agonal Newton Raphson algorithm in Cartesian coordinate space until the rms energy gradient was less than 0.04 kJ/mol Å. Vicinal coupling constants (^3J) in the candidate conformations were calculated in MACROMODEL with the appropriate coupling equation for peptide[19] and aliphatic[20] dihedral angles.

Acknowledgment. Partial research support was from NOAA, National Sea Grant College Program, Department of Commerce, University of California project number R/MP-41. The U.S. Government is authorized to produce and distribute reprints for governmental purposes. We thank Professor W. C. Still (Columbia University) for providing the program MACROMODEL (version 1.5).

Registry No. Na, 7440-23-5.

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The Structure and Conformational Properties of a Cembranolide Diterpene from *Clavularia violacea*

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The structure of a new cembranolide, pachyclavularolide (**2**), isolated from the octocoral *Pachyclavularia violacea*, was determined by extensive 2D NMR experiments. The relative stereochemistry at each of six chiral sites in **2** was assigned by using ROESY correlations, ^3J coupling constants, and molecular mechanics calculations. Results from the conformational analysis of **2** indicated that one major conformation exists in solution and corresponds to the global minimum predicted by molecular mechanics calculations. This report represents the first detailed solution conformational analysis study of a cembrane ring.

In comparison to the other major orders within the octocorals the Stoloniferia are sparse inhabitants of coral reefs, yet they are a source of a rich array of metabolites.[1] The stoloniferan families of chemical importance are the Tubiporidae (including the genera *Tubipora*), and the Clavulariidae (including the genera *Clavularia* and *Pachyclavularia*). Novel furanocembranoids **1a–c** have been previously isolated from *Pachyclavularia*.[2] By contrast, the chemistry of *Tubipora* or *Clavularia* includes norsesquiterpenes,[3] unusual sesquiterpenes,[4-6] bicyclic diterpenes,[7,8] unique prostanoids,[9] or highly oxygenated steroids.[10] Our investigation of *p. violacea* from Vanuatu[11] yielded a new cembranolide, pachyclavularolide (**2**), which is related to pachyclavulariadiol (**1a**) except that the furan ring has been oxidized to a butenolide. In this report we illustrate the effective combination of NMR and molecular mechanics calculations to provide the complete stereostructure and an understanding of the conformational properties of this new cembranolide.

Results and Discussion

The diterpenoid nature of **2** was indicated by the partial molecular formula of $C_{20}H_{28}$ established from a ^{13}C APT NMR spectrum, the presence of four methyl groups, and the complete formula of $C_{20}H_{30}O_5$ from a LREIMS ($M^+ = 350$). The unsaturated functionalities evident from NMR and IR spectra were an α,β-unsaturated ester (1750 cm^{-1}, δ 175.1 ppm/C16, 165.2/C1, 124.5/C15, 80.2/C2) and one trans-trisubstituted double bond (δ 130.0/C4, 131.0/C5, 16.6/C18); consequently, a tricyclic structure was apparent. Additional functionality included a vicinal diol (δ 76.2/C13, 68.2/C14) with two exchangeable hydrogens, and a scalar correlation was observed between H13 and H14 in a 500-MHz ROESY spectrum; however, $J_{13-14} \approx 0$ Hz. The 1,2-diol relationship in **2** was also established by the conversion of **2** to the dioxolane **3**. Consequently, the single remaining unaccounted oxygen and two oxygen-

Table I. NMR COSY Data for Pachyclavularolide (2)

$^1H-^1H$ regular	$^1H-^1H$ long range	$^{13}C-^1H$ long range ($J = 9$ Hz)
H2-H3,H3′	H2–H17	C1–H2,H3,H3′,H13,H14,H17
H3–H3′	H3–H5,H18	C2–H3,H3′,H14
H5–H6/H6′	H5–H18	C3–H2,H5,H18
H6/6′–H7,H7′	H14–H17	C4–H2,H3,H3′,H6/6′,H18
H7–H7′		C5–H3,H3′,H6/6′,H7,H18
H7′–H8		C6–H5,H7,H8
H8–H9,H19		C7–H5,H6/6′,H9,H19
H9–H10,H10′		C8–H6/6′,H7,H19
H10–H10′,H11′		C9–H7,H8,H10′,H11,H19
H10′–H11,H11′		C10–H11,H11′
		C11–H10,H13,H20
		C12–H11′,H13,H20
		C13–H11,H11′,H14,H20
		C14–H13
		C15–H2,H14,H17
		C16–H2,H17

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† UC Sea Grant Trainee Fellow, 1987–89.

