EtOAc (1 mL), filtered, and rinsed through a short (1-in.) column of silica gel with EtOAc. The solvent was removed and the peroxide mixture analyzed by NMR.

Peroxides from 7c. Ozonation of **7c** (72 mg) provided 97 mg (92%) of a mixture of **24c**, **25c**, and **26c** in a 41:29:30 ratio by NMR: ^{1}H NMR (in $CDCl_3$, after shake with D_2O to remove interfering OH signal) δ 5.20 (m, **26c**, 0.30 H), 4.69 (m, **24c** and **25c**, 0.70 H), 4.1–3.5 (m, 1 H), 3.48–3.39 (5 s, 3 H), 2.16 (s, **25c**, 0.88 H), 2.1–1.6 (m, 4 H), 1.45–1.15 (5 s, **24c** and **26c**, 2.10 H), 0.19–0.09 ppm (3 s, 9 H). Treatment of this mixture with excess $(CH_3)_2S$ caused conversion to **27c** over a 20-h period: ^{1}H δ 9.77 (t, J = 1.3 Hz, 1 H), 4.05 (t, J = 6.5 Hz, 1 H), 2.52 (t, J = 7.6 Hz, 2 H), 2.18 (s, 3 H), 2.00 (m, 2 H), 0.14 ppm (s, 9 H).

Peroxides from 7e. Ozonation of 44 mg (0.32 mmol) of **7e** provided 54 mg (77%) of a peroxide mixture containing **24e**, **25e**, and **26e** in a 41:40:19 ratio by NMR: ^{1}H δ 5.28 (m, **26e**, 0.19 H), 5.03 (m, **24e** and **25e**, 0.81 H), 4.9–4.7 (m, 1 H), 3.5–3.3 (6 s, 3 H), 2.21–2.05 (6 s, OAc for all and CH_3 for **25e**, 4.2 H), 2.1–1.7 (m, 4 H), 1.5–1.2 ppm (6 s, **24e** and **26e**, 1.8 H). Exposure of this mixture to excess $(CH_3)_2S$ overnight led to ketoaldehyde **27e**: ^{1}H δ 9.78 (br s, 1 H), 5.02 (dd, J = 7.5, 5.1 Hz, 1 H), 3.46 (s, 3 H), 2.61 (t, J = 7.3 Hz, 2 H), 2.20 (s, 3 H), 2.14 (s, 3 H), 2.13 ppm (m, 2 H).

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Notes

Rare Phenazine L-Quinovose Esters from a Marine Actinomycete

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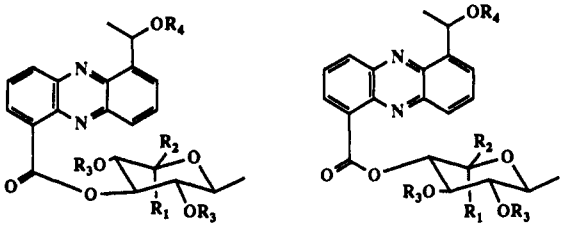
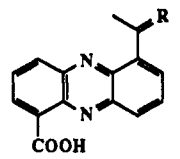
Although soil-derived bacteria have proven to be the major source for commercial antibiotics and related bioactive metabolites, similar microorganisms found in marine habitats have been almost totally ignored.[1] This has been due, in part, to the diversity of unique bacteria in marine habitats and the fact that many of these microorganisms are not readily brought into culture. As part of a continuing program to explore the nutritional requirements, distributions, and secondary metabolites produced by marine bacteria,[2] we have initiated several studies of bacteria from bay and estuarine environments. A study of the shallow sediments in Bodega Bay, CA, resulted in the isolation of a filamentous bacterium (isolate CNB-253, an unknown *Streptomyces* sp.) which was found to produce compounds with broad-screen antibacterial activity. Subsequent fermentation in saltwater-based media, followed by EtOAc extraction of the whole broth, vacuum flash chromatographic purification of the extract, and HPLC purification led to the isolation of four new alkaloid esters of the rare phenazine class (**1**–**4**, Chart I).[3] In addition, minor quantities of the known compounds

