in Figure 1, the rates exhibit a monotonous but distinctly curved free-energy relationship when plotted versus σ^+ substituent constants.[12] Such behavior is expected, if the process is not entirely diffusion-controlled, with the rate constants at the high end leveling off toward a limiting diffusive value. Admittedly, the curvature could, in part, be attributed to coincidental scatter or to the somewhat arbitrary choice of substituent constants (the curvature—but not the trend—is largely eliminated through a bilinear Yukawa-Tsuno[13] regression). However, there is independent evidence that the rate is approaching the diffusion-controlled limit for the more reactive enols. First, the absolute values of k_{Br} are close to those expected for a diffusive process in aqueous solution. Second, the low sensitivity of the reaction rate to substituent effects indicates that the changes in chemical reactivity are diluted by the influence of nonchemical diffusive steps: a straight line through the points of Figure 1 has a slope of $\rho = -0.26$ which is 1 order of magnitude less than, e.g., the slope of $\rho = -2.2$ found for the hydrolysis of a corresponding series of vinyl ethers[14] or $\rho = -4.4$ for the bromination of styrene derivatives through the carbonium ion pathway.[15]

We conclude that the bromination of simple enols is not quite—though almost—a diffusion-controlled process. A similar analysis based on rates of halogenation of acetone[2a,b] and substituted acetophenones[16] in alkaline solutions suggests that the absolute rate constants for the reaction of the hypohalous acids with enolate ions also fall short of the limit of diffusion.

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Prorocentrolide, a Toxic Nitrogenous Macrocycle from a Marine Dinoflagellate, *Prorocentrum lima*†

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Marine dinoflagellates are a source of chemically and pharmacologically significant compounds, e.g., saxitoxin, maitotoxin, and the brevetoxins. We have previously isolated okadaic acid[1] and its esters[2] from a benthic dinoflagellate, *Prorocentrum lima*.

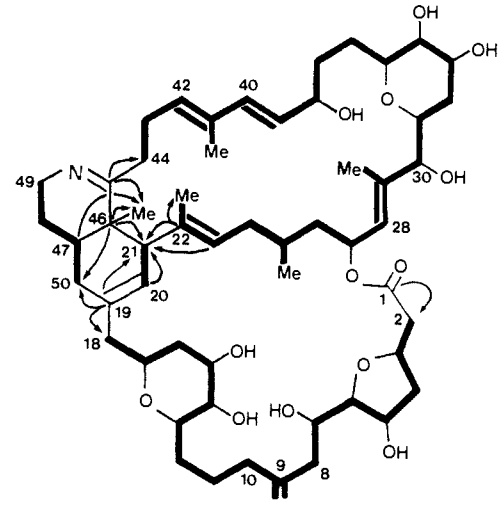

Figure 1. Connectivities established by $^1H-^1H$ COSY, $^{13}C-^1H$ COSY, and long-range $^{13}C-^1H$ COSY. Heavy lines indicate the connectivities assigned on the basis of $^1H-^1H$ and $^{13}C-^1H$ COSY (dimethyl sulfoxide-d_6, 500 MHz, AM-500). Arrows denote the correlation between carbons (tail) and protons (head) around the quaternary carbons observed in the long-range $^{13}C-^1H$ COSY (dimethyl sulfoxide-d_6, 500 MHz, GN-500). The other correlations are omitted for clarity.

From the same organisms we have isolated prorocentrolide (**1**), which is a toxic macrocycle formed from a C_{49} fatty acid and incorporating a C_{27} macrolide and a hexahydroisoquinoline in its unique structure.

The dinoflagellate was isolated at Sesoko Island, Okinawa in 1985 and cultured in seawater enriched with ES-1 nutrient[3] at 25 °C for 5 weeks. Algal cells (2.7×10^{10}) harvested from 1000 L of the culture were extracted with acetone and methanol. The combined extracts were evaporated, the residue was partitioned between diethyl ether and water, and the aqueous layer was extracted with 1-butanol. The butanol solubles were successively chromatographed with the following columns and solvents: silica gel 60, chloroform/methanol (1:1); Toyopearl HW-40 (Tosoh), methanol/water (1:1); silica gel 60, chloroform/methanol/water (25:10:1); Develosil ODS-5 (Nomura Chem.), a linear gradient elution from acetonitrile/0.05 N acetic acid (1:9) to (3:7). The toxin in the eluates was monitored by ip mouse lethality.

