Coruscol A, a New Metabolite from the Marine-Derived Fungus *Penicillium* Species

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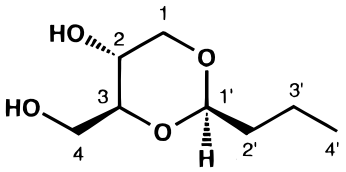
A new metabolite possessing a 1,3-dioxane ring, coruscol A (**1**), was isolated from the mycelium of the fungus *Penicillium* sp., which was separated from the Okinawan marine bivalve *Mytilus coruscus*, and the structure was elucidated by spectroscopic data.

Marine microorganisms such as bacteria, fungi, and microalgae have proven to be a rich source of structurally novel and biologically active secondary metabolites.[1] In our search for new substances from marine microorganisms,[2] a new metabolite having a 1,3-dioxane ring, coruscol A (**1**), was isolated from the mycelium of the fungus *Penicillium* sp., which was separated from the Okinawan marine bivalve *Mytilus coruscus*. In this paper we describe the isolation and structure elucidation of **1**.

The fungus *Penicillium* sp. was separated from the bivalve *M. coruscus* collected off Seragaki Beach, Okinawa Island, and grown in PYG broth [peptone (1%), yeast extract (0.5%), and glucose (2%) in seawater, pH 7.5] at 28 °C for 14 days. The mycelium (331 g from 10 L of culture) was extracted with $CHCl_3$/MeOH (1:1), and the extracts were partitioned with EtOAc and H_2O, and then the aqueous layer was extracted with *n*-BuOH. The *n*-BuOH-soluble portions were separated by a Si gel column ($CHCl_3$/MeOH, 8:1) and Sep-Pak C_{18} cartridge column (MeOH/H_2O, 4:1) to give coruscol A (**1**, 0.0037% wet wt) together with a known alkaloid, herquline A (**3**).[3−5]



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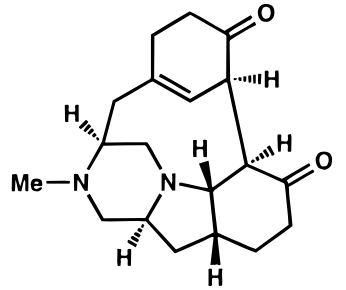

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The molecular formula, $C_8H_{16}O_4$, of coruscol A (**1**) was established by HRFABMS [*m/z* 177.1098 $(M + H)^+$, Δ −2.9 mmu]. The IR spectrum suggested the presence of hydroxy group (3435 cm^{-1}). ^1H and ^{13}C NMR data (Table 1) indicated that the molecule possessed one acetal, two oxymethines, two oxymethylenes, two methylenes, and one methyl group. Analysis of the $^1H-^1H$ COSY spectrum (Figure 1) revealed connectivities of C-1 to C-4 and C-1′ to C-4′. HMBC correlations (Figure 1) of H-1α (δ_H 3.40) and H-1β (δ_H 4.16) to C-1′ (δ_C 101.79) and H-1′ (δ_H 4.55) to C-1 (δ_C 70.53) and C-3 (δ_C 80.61) indicated the presence of a 1,3-dioxane ring. A chair conformation of the 1,3-dioxane ring and two axial protons of H-2 (δ_H 3.77) and H-3 (δ_H 3.47) were deduced from NOESY correlations (Table 1 and Figure 2) of H-1α to H-3, H-1′ to H-1α and H-3, and $^1H-^1H$ coupling constants ($J_{1\alpha,2}$ = 10.6 Hz and $J_{2,3}$ = 10.0 Hz). Treatment of **1** with pivaloyl chloride and pyridine followed by reaction with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride (MTPA-Cl) afforded a 1:1 mixture of diastereomers (**2a** and **2b**) of the (*S*)-MTPA ester (Scheme 1), indicating that **1** was a racemic mixture. Thus, coruscol A (**1**) was assigned as 1,3-*O*-butylidene-erythritol.