[1] The stolonifera make up less than 1% of the species among the five major orders of Alyconaria from different geographical tropical regions: Tursch, B.; Braekman, J. C.; Dalzoe, D.; Kaisin, M. In *Marine Natural Products Chemistry*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. II, Chapter 4 (Table I).

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[3] See for example: (a) Bowden, B. F.; Coll, J. C.; Tapiolas, D. M. *Aust. J. Chem.* **1983**, *36*, 211. (b) Krebs, H. C. *Prog. Chem. Org. Nat. Prod.* **1986**, *49*, 151.

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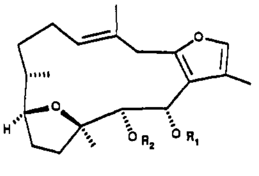
0022-3263/89/1954-2526$01.50/0

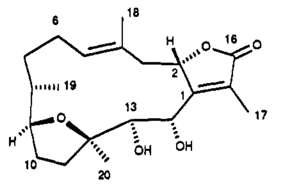
Table II. Observed and Calculated Coupling Constants (J) and Interatomic Distance H10′-H13

	observed		calculated			
J (Hz)	$CDCl_3$	C_6D_6	2A	2B	2C	2D
2-3	0.9	≈0	1.1	1.9	1.9	2.1
2-3′	8.7	8.1	10.4	11.5	6.5	6.3
8-9	9.3	9.6	10.2	9.2	9.3	1.2
9-10	5.4	5.1	6.3	7.2	5.6	4.0
9-10′	9.3	9.6	10.4	0.9	11.0	11.6
10-11	≈0	≈0	0.3	12.4	0.2	0.4
10′-11	6.9	7.2	7.4	7.2	7.8	9.8
13-14	≈0	≈0	0.1	0.4	1.1	0.2
D (Å)						
H10′-H13			2.257	4.295	2.336	3.030

bearing carbons (δ 84.8/C9, 84.0/C12) had to be tied together in a heterocyclic ring. The indication that **2** was a cembranolide with an overall framework similar to pachyclavulariadiol (**1a**) was first suggested by the similarity of a large number of the ^{13}C chemical shifts of this pair.[12] Furthermore, the COSY NMR spectra of **2** verified the connectivities beginning at C2 and extending through to C11, including Me-18 and Me-19 (see Table I). A furan ring (C9 to C12) with Me-20 attached to C12, could be proposed by the identical chemical shifts of C9, C12, and Me-20 in **1a** and **2**. The trisubstituted butenolide attached to C3 and C14 was characterized by an IR band (1750 cm^{-1}), diagnostic ^{13}C NMR shifts, long-range $^1H-^1H$ and $^1H-^{13}C$ COSY correlations (Table I).[13] Finally, the overall framework of **2** could be completely established as C13 must reside between C12 and C14.



1 a $R_1 = H$, $R_2 = H$
b $R_1 = Ac$, $R_2 = H$
c $R_1 = Ac$, $R_2 = Ac$



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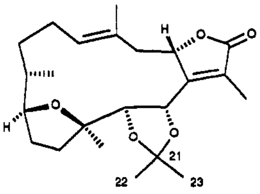

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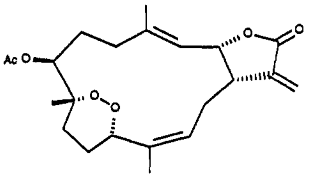