Prorocentrolide (70 mg), an amorphous solid, had a mouse lethality of 0.4 mg/kg (ip):[4] $[\alpha]^{23}_D$ +136.5° (*c* 0.147, CH_3OH); UV max (CH_3OH) 235 nm (ε 13 600); IR (KBr) 3400, 1715, 1670, 1640, 1200, and 1060 cm^{-1}. HR-FABMS and total number of carbons determined by ^{13}C NMR spectra suggested a probable molecular formula of $C_{56}H_{85}NO_{13}$ (MH^+, *m/z* 980.6100; found, *m/z* 980.6168). Positive Dragendorff's test, elemental analysis for nitrogen (1.39%), and an IR band at 1670 cm^{-1} suggested the presence of an imine group.

The proton connectivities were elucidated by detailed analyses of $^1H-^1H$ and $^{13}C-^1H$ COSY experiments. Long-range proton couplings via sp^2 carbons such as H_2-51/H_2-8, H_2-51/H_2-10, H-28/H-30, H-40/H-42, and H_2-44/H_2-49 were clearly indicated by cross-peaks. Eventually, four partial structures (C2-C18, C20-C21, C22-C44, and C49-C50) were obtained as shown in Figure 1. The fragments terminating in quaternary carbons (C1, C19, C22, C45, and C46) were assembled by a long-range $^{13}C-^1H$ COSY,[5] designed to detect $^{2,3}J_{CH}$ (Figure 1). Hetero couplings of C45/H-44 and C45/H_3-56 observed in the spectrum indicated that C45 (δ 169.9) was alkylated by two sp^3 carbons (C44 and C46) and presumably assignable to an imine group; no other carbons adjacent to two sp^3 carbons give rise to the signals in that region. The other nitrogen-bearing carbon was deduced to be C49 because of its typical chemical shift (δ 48.3) for $N-CH_2$ and because of homoallylic couplings between H_2-49 and H_2-44.

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Table I. NMR Spectral Data of Prorocentrolide (1)

positn	C[a]	H[b]	positn	C	H	positn	C	H
1	169.3		19	130.9		39	130.8	5.49
2	41.2	2.39	20	124.6	4.92	40	131.0	6.10
		2.66	21	54.3	2.73	41	129.7	
3	74.8	4.35	22	136.3		42	131.6	5.32
4	38.6	1.65	23	128.9	5.11	43	22.1	2.18
		2.10	24	34.9	1.48			2.42
5	75.8	4.16			1.78	44	34.1	2.27
6	89.3	3.47	25	27.4	1.56			2.50
7	68.8	3.32	26	42.5	1.09	45	169.9	
8	41.1	1.96			1.64	46	39.6	
		2.28	27	66.5	5.58	47	33.9	1.55
9	147.0		28	126.8	5.19	48	24.9	1.28
10	33.2	1.85	29	139.3				1.74
		1.85	30	73.7	3.98	49	48.3	3.46
11	23.0	1.39	31	71.8	3.59			3.69
		1.39	32	32.5	1.40	50	30.2	1.62
12	31.9	1.20			2.11			2.44
		1.77	33	67.9	3.54	51	110.9	4.68
13	70.5	3.11	34	76.5	2.72			4.79
14	76.3	2.66	35	74.2	2.88	52	14.1	1.32
15	68.2	3.54	36	30.6	0.97	53	16.0	0.65
16	36.6	1.58			2.19	54	9.8	1.66
		1.68	37	34.5	0.87	55	12.1	1.59
17	67.7	4.01			1.54	56	28.1	1.17
18	40.1	1.82	38	69.7	3.87			
		2.73						

[a] ^{13}C NMR chemical shifts in dimethyl sulfoxide-d_6 taken as δ 39.5 (125 MHz, Bruker AM-500). [b] ^{1}H NMR chemical shifts in dimethyl sulfoxide taken as δ 2.50 (500 MHz, AM-500).

Another deshielded signal (δ 169.3) was ascribable to an ester since its vicinal methylene (H_2-2) had the typical chemical shifts for an α position to a carbonyl group. A marked downfield shift of H-27 (δ 5.58) implied that the ester was substituted at C27. Thus the whole carbon skeleton was assembled, leaving the positions of the hydroxyl and ether groups to be determined.

