perfringens (MIC = 4 μg/mL). Phenazine **2** was more active overall, showing inhibitory activities against *E. coli* (4 μg/mL), *Salmonella enteritidis* (4 μg/mL), and *Clostridium perfringens* (4 μg/mL). The compounds were not appreciably cytotoxic against murine and human cancer cells tested in vitro.

Experimental Section

Fermentation Culture of *Streptomyces* sp. CNB-253. The bacterium, isolate CNB-253, was cultured by inoculating multiple 1-L Fernbach flasks with 100-mL subcultures. The fermentation medium was of standard composition, consisting of starch, 10 g/L, peptone, 2 g/L, yeast ext, 4 g/L, and 10 mL of 1 M Tris buffer (adjusted to pH=8), all dissolved in 75% natural seawater. The fermentation was allowed to proceed, with shaking at 250 rpm, for 10 days at 22 °C, after which the entire fermentation broth was extracted with ethyl acetate (3X). The extracts were combined and the solvents removed under vacuum to yield crude mixtures of antibacterial products.

Purification of Phenazines 1–4 and 7–8. The crude fermentation extract was fractionated by vacuum flash silica chromatography using increasing amounts in ethyl acetate in isooctane. Fractions which eluted with 60–80% ethyl acetate, which showed antibacterial properties, were combined, and final purification of **1–4** and **7–8** was achieved by silica HPLC using 80% ethyl acetate in isooctane.

Phenazine Alkaloid 1 (3′-*O*-L-Quinovosyl Saphenate). Phenazine alkaloid **1**, obtained as an amorphous yellow solid (6 mg/L fermentation yield), showed: $[\alpha]_D$ −40° (*c* 0.73, MeOH); IR (film) 3357, 2975, 2931, 1726, 1566, 1269, 1058, 752 cm^{-1}; LREIMS *m/z* (rel int) 414 (M^+, 3), 399 (25), 371 (7), 269 (41), 253 (100), 224 (67), 205 (48), 181 (75), 179 (69); HRCIMS *m/z* 415.1473 (M^+ + H), calcd for $C_{21}H_{23}N_2O_7$ 415.1505.

Phenazine Alkaloid 2 (2′-*O*-L-Quinovosyl Saphenate). Phenazine alkaloid **2**, obtained as an amorphous yellow solid (10 mg/L fermentation yield), showed: $[\alpha]_D$ −35° (*c* 0.49, MeOH); IR (film) 3362, 2975, 2932, 1727, 1567, 1268, 1059, 753 cm^{-1}; LRCIMS *m/z* (rel int) 415 (M^+ + H, 43), 399 (12), 397 (22), 269 (100), 255 (40), 129 (67), 85 (21).

