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*

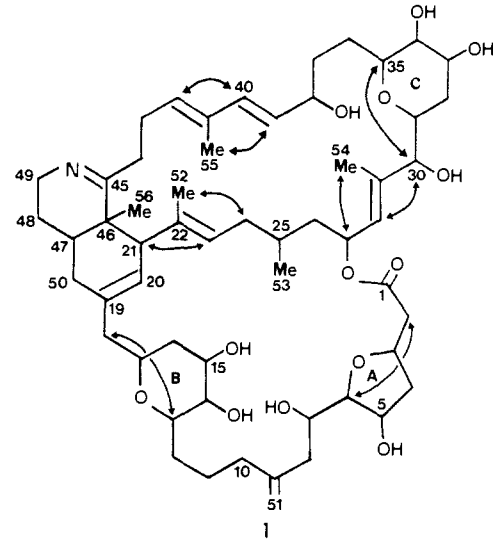

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Figure 2. Ether linkages and geometry of double bonds assigned by NOE measurements. "↔" indicates the protons around the ethers and double bonds that give cross-peaks on phase-sensitive NOESY (dimethyl sulfoxide-d_6, 500 MHz, GN-500).

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.

(5) Quast, M. J.; Zektzer, A. S.; Martin, G. E.; Castle, R. N. *J. Magn. Reson.* **1987**, *71*, 554–560.

(6) In a phase-sensitive NOESY spectrum (dimethyl sulfoxide-d_6, GN-500), NOE's were observed on H-6/H-2, H-13/H-18, and H-35/H-30. Each ether ring presumably takes a similar configuration, in which side chains are trans substituted, and thus the axial/pseudoaxial proton on the ether carbon (H-6, H-13, H-35) comes close to the proton(s) on the axially substituted side chain (H-2, H-18, H-30).

(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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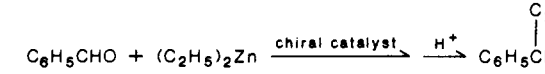
There are many reports about the highly enantioselective alkylation of aldehydes by organometallic compounds using an equimolar amount of chiral modifiers.[1] Recently, the efficient asymmetric catalysis in the carbonyl alkylation has been developed.[2] On the other hand, the most valuable and ultimate 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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(3) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353.

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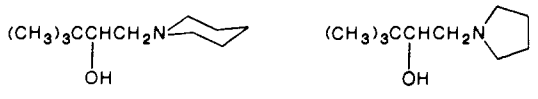
Table I. Asymmetric Amplification in Enantioselective Addition of Diethylzinc to Benzaldehyde[a]

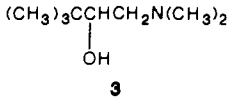
catalyst[b]	% ee of catalyst[c] ($[\alpha]^{24}_D$ (c 1.5, EtOH)) (deg)	product yield (%)	product $[\alpha]^{24}_D$ (c 2.0, EtOH) (deg)	product % ee[d] (confign)
1	3.1 (-2.3)	82	+17.6	36 (*R*)
	6.5 (-4.7)	95	+36.1	74 (*R*)
	10.7 (-7.8)	96	+40.1	82 (*R*)
	20.5 (-15.0)	96	+43.0	88 (*R*)
	59.8 (-43.6)	95	+45.0	92 (*R*)
	77.1 (+56.2)	96	-46.0	94 (*S*)
2	3.8 (+2.7)	78	-17.1	35 (*S*)
	7.4 (+5.3)	81	-25.4	52 (*S*)
	20.0 (+14.3)	92	-35.7	73 (*S*)
3	10.5 (-9.3)	88	+22.5	46 (*R*)
	19.8 (-17.5)	82	+29.4	60 (*R*)

[a] Reaction was carried out in degassed hexane at -10 °C by using 2 mol% of catalyst and 1.1 equiv of diethylzinc per benzaldehyde. [b] **1**, 1-piperidino-3,3-dimethyl-2-butanol; **2**, 1-pyrrolidino-3,3-dimethyl-2-butanol; **3**, *N,N*-dimethyl-2-hydroxy-3,3-dimethylbutylamine. [c] Determined by HPLC (Sumipax OA 4000) of 3,5-dinitrophenylurethane derivatives. [d] Absolute configuration: Macleod, R.; Welch, F.; Mosher, H. S. *J. Am. Chem. Soc.* **1960**, *82*, 876.

group, for instance, 1-piperidino-3,3-dimethyl-2-butanol (PDB), **1**, 1-pyrrolidino-3,3-dimethyl-2-butanol, **2**, and *N,N*-dimethyl-2-hydroxy-3,3-dimethylbutylamine, **3**.[4] Thus, under the influence