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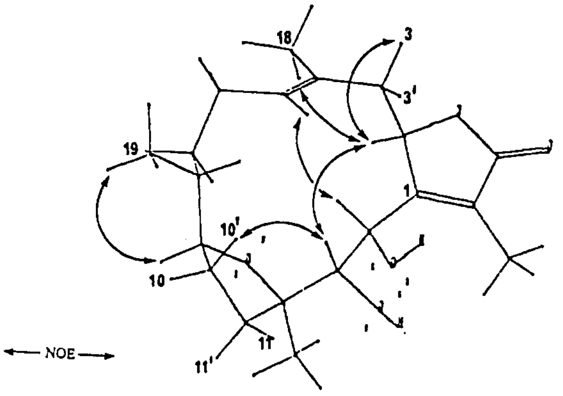

2A

Figure 1. NOE correlations in pachyclavularolide (**2**).

The relative stereochemistry at the six chiral centers and the prochirality of the diastereotopic hydrogens[14] at C3, C10, and C11 were assigned in **2** by the following general strategy. Stereochemical assignments were based on NMR ^1H coupling constants (J), ROESY correlations, and molecular mechanics calculations. The ROESY and coupling data was initially used to construct a Dreiding model, which incorporated distance and angle constraints. The trial Dreiding models were next entered into MACROMODEL[15] and energy minimized. The distances and coupling values in the minimized structures were then calculated and compared to the experimental data in order to asses how well the proposed chirality fit the experimental data. Once a good fit of the overall relative stereochemistry was obtained, an extensive conformational search was carried out on the complete model to insure that the minimized conformation was the global minimum.

Determination of the relative configuration of the chiral centers in **2** first began at C2. The ROESY correlation from H2 to H3, H13, and $H_3$18, indicated that these respective hydrogens must be in close proximity to H2 (see Figure 1). The diastereotopic shift difference between H3 and H3′, $\Delta\delta = 0.36$ ppm, and the divergent coupling values, $J_{2\text{-}3} = 0.9$ Hz and $J_{2\text{-}3'} = 8.7$ Hz, indicated that this region of the macrocycle was rigid.[16] Assuming a 2S* stereochemistry at C2, H3′ was oriented anti to H2 given the above ROESY correlations and coupling values. Consequently, the prochiralities of H3 and H3′ were assigned as *pro-R**, *pro-S**, respectively. The stereochemistry at C13 and C14 was assigned next based on ROESY correlations between H13 to H2 and H14 to H5 and no meas-

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(9) (a) Kitagawa, I.; Kobayashi, M.; Yasuzawa, T.; Son, B. W.; Yoshihara, M.; Kyogoku, Y.; *Tetrahedron* **1985**, *41*, 995. (b) Iguchi, K.; Yamada, Y.; Kikuchi, H.; Tukitani, Y. *Tetrahedron Lett.* **1983**, *24*, 4433. (c) Corey, E. J.; Lansbury, P. T., Jr.; Yamada, Y. *Tetrahedron Lett.* **1985**, *26*, 4171.

(10) Kobayashi, M.; Lee, N. K.; Son, B. W.; Yangi, K.; Kyogoku, Y.; Kitagawa, I. *Tetrahedron Lett.* **1984**, *25*, 5925.

(11) Our collection of *P. violacea* (family Clavulalriidae, order Stolonifera) was identified by Dr. Hank Chaney (Alan Hancock Foundation, University of Southern California).