Acetylation of Phenazines 1 and 2. In a typical experiment, phenazine **1** (10.0 mg) was combined with excess acetic anhydride and dry pyridine (ca. 1 mL each) and allowed to sit overnight. Removal of solvents under high vacuum, followed by silica HPLC purification (50% EtOAc in isooctane) yielded the tetraacetate **5** (5.9 mg, 42%), which showed the following spectral properties: IR (film) 2980, 1752, 1369, 1224, 1158, 1042, 755 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.42 (1 H, bd, H4), 8.21 (1 H, dd, 3.2, 7.6), 8.13 (1 H, bd, 6.9, H2), 7.85 (3 H, m), 7.20 (1 H, q, 6.5, H12), 6.37 (1 H, d, 3.6, H1′), 5.95 (1 H, t, 10, H3′), 5.30 (1 H, dd, 3.6, 10, H2′), 5.10 (1 H, t, 10, H4′), 4.15 (1 H, dq, 6, 10, H5′), 2.25 (3 H, s), 2.18 (3 H, s), 2.10 (3 H, s), 2.02 (3 H, s), 1.73 (3 H, d, 6.5, H13), (3 H, d, 6, H6′) ppm; EIMS *m/z* (rel int) 582 (M^+, 0.1), 540 (8), 522 (7), 293 (20), 267 (20), 251 (11), 222 (15), 206 (22), 43 (100); HRCIMS *m/z* 583.1886 (M^+ + H), calcd for $C_{29}H_{31}N_2O_{11}$ 583.1928. A small amount, 2.0 mg, of the tetraacetate of the C-1′ anomer was also isolated, but the compound was not fully characterized. In a similar experiment, phenazine **2** (8.8 mg) was acetylated to yield the tetraacetate **6** (9.2 mg, 74%), which showed the following spectral characteristics: IR (film) 2986, 1754, 1536, 1370, 1235, 1157, 1045, 919, 755, 732 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.42 (1 H, dd, 1.4, 8.6, H4), 8.23 (1 H, dd, 1.8, 7.9), 8.14 (1 H, dd, 1, 6.8, H2), 7.8 (2 H, m), 7.83 (1 H, dd, 6.8, 8.6, H3), 7.20 (1 H, q, 6.5, H12), 6.57 (1 H, d, 3.6 H1′), 5.65 (1 H, t, 9.4, H3′), 5.59 (1 H, dd, 3.6, 9.4, H2′), 5.01 (1 H, t, 9.4, H4′), 4.09 (1 H, dq, 6.1, 9.4, H5′), 2.18 (3 H, s), 2.09 (3 H, s), 2.07 (3 H, s), 2.04 (3 H, s), 1.74 (3 H, d, 6.5, H13), 1.27 (3 H, d, 6.1, H6′) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.5, 170.2, 169.7, 169.0, 165.1, 143.4, 141.8, 141.1, 140.6, 134.5, 132.5, 130.8, 129.6 128.8, 126.4, 89.2, 73.3, 70.2, 68.1, 67.9, 22.2, 21.4, 20.9, 20.8, 20.7, 17.4 ppm; EIMS *m/z* (rel int) 582 (M^+, 1), 540 (10), 522 (13), 293 (86), 266 (23), 249 (41), 222 (54), 206 (69), 43 (100).

Acid Hydrolyses of Phenazines 1 and 2. Phenazine **1** (13.0 mg) and 0.25 mL of Dowex 50X4-400 cation exchange resin were mixed in 4 mL of distilled H_2O and stirred at 60 °C under N_2 for 5 h. The resin was filtered and rinsed with MeOH. The aqueous filtrate and MeOH rinse were combined, reduced under vacuum to ca. 2 mL, and repeatedly extracted with EtOAc (3 × 5 mL). The EtOAc extracts were combined, and the solvents were removed under vacuum to leave 5.6 mg (67%) of pure, but racemic saphenic acid (**8**). Lyophilization of the aqueous phase gave 1.6 mg (35%) of pure L-quinovose.

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Registry No. **1**, 137570-42-4; **2**, 137570-43-5; **3**, 137570-44-6; **4**, 137570-45-7; **5**, 137570-46-8; **6**, 137593-95-4; **7**, 120464-88-2; **8**, 94448-14-3.

A Facile Synthesis of Optically Active 3-Ethyl- and 3-*n*-Butylphthalides via Catalytic Enantioselective Addition of Dialkylzinc Reagents to *o*-Phthalaldehyde

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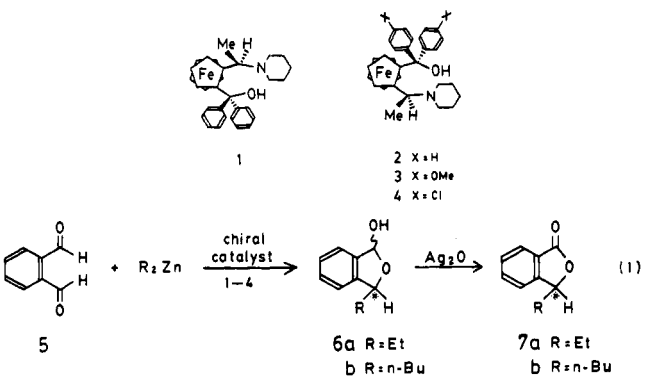
Recently we reported the high enantioselectivity of chiral 1,2-disubstituted ferrocenyl amino alcohols as a chiral catalyst of asymmetric addition of dialkylzincs to aldehydes.[1] In particular, (−)- and (+)-DFPE (**1** and **2**) gave the highest enantioselectivity and catalytic activity. We here describe a facile preparation of optically active 3-ethyl- and 3-*n*-butylphthalides (**7**). Optically active phthalides are naturally occurring substances many of which possess biological activity.[2] The approaches to the asymmetric synthesis of the phthalides can be classified into the following three procedures; (1) the addition of chiral (*o*-substituted aryl)lithium reagents to carbonyl compounds,[2c,3] (2) the addition of organometallics or metal hydride to chiral (*o*-acylaryl)oxazolines,[3b] and (3) the stoichiometric or catalytic asymmetric reduction of prochiral *o*-acylbenzoic esters.[2c,4] The present procedure is a new one based on the highly enantioselective addition of dialkylzinc reagents to *o*-phthalaldehyde (**5**), catalyzed by chiral 1,2-disubstituted ferrocenyl amino alcohols **1–4**, followed by oxidation of the resulting lactols **6** (eq 1).