Isotope shifts in ^{13}C NMR signals, as observed by the chemical shift differences between CD_3OD–C_6D_6 and CD_3OH–C_6D_6 solutions, led to identification of hydroxyl-bearing carbons; significant shifts (0.09–0.12 ppm) were observed for C5, C7, C14, C15, C30, C33, C34, and C38, indicating the presence of eight hydroxyl groups, while the other signals were superimposable within 0.03 ppm.

The degree of unsaturation derived from the molecular formula and the structural features described above suggested the presence of three ether rings. The oxycarbons other than those bearing hydroxyl or acyloxy groups were arranged to form one five- and two six-membered ether rings: A, B, and C. These ether linkages were confirmed by NOE experiments[6] (Figure 2) and coupling constants of the ring protons.[7] Geometry of all double bonds except for C19–C20 were determined to be *E* on the basis of phase sensitive NOESY (Figure 2).

All of these data allowed us to assign the planar structure of prorocentrolide (**1**). Assignments of all protons and carbons are shown in Table I. Its co-occurrence with okadaic acid in *P. lima*

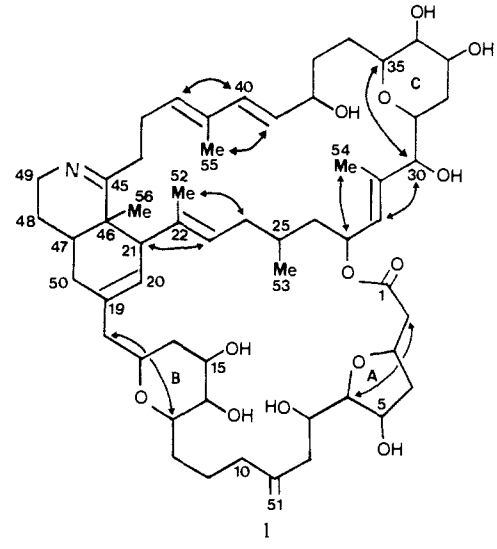

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Figure 2. Ether linkages and geometry of double bonds assigned by NOE measurements. "↔" indicates the protons around the ethers and double bonds that give cross-peaks on phase-sensitive NOESY (dimethyl sulfoxide-d_6, 500 MHz, GN-500).

indicates that dinoflagellates are capable of producing polyethers of entirely different skeletons.

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(4) Cytotoxicity against L-1210 was 20 μg/mL (IC_{50}); antimicrobial activities against *Aspergillus niger*, *Candida rugosa*, and *Staphylococcus aureus* were negative at a dose of 80 μg/disk.

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(7) ^{3}J in Hz (dimethyl sulfoxide-d_6); ring A, H-4/H-4, −13.0; H_2-4/H-5 4.0, 6.5; H-5/H-6, 4.0. Deoxycytidine-5′-monophosphate (dCMP-5′), H-2′/H-2′, −14.1; H-2′/H-3′, 4.0, 6.0; H-3′/H-4′, 3.2 (Davies, D. B.; Danyluk, S. S. *Biochemistry* **1974**, *12*, 4417–4434). Ring B, H-13/H-14, 9.5; H-14/H-15, 9.0. Ring C, H-34/H-35, 9.0; H-33/H-34, 8.5. Glucopyranose, H-5/H-6, 8.9; H-4/H-5 8.8 (DeBruyn, A.; Anteunis, M. *Bull. Soc. Chim. Belg.* **1975**, *84*, 1201–1209).

Asymmetric Amplifying Phenomena in Enantioselective Addition of Diethylzinc to Benzaldehyde

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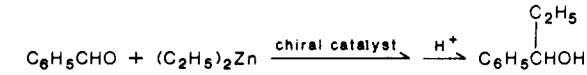
There are many reports about the highly enantioselective alkylation of aldehydes by organometallic compounds using an equimolar amount of chiral modifiers.[1] Recently, the efficient asymmetric catalysis in the carbonyl alkylation has been developed.[2] On the other hand, the most valuable and ultimate method in asymmetric synthesis would be the asymmetric amplification which is the asymmetric reaction giving the very high ee's product with chiral auxiliary of low ee's. Kagan et al. discussed nonlinear effects in the asymmetric synthesis and described the first example, which is a significant amplification in Sharpless oxidation.[3] We disclose here the highly asymmetric amplifying phenomena in the ethylation of benzaldehyde with diethylzinc. The reaction was catalyzed by sterically constrained, tertiary β-aminoalcohols with



a bulky *tert*-butyl substituent on the carbon bonded to the hydroxy

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