Chart I

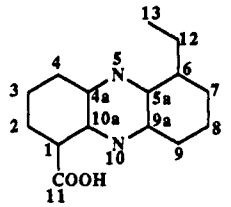


1. R_1=OH, R_2=R_3=R_4=H
4. R_1=R_3=R_4=H, R_2=OH
5. R_1=OAc, R_2=H, R_3=R_4=Ac

2. R_1=OH, R_2=R_3=R_4=H
3. R_1=R_3=R_4=H, R_2=OH
6. R_1=OAc, R_2=H, R_3=R_4=Ac



7. R= =O
8. R=H, OH



6-acetylphenazine-1-carboxylic acid (**7**) and saphenic acid (**8**) were also isolated.[4]

Revealing their isomeric relationships, all four phenazine alkaloid esters (**1**–**4**) showed identical molecular ions at m/z 414 amu (LREIMS), which was analyzed by high-resolution methods for $C_{21}H_{22}N_2O_7$. The ^{1}H NMR spectra for all four compounds (Table I) showed six aromatic protons and those from a hexose sugar pyranose functionality. The ^{1}H NMR spectrum of the major compound, **2**, resolved the aromatic resonances, and decoupling experiments revealed that they belonged to two isolated spin systems each involving three contiguous protons. All four compounds also showed a methyl group at δ 1.8 ppm (d, J = 6.5 Hz) that was coupled to a deshielded methine proton at δ 5.8 ppm (dq, J = 2.0, 6.5 Hz) which simplified to a quartet upon changing the NMR solvent from pure

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Table I. ^{1}H NMR Data for the Phenazine Esters 1–4[a]

C no.	1	2	3	4
2	8.26 (dd, 1.5, 6.9)	8.25 (dd, 1.5, 6.9)	8.27 (dd, 1.4, 6.8)	8.25 (dd, 1.4, 6.8)
3	7.9 (m)	7.87 (m)	7.9 (m)	7.9 (m)
4	8.38 (dd, 1.5, 8.8)	8.38 (dd, 1.5, 8.8)	8.43 (dd, 1.4, 8.6)	8.36 (dd, 1.0, 8.6)
7	7.9 (m)	7.87 (m)	7.9 (m)	7.9 (m)
8	7.9 (m)	7.87 (m)	7.9 (m)	7.9 (m)
9	8.17 (dd, 2.0, 8.0)	8.15 (dd, 2.0, 8.0)	8.21 (dd, 2.0, 8.2)	8.16 (dd, 2.9, 7.2)
12	5.90 (q, 6.5)	5.85 (q, 6.5)	5.87 (q, 6.5)	5.83 (q, 6.5)
13	1.75 (d, 6.5)	1.75 (d, 6.5)	1.75 (d, 6.5)	1.75 (d, 6.5)
1′	5.32 (d, 4.0)	5.55 (d, 3.5)	4.79 (d, 7.9)	4.82 (d, 7.9)
2′	3.81 (dd, 4.0, 8.0)	5.18 (dd, 3.5, 9.5)	5.09 (dd, 7.9, 9.4)	3.58 (dd, 7.9, 9.4)
3′	5.58 (t, 9.5)	4.21 (t, 9.5)	3.85 (t, 9.4)	5.29 (t, 9.4)
4′	3.45 (t, 9.5)	3.43 (t, 9.5)	3.45 (m)	3.47 (t, 9.4)
5′	4.19 (dq, 6.5, 9.5)	4.06 (dq, 6.5, 9.5)	3.45 (m)	3.65 (dq, 6.5, 9.4)
6′	1.41 (d, 6.5)	1.40 (d, 6.5)	1.42 (d, 6.5)	1.41 (d, 6.5)

[a] Recorded in 10% CD_3OD in $CDCl_3$ at 360 MHz. All chemical shifts are reported with reference to internal TMS at 0.00 ppm. Coupling constants are given in Hz after the multiplicity for each resonance.