Table 1. ^1H and ^{13}C NMR Data of Coruscol A (**1**) in $CDCl_3$

position	$^1H^a$		*J*(Hz)	$^{13}C^a$	NOESY correlations
1 (α)	3.40	t	10.6	70.53	H-3, H-1′
(β)	4.16	dd	10.6, 5.4		
2	3.77	m		62.78	H-1β, H-4
3	3.47	dt	10.0, 4.0	80.61	H-1α, H-4, H-1′
4	3.86	d	4.0	62.79	H-2
1′	4.55	t	5.0	101.79	H-1α, H-3
2′	1.60	m		36.35	
3′	1.43	m		17.48	
4′	0.93	m		13.91	

[a] Values are given in parts per million.

This is the first isolation of 1,3-*O*-butylidene-erythritol (**1**) from natural sources, although it has been reported as a synthetic compound.[6] Coruscol A (**1**) may be biosynthetically derived from erythritol (C-1−C-4) and *n*-butyraldehyde (C-1′−C-4′). It is noted that a unique pentacyclic alkaloid, herquline A (**3**), is contained in the same marine-derived fungus *Penicillium* sp., although compound **3** has been isolated from the terrestrial fungus *P. herquei*.[3−5]

Experimental Section

General Experimental Procedures. The 7.26-ppm resonance of residual $CHCl_3$ and the 77.0-ppm resonance of $CDCl_3$ were used as internal references for ^1H and ^{13}C NMR spectra, respectively. FABMS were obtained using glycerol as a matrix.

Collection and Cultivation. The fungus *Penicillium* sp. (K029) was separated from the marine bivalve *M. coruscus*, which was collected off Seragaki Beach, Okinawa Island.

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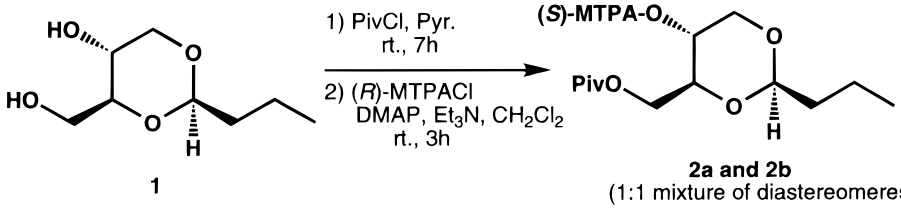
Scheme 1. Preparation of (*S*)-MTPA Esters (**2a** and **2b**) of Coruscol A (**1**)



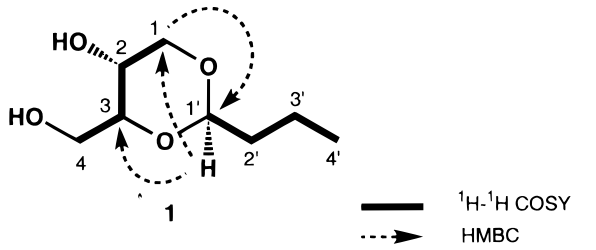


Figure 1. Selected $^1H-^1H$ COSY and HMBC correlations of coruscol A (**1**).

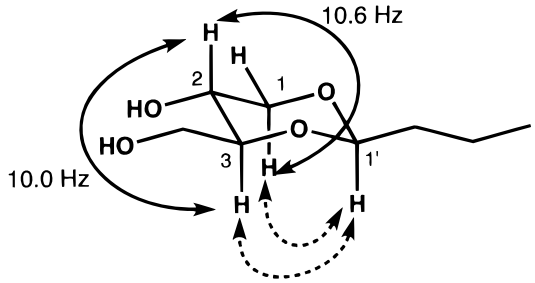


Figure 2. Relative stereochemistry of coruscol A (**1**). Dotted arrows denote NOESY correlations.

Subcultures of the organism are deposited at the Graduate School of Pharmaceutical Sciences, Hokkaido University. The fungus was grown in the PYG broth [peptone (1%), yeast extract (0.5%), and glucose (2%) in seawater, pH 7.5] at 28 °C for 14 days. The cultured broth (1 L) was filtered.

