shifts (δ) from Me_4Si [[atom number], ^{13}C δ's at 75 MHz, ^1H δ's at 300 MHz (*J*'s (hertz at 300 MHz)]: [1] 18.3, 1.34 (d, *J* = 6.0); [2] 74.6, 3.88 (dq, *J* = 8.4, 6.0); [3] 82.6, 3.72 (dd, *J* = 8.4, 4.5); [4] 76.6, 4.54 (ddd, *J* = 8.7, 4.5, 2.4); [5] 31.6, 2.62 (ddd, *J* = 15.3, 8.7, 2.4), 2.31 (ddd, *J* = 15.3, 8.7, 8.4); [6] 67.0, 4.63 (dd, *J* = 8.7, 8.4); [7] 177.2; [8] 109.6; [9] 27.3, 1.40 (s); [10] 26.9, 1.30 (s). $C_{10}H_{16}O_5$ LREIMS *m/z* (rel intens): 216 [M^+ (7)].

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2-[(Trimethylsilyl)methyl]-1-(trimethylsilyl)propen-3-yl Carboxylates in Cycloaddition. A Novel Approach for Substitutive Cyclopentannulation

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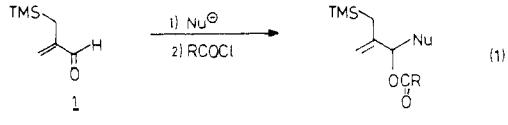
Abstract: Twofold sequential metalation–silylation of methallyl alcohol followed by acid hydrolysis provides 2-[(trimethylsilyl)methyl]-1-(trimethylsilyl)-1-propen-3-ol from which the corresponding acetate and carbonate are readily available. The acetate participates in palladium-catalyzed cycloadditions to give the trimethylsilyl-substituted methylenecyclopentanes. Unlike other substituted trimethylenemethane cycloadditions via their palladium complexes, the regioselectivity of the cycloaddition is dependent upon ligand. With triphenylphosphine as ligand, the cycloadduct that places the trimethylsilyl substituent on the carbon of the trimethylenemethane unit that becomes bonded to the β-carbon of the acceptor is preferentially formed. In complete contrast to the acetate, the corresponding carbonate gives the cycloadducts possessing a carboxylic acid function in lieu of the trimethylsilyl substituent. The in situ carboxylation–cycloaddition is a highly general reaction as demonstrated by α,β-unsaturated esters, ketones, and sulfones participating as acceptors. Excellent diastereoselectivity may accompany this cycloaddition. The facts that olefin geometry is faithfully translated into ring geometry and that β-methoxyenones react without β-elimination suggest that it may be a concerted process. In some cases, cycloaddition proceeds more smoothly than with the parent system; 2-cyclohexenone is a notable case. Thus, a single substrate can provide cycloadducts bearing either a trimethylsilyl or carboxyl substituent by the simple expedient of choice of leaving group. This is the first case of carboxylation accompanying use of carbonates in palladium-catalyzed reactions.

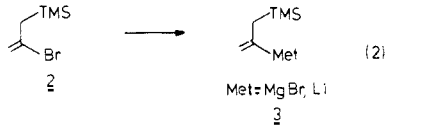
The success of (trimethylenemethane)palladium–L_2 in cycloadditions with a wide variety of acceptors[1,2] led us to seek the ability to incorporate substituents in the TMM unit. We have developed the use of 2-[(trimethylsilyl)methyl]acrolein (**1**) as a convenient general precursor whereby the substituent is introduced in the form of a nucleophile.[3] To expand the scope and ease of



(1)

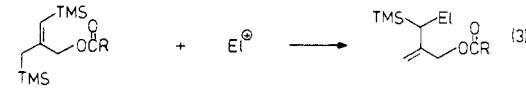
1

introduction of substituents, we chose to inverse the electronic sense by using the silicon-containing fragment as a nucleophile to condense with an electrophilic partner. 2-Bromo-3-(trimethylsilyl)-1-propene (**2**) is one such reagent.[4] Conceptually, 1-(trimethylsilyl)-2-(trimethylsilyl)methallyl alcohol esters represented by **4** could be a very useful alternative as illustrated in eq 3.[5] A



(2)

2 3



(3)

4

slight varient invokes telescoping the electrophilic substitution with the cycloaddition step in which we can envision a novel pathway as outlined in eq 4. In this concept, the initial trimethylsilyl-

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