Table II. ^{13}C NMR Data for the Phenazine Esters 1–4[a]

C no.	1	2	3	4
1	131.3 (C)	130.5 (C)	130.7 (C)	131.2 (C)
2	132.5 (CH)	133.3 (CH)	132.9 (CH)	132.5 (CH)
3	127.2 (CH)[b]	121.2 (CH)[b]	127.3 (CH)[b]	127.2 (CH)[b]
4	133.2 (CH)	134.0 (CH)	133.8 (CH)	133.2 (CH)
4a	139.4 (C)[c]	139.4 (C)[c]	139.2 (C)[c]	139.3 (C)[c]
5a	141.5 (C)[c]	141.4 (C)[c]	141.4 (C)[c]	141.2 (C)[c]
6	143.3 (C)	143.7 (C)	142.7 (C)	143.3 (C)
7	127.4 (CH)[b]	127.6 (CH)[b]	127.3 (CH)[b]	127.5 (CH)[b]
8	129.5 (CH)[b]	129.3 (CH)[b]	129.3 (CH)[b]	129.4 (CH)[b]
9	132.0 (CH)	132.1 (CH)	132.1 (CH)	132.0 (CH)
9a	141.8 (C)[c]	141.6 (C)[c]	141.6 (C)[c]	141.8 (C)[c]
10a	143.0 (C)[c]	142.8 (C)[c]	143.9 (C)[c]	143.0 (C)[c]
11	168.5 (C)	167.3 (C)	167.6 (C)	168.3 (C)
12	67.2 (CH)	66.9 (CH)	66.9 (CH)	67.2 (CH)
13	23.7 (CH_3)	23.6 (CH_3)	23.6 (CH_3)	23.7 (CH_3)
1′	92.3 (CH)	90.6 (CH)	94.6 (CH)	96.4 (CH)
2′	70.9 (CH)	76.9 (CH)	79.1 (CH)	73.0 (CH)
3′	79.7 (CH)	71.3 (CH)	72.8 (CH)	81.5 (CH)
4′	73.9 (CH)	75.5 (CH)	75.0 (CH)	73.6 (CH)
5′	67.5 (CH)	67.7 (CH)	67.7 (CH)	71.8 (CH)
6′	17.5 (CH_3)	17.7 (CH_3)	17.7 (CH_3)	17.5 (CH_3)

[a] Recorded in 10% CD_3OD in $CDCl_3$ at 50 MHz. Chemical shifts are reported with reference to $CDCl_3$ at 77.0 ppm. [b,c] Carbon resonances may be interchanged.

$CDCl_3$ to $CDCl_3/CD_3OD$. This indicated the presence of a CH_3CHOH fragment attached to the other part of the molecule via a quaternary carbon. Through analyses of ^{1}H NMR couplings, and by COSY NMR experiments, it was relatively easy to deduce the presence of a quinovose (6-deoxyglucose) ester residue in all four compounds. When these data were combined, it was apparent that compounds 1–4 were quinovose esters of saphenic acid (8), a phenazine carboxylic acid previously isolated from culture broths of the soil-derived actinomycete (*Streptomyces luteogriseus*[5] Proton and ^{13}C NMR data assigned to the phenazine ring portion of 1–4 were in excellent agreement with those values observed by us and reported for 8.[5,6] Acid hydrolysis of 1 and 2 yielded saphenic acid and quinovose in modest yield. Saphenic acid was identified by comparison of its ^{1}H NMR and MS data with the reported values, and quinovose was identified by HPLC, ^{1}H NMR, and MS comparison with an authentic sample.[7]

Because acid hydrolysis of 1 and 2 gave identical products, saphenic acid and quinovose, the alkaloids 1–4 were concluded to be regioisomeric esters of quinovose linked at two different hydroxyl positions. In the ^{1}H NMR spectrum of 1, the resonance assigned to H3′ was observed at δ 5.58, a chemical shift indicating the site of esterification of the sugar ring. This, in combination with the lack of further coupling of H3′ to a hydroxyl proton, confirmed this assumption. Upon treatment with acetic anhydride and pyridine, 1 yielded the tetraacetate 5. Whereas most protons in 5 were shifted to low field upon acetylation, H3′ was not appreciably shifted. Hence, the structure of 1 was confirmed as 3′-*O*-quinovosyl saphenate. Isomer 2 was then recognized as a regioisomer in which esterification had taken place at another sugar hydroxyl position. The ^{1}H NMR resonances assigned to H1′, H3′, and H4′ in 2 each showed couplings to an exchangeable proton. The low-field shift for the H2′ methine proton, coupled with the fact that no hydroxyl proton coupling was observed, implied that the ester linkage was attached to the sugar moiety at C2′. A three-bond NMR correlation from H2′ to the carboxyl carbon, C11, in the COLOC experiment confirmed this assignment. Hence, the structure of 2 was assigned as 2′-*O*-quinovosyl saphenate.