Extraction and Separation. The mycelium (331 g of wet wt) of the culture was extracted with $CHCl_3$/MeOH (1:1, 500 mL × 2) and evaporated under reduced pressure. The extracts were partitioned between EtOAc (400 mL × 3) and H_2O (400 mL), and then the H_2O layer was extracted with *n*-BuOH (400 mL × 3). The *n*-BuOH-soluble portions (3.2 g) were subjected to a Si gel column ($CHCl_3$/MeOH, 8:1) to afford herquline A (10 mg) and a fraction (18 mg), the latter of which was separated by a Sep-Pak C_{18} cartridge column (MeOH/H_2O, 4:1) to give coruscol A (**1**, 12.4 mg).

Coruscol A (1): colorless amorphous solid; IR (KBr) ν_{max} 3435, 2926, and 2854 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; FABMS *m*/*z* 177 $[M + H]^+$; HRFABMS *m*/*z* 177.1098 $[M + H]^+$ (calcd for $C_8H_{17}O_4$, 177.1127); HMBC correlations: H-1α/C-2, H-1α/C-3, H-1α/C-1′, H-1*β*/C-2, H-1*β*/C-3, H-1*β*/C-1′, H-2/C-4, H-3/C-4, H-3/C-1, H_2-4/C-2, H_2-4/C-3, H-1′/C-1, H-1′/C-3, H-1′/C-3′, H_2-2′/C-1′, H_2-2′/C-3′, H_2-2′/C-4′, H_2-3′/C-1′, H_2-3′/C-2′, H_2-3′/C-4′, H_3-4′/C-2′, and H_3-4′/C-3′.

***(S)*-MTPA Ester (2) of 1.** To a solution of coruscol A (**1**, 1.3 mg) in pyridine and CH_2Cl_2 (1:1, 40 μL), pivaloyl chloride (5 μL) was added at room temperature for 30 min. After addition of saturated NH_4Cl aqueous solution (100 μL), the mixture was extracted with EtOAc (100 μL × 3), washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a residue that was purified on a Si gel column (hexane/EtOAc, 1:1) to afford the pivaloyl ester (1.4 mg, 72%). To a pyridine solution (20 μL) of the pivaloyl ester (0.5 mg), (*R*)-MTPA-Cl (5 μL) was added and stirred at room temperature overnight. After evaporation of solvent, the residue was purified by a Si gel column (hexane/EtOAc, 1:1) to give the (*S*)-MTPA esters (**2a** and **2b**) as colorless oil.

Compound 2a: ^1H NMR ($CDCl_3$) δ 3.35 (1H, t, *J* = 10.6 Hz, H-1a), 4.30 (1H, dd, *J* = 10.6, 5.4 Hz, H-1b), 3.80 (1H, m, H-2), 5.06 (1H, m, H-3), 4.27 (1H, dd, *J* = 12.4, 3.7 Hz, H-4a), 4.10 (1H, dd, *J* = 12.4, 2.2 Hz, H-4b), 4.51 (1H, t, *J* = 5.1 Hz, H-1′), 1.61 (2H, m, H-2′), 1.40 (2H, m, H-3′), 0.90 (3H, m, H-4′), 1.56 (9H, s, Piv), 7.40 (2H, m, Ph), 7.19 (3H, m, Ph), 3.45 (3H, s, OMe).

Compound 2b: ^1H NMR ($CDCl_3$) δ 3.35 (1H, t, *J* = 10.6 Hz, H-1a), 4.36 (1H, dd, *J* = 10.6, 5.4 Hz, H-1b), 3.76 (1H, m, H-2), 5.10 (1H, m, H-3), 4.16 (1H, dd, *J* = 12.4, 3.7 Hz, H-4a), 3.86 (1H, dd, *J* = 12.4, 2.2 Hz, H-4b), 4.54 (1H, t, *J* = 5.1 Hz, H-1′), 1.61 (2H, m, H-2′), 1.40 (2H, m, H-2′), 0.90 (3H, m, H-4′), 1.56 (9H, s, Piv), 7.39 (2H, m, Ph), 7.18 (3H, m, Ph), 3.44 (3H, s, OMe).

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