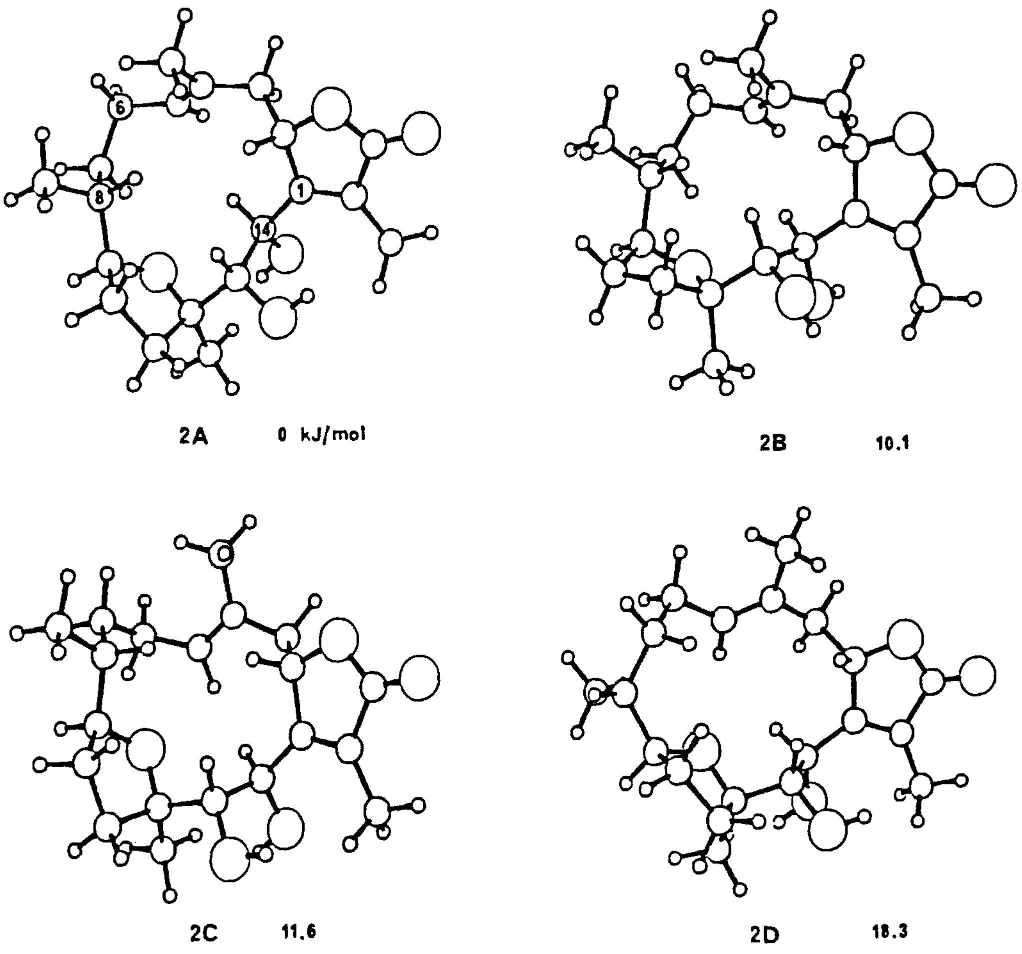
(12) These include the following signals of **1a** assigned in ref 2: (C-6,7,10,11 were unassigned) δ 131.1 (C4) 127.7 (C5), 38.8 (C8), 85.4 (C9), 84.1 (C12), 75.8 (C13), 62.6 (C14), 10.5 (Me-17), 15.5 (Me-18), 17.4 (Me-19), 21.4 (Me-20).

(13) These ^{13}C shifts were comparable to those of sesterterpene butenolides including compounds **28**, **29**, **105**, **128**, **154** summarized by Crews, P.; Naylor, S. *Prog. Chem. Org. Nat. Prod.* **1985**, *48*, 203. Relevant long-range COSY correlations included those between H2 and H17, between H14 and H17, H2 and C16.

(14) We assign the diastereotopic hydrogen resonance, H′, high field relative to H in the ^1H NMR spectra.

(15) MACROMODEL (version 1.5) kindly provided by Professor W. C. Still, Columbia University.

(16) We have previously discussed how the combination of a diastereotopic shift difference and divergent coupling constants (^3J) can be used to asses rigidity/flexibility in $-CH_2-CH-$ arrays: Inman, W.; Crews, P. *J. Am. Chem. Soc.*, in press.



2A 0 kJ/mol

2B 10.1

2C 11.6

2D 18.3

Figure 2.