1, PDB **2**



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of 2 mol% of (-)-PDB (10–20% ee), diethylzinc reacted with benzaldehyde (1.1:1 molar ratio) in hexane at -10 °C, and (*R*)-1-phenylpropanol was obtained in 80–90% ee and in high chemical yield. Table I exemplifies the asymmetric amplification. Wynberg and Feringa established the origin of the different chemical behaviors in reaction rates and product distribution of an enantiomerically pure compound and the corresponding racemic mixture in the absence of chiral reagents.[5] The asymmetric amplification observed in the reaction of diethylzinc with benzaldehyde will provide important insights into the reaction mechanism of the asymmetric alkylation. For instance, the equimolar reaction products of optically pure PDB and racemic PDB with diethylzinc both form dimers in benzene solution, as determined by cryoscopic molecular weight measurements. Also, the ee of the auxiliary used in the reaction has a marked effect on the reaction rate. For the typical example, the reaction rate with 60% ee of PDB was 5.5 times the one observed with completely racemic PDB under the same reaction condition of diethylzinc with benzaldehyde.

A typical experimental procedure is illustrated as follows: In a flame-dried Schlenk tube was placed (-)-PDB of 10.7% ee (167 mg, 0.9 mmol) and dry hexane (100 mL), and the whole mixture was degassed and covered with argon. Tc this solution was added diethylzinc (5.5 mL, 45.5 mmol), and the resulting solution was stirred at 20 °C for 15 min. After cooling to -10 °C, benzaldehyde (4.8 g, 45 mmol) was added, and the mixture was stirred for 12 h and quenched by adding 10% aqueous HCl. The usual extractive workup and distillation gave (*R*)-1-phenylpropanol in 82% ee (5.9 g, 96% yield), $[\alpha]^{22}_D$ +40.1° (*c* 2.26 $CHCl_3$).[6] The ee was determined by HPLC analysis (column, Daicel Chirapak OB; eluent, 0.2% 2-propanol in hexane; flow rate, 1.0 mL/min; detection, 254 nm light).

The detailed mechanism of the asymmetric amplifying phenomena observed in this work will be published in the near future.

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(4) 1-Piperidino-3,3-dimethyl-2-butanol was prepared by the following procedure. 1-Bromo-3,3-dimethyl-2-butanone was reacted with piperidine in benzene in the presence of triethylamine to give 1-piperidino-3,3-dimethyl-2-butanone. The product was reduced by $LiAlH_4$ (molar ratio, 1:0.5) in ether, which gave 1-piperidino-3,3-dimethyl-2-butanol in quantitative yield under usual experimental workup. The resulting racemic product was optically resolved by repeated crystallizations of a salt with (-)-dibenzoyl-L-tartaric acid (molar ratio, 1:1). The chemical analysis and NMR data of **1** coincided with its structure. $[\alpha]^{22}_D$ -71.5° (*c* 1.91, ethanol) for 98% ee's. The compounds **2** and **3** were also prepared similarly as the preparative method of **1**. $[\alpha]^{23}_D$ -14.3° *c* 2.13, ethanol) for 20% ee of **2**. $[\alpha]^{21}_D$ -17.5° (*c* 2.08, ethanol) for 19.8% ee of **3**. The ee's of the compounds **1–3** were determined by HPLC analysis of their 3,5-dinitrophenylurethane derivatives in comparison with racemic ones (column; Sumipax OA 4000; eluent, 0.2% methanol in hexane; flow rate, 1.0 mL/min; detection, 254 nm light).

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(6) Reported value; $[\alpha]_D$ -45.45° (*c* 5.15, $CHCl_3$). Pickard, R. H.; Kenyon, J. *J. Chem. Soc.* **1914**, 1115.

Stereochemistry of Enzymatic Formation of the Berberine Bridge in Protoberberine Alkaloids

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An intriguing facet in the biosynthesis of the protoberberine family of benzylisoquinoline alkaloids is the formation of the "berberine bridge". Barton et al.[1] and Battersby and co-workers[2] demonstrated 25 years ago that the berberine bridge, C-8 of scoulerine (**4**) and columbamine (**7**) (Scheme I), arises by an oxidative cyclization from the *N*-methyl group of reticuline (**3**). The reaction sequence has since been elucidated in detail,[3] and the enzymes involved have been purified.[4] As shown in Scheme I, it leads from *S*-adenosyl-L-methionine (AdoMet, **1**) and *S*-*N*-

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