(1)

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Table I. Asymmetric Addition of Dialkylzinc Reagents to *o*-Phthalaldehyde in the Presence of Chiral Catalysts 1–4[a]

entry	catalyst	R_2Zn	temp, °C	time, h	yield,[b] %	% ee	config[c]
1	1	Et_2Zn	0	4	54	86	*S*
2	1	Et_2Zn	rt	1	95	88	*S*
3[d]	1	Et_2Zn	rt	1	92	87	*S*
4	2	Et_2Zn	rt	1	92	88	*R*
5	3	Et_2Zn	rt	1	86	86	*R*
6	4	Et_2Zn	rt	0.5	85	90	*R*
7[e]	none	Et_2Zn	rt	1	30		
8[f]	2	Et_2Zn	rt	3	85	92	*R*
9[f,g]	2	Et_2Zn	rt	3	87	95	*R*
10[f,g]	4	Et_2Zn	rt	3	88	98	*R*
11	1	$(n\text{-}Bu)_2Zn$	rt	1	50	89	*S*[h]
12[f,g]	4	$(n\text{-}Bu)_2Zn$	rt	3	57	94	*R*[h]

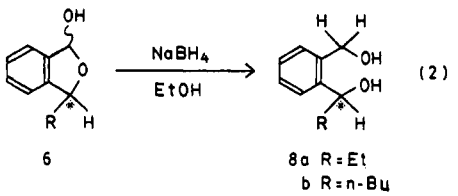
[a] Unless otherwise noted, the reaction was carried out in hexane with 5 mol % of catalyst, and 1.2 equiv of dialkylzinc was added to a suspension of powdered *o*-phthalaldehyde. [b] Isolated yield. [c] The configuration at the 3-position of lactols **6**. Unless otherwise noted, tentatively assigned by that *R,S* catalyst **1** afforded the (*S*)-alcohols in the alkylation of simple aldehydes.[1] [d] Toluene was used as solvent. [e] The reaction was conducted without catalyst. [f] A solid mass of *o*-phthalaldehyde was used. [g] 10 mol % of catalyst to aldehyde was used. [h] Assigned by the observation that (*S*)-(−)-3-*n*-butylphthalide (**7b**) was obtained by oxidation of the (−)-lactol **6b**.[9]

(*S,R*)-Bis(4-methoxyphenyl)carbinol (**3**) and (*S,R*)-bis(4-chlorophenyl)carbinol (**4**) were newly prepared from (*S*)-1-((*R*)-2-iodoferrocenyl)-1-piperidinoethane and substituted benzophenones in a similar manner to that reported for **1** and **2**.[1]

The reaction of diethyl- and di-*n*-butylzincs with *o*-phthalaldehyde (**5**) was carried out in the presence of **1**–**4** (5–10 mol %) in hexane at room temperature to afford monoadducts **6**[5] with high optical purity. The reaction conditions and results are summarized in Table I.

In the presence of 5 mol % of **1** the ethylation was sluggish at 0 °C (entry 1), but the reaction was smoothly completed in an hour at room temperature (entry 2).[6] Comparable selectivity was obtained in toluene, in which **5** is easily soluble (entry 3). With the enantiomer of **1**, (+)-DFPE **2**, the enantiomeric *R* lactol **6a** was obtained (entry 4). Of the two para-substituted analogues **3** and **4**, the *p*-chloro derivative **4** gave a slightly higher enantioselectivity (entry 6, 90% ee). As the reaction was found to proceed even without the catalyst in hexane at room temperature to afford the racemic lactol **6a** in a low yield (entry 7), we tried to reduce the uncatalyzed reaction by changing the physical form of **5** and the amount of catalyst. By using of a few pieces of solid mass (not powder) of **5**, the optical yield of **6a** was improved to 92% ee (entry 8).[7] It seems that the small surface area of solid mass of **5** lowered the concentration of **5** in hexane and hence increased the relative catalyst concentration to **5**. Further, the use of 10 mol % of **2** afforded a better result (entry 9, 95% ee). Bis(*p*-chlorophenyl) derivative **4** was superior to **2** (entry 10, 98% ee). The electron-withdrawing *p*-chloro groups of **4** are considered to lower the electron density on the zinc metal in the complex formed from **4** and dialkylzinc. This increases the Lewis acidity and the reactivity of the complex and consequently reduces the uncatalyzed reaction. The reaction of **5** with di-*n*-butylzinc in the presence of **4** (10 mol %) in hexane at room temperature afforded lactol **6b** in 94% ee (entry 12).