Table III. Summary of Energies and Torsion Angles for 1a[2] and Conformations of 2

	1a	2A	2B	2C	2D
relative energy (kJ/mol)		0	10.1	11.6	18.3
torsion angle					
14-1-2-3	-3.9	-65.2	-69.9	-61.1	-59.7
1-2-3-4	80.4	100.0	86.6	114.4	115.2
2-3-4-5	-128.7	-110.2	-116.5	-96.7	-106.9
3-4-5-6	179.1	177.8	-178.4	174.5	-176.3
4-5-6-7	-108.7	-102.4	-100.9	-52.0	-96.8
5-6-7-8	74.3	65.3	76.0	-39.3	-79.6
6-7-8-9	-140.2	-149.7	-154.4	-58.9	100.5
7-8-9-10	-178.5	176.7	-170.6	-167.7	62.9
8-9-10-11	-150.0	-147.0	-83.6	-156.1	-166.9
9-10-11-12	35.5	34.2	-34.8	37.2	26.7
10-11-12-13	87.6	84.6	-83.6	86.9	112.6
11-12-13-14	-175.7	-161.4	141.3	-176.9	-172.8
12-13-14-1	155.2	169.6	-155.2	143.7	158.2
13-14-1-2	-115.2	-81.4	179.1	-84.7	-76.0

urable coupling between H13 and H14. Only the 13*S** and 14*R** configurations having the *cis*-1,2-diol stereochemistry were found to satisfy both the close-distance relationships (H13 to H2 and H14 to H5) and coupling value of $J_{13\text{-}14} \approx 0$ Hz. Next, a weak ROESY correlation observed between H10′ and H13 was used to assign the C9/C12 relative stereochemistry. Molecular mechanics calculations on macrocyclic structures containing the four possible stereochemical arrangements at C9 and C12 showed that only the 9*S** and 12*R** relative stereochemistry allowed H10′ and H13 to be in close proximity (see **2A**, Figure 2, and discussion below). Finally, 8*R** stereochemistry was proposed based on the ROESY correlation between $H_3$19 and H9 and the coupling between H8 and H9 ($J_{8\text{-}9}$ = 9.3 Hz), which indicated an anti relationship between these two protons. Minimization of a complete model of **2** with stereochemistry 2*S**,8*R**,9*S**,12*R**,13*S**,14*R** yielded conformer **2A**, which showed good agreement between the predicted and experimental coupling constants (Table II). The relative stereochemistry proposed for **2A** at positions C8, C9, C12, C13, and C14 were identical with the assignments made for **1a** by X-ray analysis.

It was now necessary to verify that the minimized conformation **2A** was the global minimum and corresponded to the solution conformation. The MM2 calculations revealed tetrahydrofuran pseudorotation conformers **2A** and 2B, whose relative energies and torsion angles are listed in Table III.[17] Conformer **2A** was predicted to be the

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[17] Candidate conformations were generated by dihedral driving using constrained minimization. Once the alternate conformation was generated, constraints were removed and the structure reminimized.

major conformation, as **2A** was calculated to be 10.1 kJ/mol lower than **2B**. Additionally, **2A** and not **2B** provided a good correspondence between the calculated coupling constants and distance between H10′ and H13 (see Table II). The relatively large diastereotopic shift differences between H10/H10′ (0.6 ppm) and H11/H11′ (0.59 ppm) and the divergent coupling values for $J_{9-10}/J_{9-10'}$ and $J_{10-11}/J_{10'-11}$ (Table II) also suggested that the furan ring exists predominantly in the **2A** conformation in solution. The assignments of the prochirality for H10 (*pro-R**), H10′ (*pro-S**), H11 (*pro-R**), and H11′ (*pro-S**) are shown in Figure 1 and are based on coupling values and ROESY correlations. A similar furan ring conformation is observed between **2A** in solution and **1a** in the solid state as shown by the torsion angles 7–8–9–10, 8–9–10–11, 9–10–11–12, 10–11–12–13 in **2A**, which are within 6° of the values reported for the X-ray structure of **1a** (Table III). The remaining possible regions of flexibility are about torsion angles 5–6–7–8 and 6–7–8–9. Overall nine possible staggered conformations may exist when considering both torsion angles.[18] Conformer **2A** has the 5–6–7–8, 6–7–8–9 torsion angles in the g^+a conformation, respectively.[19] All nine combinations were generated and only two with the 5–6–7–8, 6–7–8–9 torsion angles in the g^-g^- (**2C**) and g^-g^+ (**2D**) conformations were within 11.6 and 18.3 kJ/mol of **2A**, respectively.