The coupling constants between the anomeric protons and the axial H2′ protons in both 1 and 2 (4 and 3.5 Hz, respectively) indicated that H1′ is equatorial; hence, 1 and 2 are α anomers. On standing, 1 and 2 slowly equilibrated to their corresponding β anomers, 3 and 4. These compounds, also isolated and purified as natural products from the extract, showed large axial–axial coupling (7.9 Hz) between H1′ and H2′, confirming the equatorial orientation of the C1′ hydroxyl.

In an attempt to assign the absolute stereochemistry of these esters, the optical rotations of both hydrolysis products, saphenic acid and quinovose, were obtained. Saphenic acid, from both 1 and 2, showed $[\alpha]_D = 0°$, hence it was assumed to be racemic. The lone chiral carbon in saphenic acid has been reported to racemize under basic conditions.[4] Our observations here suggest racemization occurs rapidly in mild acid as well. The CD spectrum of quinovose, isolated from both 1 and 2, showed $[\theta] = -82.6°$ cm^{-1} M^{-1} at 195 nm. For comparison purposes, the CD spectrum of a commercial sample of D-quinovose[6] showed $[\theta] = +86.4°$ cm^{-1} M^{-1} at 195 nm. Since the sign of the Cotton effect at 195 nm was opposite that of the commercial sample, the natural quinovose in the phenazine esters 1–4 must possess the rare L configuration.

The phenazine alkaloids 1–4 are new members of a moderately rare family of naturally occurring compounds. The sugar–ester functionalities of 1–4 are uncommon, although D-quinovose is a common hexose found in the saponin glycosides isolated from marine sea cucumbers.[8] To the best of our knowledge, however, this is the first or one of the rare observations of L-quinovose in nature.

Comprehensive antibacterial testing with 1 and 2 showed these compounds to exhibit modest broad spectrum activity against numerous Gram-positive and Gram-negative bacteria. Phenazine 1 shows its most potent activity against *Hemophilus influenzae* (MHB+1% supp C) with MIC values of 1 μg/mL and also inhibits *Clostridium*

(5) Takahashi, K.; Takahashi, I.; Morimoto, M.; Tomita, F. *J. Antibiotics* **1986**, *39*, 624.
(6) (a) Romer, A. *Org. Magn. Res.* **1982**, *19*, 66. (b) Romer, A. *Org. Magn. Res.* **1983**, *21*, 131.
(7) D-Quinovose (6-deoxy-D-glucose) was purchased from Sigma Chemical Co., St. Louis, MO, catalog no. D 9761.
(8) See for example: Chanley, J. D.; Ledeen, R.; Wax, J.; Nigrelli, R. F.; Sobotka, H. *J. Am. Chem. Soc.* **1959**, *81*, 5180.

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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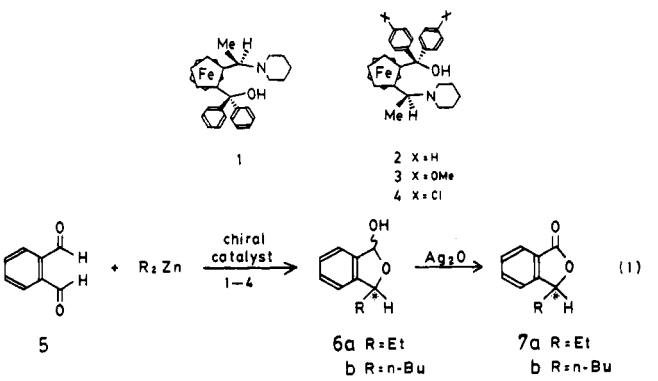
Recently we reported the high enantioselectivity of chiral 1,2-disubstituted ferrocenyl amino alcohols as a chiral catalyst of asymmetric addition of dialkylzincs to aldehydes.[1] In particular, (−)- and (+)-DFPE (**1** and **2**) gave the highest enantioselectivity and catalytic activity. We here describe 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).



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