The enantioselectivities of **6a** and **6b** were estimated by HPLC analysis of the corresponding diols **8** obtained by sodium borohydride reduction of **6** (eq 2).



(2)

6 **8a** R = Et, **b** R = n-Bu

The lactols **6** obtained were oxidized with silver oxide[8] to optically active 3-alkylphthalides (**7**) in 80–81% yield without racemization.[3a] The absolute configuration of 3-butylphthalide (**7b**) was determined by the comparison with the literature.[3a,9]

Experimental Section

Materials. (−)- and (+)-DFPE (**1** and **2**) and (*S*)-1-((*R*)-2-iodoferrocenyl)-1-piperidinoethane were prepared according to the reported procedure.[1] Commercially available *o*-phthalaldehyde was recrystallized from hexane, and the powder or solid mass was used for the reactions. Diethylzinc in hexane was obtained from Kanto Chemical Co. Di-*n*-butylzinc was prepared from zinc chloride and 2 equiv of *n*-butyllithium in ether and purified by distillation.

(*S,R*)-1-[2-[Bis(*p*-substituted phenyl)hydroxymethyl]-ferrocenyl]-1-piperidinoethane (3 and 4). The following procedure for the preparation of **4** is typical: To a solution of (*S*)-1-((*R*)-2-iodoferrocenyl)-1-piperidinoethane (168 mg, 0.397 mmol)[1] in ether (1 mL) was added *n*-butyllithium (0.29 mL, 0.47 mmol, as a 1.63 M hexane solution) at 0 °C. After 10 min, 4,4′-dichlorobenzophenone (116 mg, 0.460 mmol) in THF (2 mL) was added at 0 °C, and the mixture was stirred at rt for 30 min and quenched with water. The resulting mixture was extracted with ether. The extract was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by TLC on silica gel (hexane–AcOEt, 4:1) to give **4** (176 mg, 0.321 mmol, 81%): R_f = 0.5; mp 83–89 °C; $[\alpha]^{22}_D$ +198.2° (*c* 0.660, EtOH); ^1H NMR ($CDCl_3$) δ 0.40–1.40 (m, 6 H), 1.21 (d, *J* = 6.9 Hz, 3 H), 2.24 (t, *J* = 4.2 Hz, 4 H), 3.83 (s, 6 H), 4.07–4.20 (m, 1 H), 4.20–4.55 (m, 2 H), 7.13 (s, 4 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.55 (d, *J* = 8.4 Hz, 2 H), 8.84 (s, 1 H); IR (KBr) 3450, 3100, 2950, 2820, 1590, 1578, 1490, 1400, 1380, 1095, 1018, 1000, 820 cm^{-1}. Anal. Calcd for

(1) Watanabe, M.; Araki, S.; Butsugan, Y.; Uemura, M. *J. Org. Chem.* **1991**, *56*, 2218.

(2) (a) Barton, D. H. R.; de Vries, J. X. *J. Chem. Soc.* **1963**, 1916. (b) Elander, M.; Leander, K.; Luning, B. *Acta Chem. Scand.* **1969**, *23*, 2177. (c) Ogawa, Y.; Hosaka, K.; Chin, M.; Mitsuhashi, H. *Heterocycles* **1989**, *29*, 865.

(3) (a) Asami, M.; Mukaiyama, T. *Chem. Lett.* **1980**, 17. (b) Meyers, A. I.; Hanagan, M. A.; Trefonas, L. M.; Baker, R. J. *Tetrahedron* **1983**, *39*, 1991.

(4) Ohkuma, T.; Kitamura, M.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 5509.