Surprisingly, although there are many biologically active cembranes known from marine and terrestrial sources,[3b,20] none have been the subject of a rigorous solution conformational investigation. Part of the difficulty in determining the solution conformation of a cembrane may be due to the flexibility within the cembrane skeleton.[21] By contrast, the above data showed that pachyclavulariolide (**2**), where the cembrane ring contains a bridged oxygen, has a single major solution phase conformation, **2A**. Furthermore, the solution conformation of **2A** is similar to that in the solid state for **1a**, excluding the functional group differences about the 14–1–2–3 torsion angle. A parallel situation may exist for denticulatolide **4**, which represents the only other example of a cembrane ring system that has a been subjected to conformational study.[22]

Experimental Section

NMR spectra were recorded on a GN-300 spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C). Multiplicities of ^{13}C NMR peaks were determined from APT data, and 2D COSY NMR experiments were done on the GN-300 instrument. ROESY and long-range ^1H–^{13}C spectra were recorded on a Bruker 500 spectrometer (at Bruker Applications lab, San Jose, CA). Mass spectrometry data were obtained on a Finnigan 4000 (6000 LS7 computer system). High-performance liquid chromatography (HPLC) was done on a Waters liquid chromatograph using a Regis 10 μm silica gel column (25 × 1.0 cm). All solvents were distilled and dried for HPLC and were spectral grade for spectroscopy. Rotations were measured on a Perkin-Elmer 141 polarimeter.

Two-Dimensional NMR Procedures. Standard pulse sequences were used for the ^1H–^1H COSY, ^1H–^{13}C COSY, long-range ^1H–^{13}C (256 × 1K), and ROESY (τ_m = 200 ms) experiments.[23]

Computational Methods. Computer modeling was carried out with the MACROMODEL program (version 1.5) on a Vax 11/750 computer with an Evans and Sutherland (PS 330) picture system. Molecular mechanics calculations were performed with the MM2 force field with a distance dependent dielectric. Structures were energy minimized with the Block Diagonal Newton Raphson algorithm in Cartesian coordinate space until the rms energy gradient was less than 0.04 kJ/mol Å. Vicinal coupling constants (^3J) in the candidate conformations were calculated in MACROMODEL with the Altona coupling equation.[24]

Isolation Procedures. Aqueous methanol extracts of the preserved organism (0.6 kg, wet) yielded a dark viscous oil (3.3 g). A portion of the crude oil (1.2 g) was then partitioned between aqueous MeOH and the solvent series of hexanes, CCl_4, CH_2Cl_2. The CH_2Cl_2 partition fraction was then column chromatographed (Aldrich silica gel, grade 60, 60A) and further purified on a normal-phase HPLC column (10 μm silica gel, 25 × 1.0 cm; hexanes/ethyl acetate solvent system), which afforded **4** (0.020 g, 0.009% yield based on the weight of the organism).

Pachyclavularolide (2): colorless oil; $[\alpha]^{20}{}_D = -2.3°$ (c = 2.16 g/100 mL, $CDCl_3$); LREIMS (M^+) 350, $C_{20}H_{30}O_5$; IR (cm^{-1}) 3490, 2960, 1749, 1455, 1384; ^1H NMR ($CDCl_3$, 300 MHz, δ in ppm, multiplicities, J (Hz), atom number) δ 4.57 (dd, 8.7, 0.9, H2), 2.70 (d, 13.5, H3), 2.34 (dd, 13.8, 8.7, H3′), 5.40 (t, 7.5, H5), 2.0 (m, H6/H6′), 1.85 (m, H7), 1.2 (m, H7′), 1.05 (m, H8), 3.63 (ddd, 9.3, 9.3, 5.4, H9), 2.0 (m, H10), 1.4 (m, H10′), 2.24 (dd, 12.9, 6.9, H11), 1.65 (m, H11′), 3.24 (s, H13), 5.15 (s, H14), 2.00 (s, Me-17), 1.72 (s, Me-18), 0.83 (d, 6.6, Me-19), 1.38 (s, Me-20); ^{13}C NMR ($CDCl_3$, 75 MHz, δ in ppm, multiplicity, atom number) δ 165.2 (s, C1), 80.2 (d, C2), 43.7 (t, C3), 130.0 (s, C4), 131.0 (d, C5), 25.3 (t, C6), 33.2 (t, C7), 39.2 (d, C8), 84.8 (d, C9), 31.3 (t, C10), 38.5 (t, C11), 84.0 (s, C12), 76.2 (d, C13), 68.2 (d, C14), 124.5 (s, C15), 175.1 (s, C16), 10.0 (q, C17), 16.6 (q, C18), 16.7 (q, C19), 22.5 (q, C20); ^1H NMR (C_6D_6) δ 4.56 (d, 8.1, H2), 2.53 (d, 14.1, H3), 2.21 (dd, 14.7, 8.7, H3′), 5.22 (t, 7.5, H5), 1.93 (m, H6/H6′), 1.92 (m, H7), 1.07 (m, H7′), 0.96 (m, H8), 3.46 (ddd, 9.6, 9.6, 5.1, H9), 1.68 (m, H10), 1.25 (m, H10′), 2.36 (dd, 12.6, 7.2, H11), 1.45 (m, H11′), 3.31 (s, H13), 5.12 (s, H14), 2.14 (s, Me-17), 1.59 (s, Me-18), 0.70 (d, 6.6, Me-19), 1.63 (s, Me-20); ^{13}C NMR (C_6D_6) δ 166.8 (s, C1), 80.7 (d, C2), 43.8 (t, C3), 130.1 (s, C4), 131.0 (d, C5), 25.8 (t, C6), 33.8 (t, C7), 39.4 (d, C8), 84.8 (d, C9), 31.7 (t, C10), 38.8 (t, C11), 84.4 (s, C12), 76.2 (d, C13), 68.4 (d, C14), 124.4 (s, C15), 175.6 (s, C16), 10.2 (q, C17), 16.5 (q, C18), 17.0 (q, C19), 22.9 (q, C20).

Preparation of Dioxolane 3. Two equivalents of 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid were added to 5 mg (0.014 mmol) of **2** in dry *N,N*-dimethylformamide (2 mL) and stirred under nitrogen for 12 h. The mixture was then neutralized with aqueous $NaHCO_3$ and extracted with CH_2Cl_2, the organic phase was evaporated to dryness and chromatographed (normal-phase HPLC, 10 μm silica gel, 25 × 1.0 cm, solvent = EtOAc–hexanes, 60:40), yielding 3 mg of **3** (0.0077 mmol, 55%); ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 (t, 7.5, H5), 5.02 (d, 7.8, H14), 4.93 (m, H2), 3.71 (m, H9), 3.30 (d, 7.8, H13), 2.0 (m, H6/H6′), 1.98 (s, Me-17), 1.71 (s, Me-18), 1.52 (s, Me-22*), 1.49 (s, Me-23*), 0.87 (d, 6.6, Me-19), (*) interchangeable.

Acknowledgment. Partial research support was from NOAA, National Sea Grant College Program, Department of Commerce, University of California project number R/MP-41. The U.S. Government is authorized to produce and distribute reprints for governmental purposes. Other grant support was from Syntex Inc. We thank Jim Loo (UCSC) and Mark Oneil-Johnson (Bruker Instruments) for assistance with NMR experiments and Professor W. C. Still (Columbia University) for providing the program MACROMODEL (version 1.5).

Registry No. 2, 119770-11-5; 3, 119770-12-6.

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[18] Number of possible conformations = $(360°/\Delta)^n$; where Δ is the rotational increment angle (e.g., 120°) and n is the number of bonds about which rotation occurs (e.g., 2).

[19] The $g^+/g^-/a$ nomenclature describes the dihedral angular relationship of the carbon-carbon backbone, $g^- \approx 60°$, $g^- \approx -60°$, $a \approx 180°$.

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