(5) The diastereomer ratio of lactols **6** at the 1-position was determined to be 1:1 by ^1H NMR: see the Experimental Section.

(6) Powdered *o*-phthalaldehyde (**5**) is slightly soluble in hexane, but gradually went into the solution during the reaction, and an almost clear solution was obtained at the end point.

(7) This increase in percent ee resulting from the use of solid mass of **5** was confirmed to be reproducible and significant by repeated experiments.

(8) Rosenberger, M.; Andrews, D.; DiMaria, F.; Duggan, A. J.; Saucy, G. *Helv. Chim. Acta* **1972**, *55*, 249.

(9) Nagai, U.; Shishido, T.; Chiba, R.; Mitsuhashi, H. *Tetrahedron* **1965**, *21*, 1701.

$C_{30}H_{31}Cl_2FeNO$: C, 65.71; H, 5.70; N, 2.55. Found: C, 65.72; H, 5.57; N, 2.45.

3: from (*S*)-1-((*R*)-2-iodoferrocenyl)-1-piperidinoethane and 4,4′-dimethoxybenzophenone, purified by TLC on silica gel (ether–CH_2Cl_2 = 1:1, R_f = 0.3); 47% yield; mp 84–90 °C; $[\alpha]^{22}_D$ +214.5° (*c* 0.667, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.20–1.44 (m, 6 H), 1.24 (d, *J* = 6.9 Hz, 3 H), 2.25 (t, *J* = 4.5 Hz, 4 H), 3.71 (s, 3 H), 3.80 (s, 3 H), 3.83 (s, 6 H), 4.02–4.17 (m, 1 H), 4.17–4.28 (m, 1 H), 4.38 (q, *J* = 6.9 Hz, 1 H), 6.66 (d, *J* = 8.7 Hz, 2 H), 7.09 (d, *J* = 8.7 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 7.51 (d, *J* = 8.7 Hz, 2 H), 8.57 (s, 1 H); IR (KBr) 3450, 3100, 2948, 2840, 1605, 1580, 1508, 1378, 1360, 1250, 1170, 1107, 1035, 1000, 820 cm^{-1}. Anal. Calcd for $C_{32}H_{37}FeNO_3$: C, 71.24; H, 6.91; N, 2.60. Found: C, 70.98; H, 7.11; N, 2.73.

General Procedure for the Enantioselective Addition of Dialkylzinc Reagents to *o*-Phthalaldehyde in the Presence of Chiral 1,2-Disubstituted Ferrocenyl Amino Alcohols. To a mixture of chiral 1,2-disubstituted ferrocenyl amino alcohol (**1–4**) (0.048 mmol) and *o*-phthalaldehyde (129 mg, 0.962 mmol) in hexane (3 mL) was added dialkylzinc (1.2 mmol, about 1 M hexane solution) at rt. The whole was stirred at rt for 1–3 h. Aqueous HCl (1 N) was added under cooling with ice–water. The resulting mixture was extracted with ether, and the extract was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by TLC on silica gel (CH_2Cl_2–ether, 5–6:1). The product was characterized by the ^{1}H NMR and IR spectra. The chiral 1,2-disubstituted ferrocenyl amino alcohol was recovered in over 90% yield from the aqueous acid solution by making it alkaline with concd aqueous NaOH followed by extraction with ether.

3-Ethyl-2-oxaindan-1-ol (6a): mp 62–66 °C in 98% ee; $[\alpha]^{22}_D$ +49.2° (*c* 1.03, C_6H_6) in 98% ee [lit.[3a] $[\alpha]_D$ −42.6° (*c* 5.35, C_6H_6) for the enantiomer in 88% ee]; R_f = 0.50 (CH_2Cl_2–ether, 5:1); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J* = 7.3 Hz, 1.5 H), 1.00 (t, *J* = 7.1 Hz, 1.5 H), 1.46–2.25 (m, 2 H), 3.36 (br d, *J* = 7.5 Hz, 0.5 OH), 3.47 (br d, *J* = 7.5 Hz, 0.5 OH), 5.12 (t, *J* = 5.0 Hz, 0.5 H), 5.25–5.52 (m, 0.5 H), 6.28–6.60 (m, 1 H), 7.02–7.60 (m, 4 H); IR (KBr) 3370, 3040, 2960, 2940, 2880, 1610, 1460, 1360, 990, 910, 755 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.43; H, 7.38.

(3*R*)-3-*n*-Butyl-2-oxaindan-1-ol (6b): oil; $[\alpha]^{22}_D$ +42.7° (*c* 1.43, C_6H_6) in 94% ee [lit.[3a] $[\alpha]_D$ −36.9° (*c* 3.47, C_6H_6) for 3*S* isomer in 87% ee]; R_f = 0.60 (CH_2Cl_2–ether, 6:1); ^{1}H NMR (CCl_4)[10] δ 0.91 (br s, 3 H), 1.08–2.00 (m, 6 H), 3.70 (br s, OH), 5.02 (t, *J* = 4.5 Hz, 0.5 H), 5.10–5.40 (m, 0.5 H), 6.12–6.43 (m, 1 H), 6.90–7.48 (m, 4 H); IR (neat) 3370, 3030, 2930, 2860, 1600, 1460, 1350, 1180, 1110, 990, 750 cm^{-1}.

Dimer 9: R_f = 0.90 (CH_2Cl_2–ether, 6:1, silica gel); ^{1}H NMR ($CDCl_3$)[10] δ 0.94 (br s, 6 H), 1.10–2.25 (m, 12 H), 5.15 (t, *J* = 6.0 Hz, 0.6 H), 5.29–5.58 (m, 1.4 H), 6.37–6.76 (m, 2 H), 6.97–7.70 (m, 8 H).

Determination of the Optical Purity of 3-Alkyl-2-oxaindan-1-ols (6). 3-Alkyl-2-oxaindan-1-ol (**6**) (20–30 mg) was reduced with $NaBH_4$ (3 equiv) in ethanol (1 mL) at 0 °C for 10 min. Water was added, and the resulting mixture was extracted with ether. The extract was washed with brine, dried (Na_2SO_4) and evaporated. Purification of the residue by TLC on silica gel gave 1-[2-(hydroxymethyl)phenyl]alkanol (**8**) in over 90% yield.

1-[2-(Hydroxymethyl)phenyl]propanol (8a): mp 53–56 °C in 98% ee; $[\alpha]^{22}_D$ +18.4° (*c* 0.870, $CHCl_3$) in 98% ee, which was determined by HPLC analysis: chiral column, Chiralcel OB, 4.6 × 250 mm; detection, 254-nm light; eluent, 6% 2-propanol in hexane; flow rate, 0.20 mL/min; t_R (min), 33.0 and 40.9; R_f = 0.30 (CH_2Cl_2–ether, 5:1); ^{1}H NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.5 Hz, 3 H), 1.58–2.05 (m, 2 H), 3.24 (br s, 2 H), 4.63 (d, *J* = 2.0 Hz, 2 H), 4.76 (t, *J* = 7.0 Hz, 1 H), 7.07–7.55 (m, 4 H).

(*R*)-1-[2-(Hydroxymethyl)phenyl]pentanol (8b): mp 72–73 °C in 94% ee; $[\alpha]^{22}_D$ +21.5° (*c* 0.805, $CHCl_3$) [lit.[2a] mp 73–74 °C; $[\alpha]_D$ −27° (*c* 1.07, $CHCl_3$), recrystallized from CH_2Cl_2 and petroleum ether] in 94% ee, which was determined by HPLC analysis: conditions of HPLC analysis were the same as mentioned as above except for using 4% 2-propanol in hexane as eluent; t_R (min), 46.8 and 56.0; R_f = 0.40 (CH_2Cl_2–ether, 5:1); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J* = 6.4 Hz, 3 H), 1.03–2.08 (m, 6 H), 3.09 (br s, 2 H), 4.65 (d, *J* = 2 Hz, 2 H), 4.85 (t, *J* = 6.8 Hz, 1 H), 7.10–7.65 (m, 4 H).

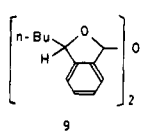
Optically Active 3-Ethyl- and 3-*n*-Butylphthalides (7a and 7b) were obtained by oxidation of the corresponding lactols **6a** and **6b** with silver oxide according to the reported procedure.[8] The compounds were purified by Kugelrohr distillation at 150–170 °C (1 mmHg) for **7a** and at 160–190 °C (1 mmHg) for **7b**.

3-Ethylphthalide (7a): yield, 58 mg (81%); $[\alpha]^{22}_D$ +76.9° (*c* 1.47, $CHCl_3$) in 98% ee; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, *J* = 7.5 Hz, 3 H), 1.55–2.40 (m, 2 H), 5.45 (dd, *J* = 4.4 Hz, 7.5 Hz, 1 H), 7.32–8.03 (m, 4 H); IR (neat) 3050, 2970, 1758, 1610, 1595, 1460, 1280, 1060, 960 cm^{-1}.

(*R*)-3-*n*-Butylphthalide (7b): yield, 71 mg (80%); $[\alpha]^{22}_D$ +62.7° (*c* 1.20, $CHCl_3$) in 94% ee [lit.[2a] $[\alpha]_D$ −57° (*c* 1.96, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, *J* = 7.3 Hz, 3 H), 1.10–2.30 (m, 6 H), 5.48 (dd, *J* = 4.2 Hz, 6.9 Hz, 1 H), 7.30–8.10 (m, 4 H); IR (neat) 3080, 2960, 1760, 1610, 1595, 1463, 1282, 1208, 1060, 720, 695 cm^{-1}.

Registry No. **3**, 137333-73-4; **4**, 137333-74-5; **5**, 643-79-8; **6a**, 75141-86-5; **6b**, 75141-85-4; (*R*)-**7a**, 137333-66-5; (*S*)-**7a**, 137333-67-6; (*R*)-**7b**, 125412-70-6; (*S*)-**7b**, 3413-15-8; (*R*)-**8a**, 137333-68-7; (*S*)-**8**, 137333-69-8; (*R*)-**8b**, 137333-70-1; (*S*)-**8b**, 137333-71-2; **9**, 137333-72-3; (*S*)-1-((*R*)-2-iodoferrocenyl)-1-piperidinoethane, 132644-66-7; 4,4′-dichlorobenzophenone, 90-98-2; 4,4′-dimethoxybenzophenone, 90-96-0.

(10) When the lactol **6b** was dissolved in $CDCl_3$, the solution soon became turbid and the hydroxy peak in the ^{1}H NMR spectrum gradually disappeared, probably owing to the presence of a trace of acid, to form the dimer **9**.



9

Quinolone Antibacterials: A Hydroxymethylation–Intramolecular Cyclization Route to Pyrido[3,2,1-*ij*]-1,3,4-benzoxadiazines

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Of the many structural variations of quinolone antibacterials examined to date, the incorporation of the N-1-α carbon atom into a ring joined at position 8 continues to show great promise. The prototype flumequine (FLU, Figure 1) contains an all carbocyclic bridge and was the first clinically useful quinolone possessing a 1,8-bridge. From this, a number of modifications of the 1,8-bridge ensued,[1] including replacement of carbon with heteroatoms,[2–4] variations of ring size[5] and substituents,[1] and stereocontrol of chiral centers within the bridge.[6–9]

(1) Wentland, M. P. In *The New Generation of Quinolones*; Siporin, C., Heifetz, C. L., Domagala, J. M., Eds.; Marcel Dekker: New York, 1990.
(2) Riker Laboratories. U.S. Patent 3,984,548, 1976.
(3) Daiichi Seiyaku. Japan Patent 57/203-085, 1982.
(4) Cecchetti, V.; Fravolini, A.; Fringuelli, R.; Mascellani, G.; Pagella, P.; Palmioli, M.; Segre, G.; Terni, P. *J. Med. Chem.* **1987**, *30*, 465.
(5) Otsuka. U.S. Patent 4,416,884, 1983.
(6) Gerster, J. F.; Rohling, S. F.; Winandy, R. M. *J. Med. Chem.* **1987**, *30*, 839.
(7) Mitscher, L. A.; Sharma, P. N.; Chu, D. T. W.; Shen, L. L.; Pernet, A. G. *J. Med. Chem.* **1987**, *30*, 2283.
(8) Haykawa, I.; Atarashi, S.; Yokohama, S.; Imamura, M.; Sakano, K.; Furukawa, M. *Antimicrob. Agents Chemother.* **1986**, *29*, 163.
(9) Imamura, M.; Shibamura, S.; Hayakawa, I.; Osada, Y. *Antimicrob. Agents Chemother.* **1987**, *31*, 325.

0022-3263/92/1957-0744$03.00/0