Synthetic Study of Piericidins. II. Synthesis of Piericidin Analogues

Machiko ONO,* Norio YOSHIDA, and Hiroyuki AKITA*

School of Pharmaceutical Sciences, Toho University, 2–2–1 Miyama, Funabashi, Chiba, 274, Japan.
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Two piericidin analogues having a simple aromatic ring were synthesized based on a palladium-catalyzed cross-coupling reaction and the reaction of sulfone and aldehyde by the Julia coupling procedure. The reaction of 3-methoxyphenyl-tri-*n*-butyltin (8) and a mixture of allylic chlorides ((*E*)-9 and (*Z*)-10) in the presence of tetrakis(triphenylphosphine) palladium(0) afforded a mixture of 5-arylacetals (*E*)-11 and (*Z*)-12. The coupling reaction of the non-conjugated aldehyde (*E*)-13 or (*Z*)-14 prepared from the 5-arylacetal (*E*)-11 or (*Z*)-12 and the sulfone 4 provided (2*E*)-19 or (2*Z*)-20. Benzoylation of (2*E*)-19 or (2*Z*)-20 followed by reductive olefin-formation with sodium amalgam gave the piericidin analogue (2*E*)-1 or (2*Z*)-2. Analogue (2*E*)-1 has the same side chain as natural piericidin and analogue 2 is the (2*Z*)-isomer of analogue 1 at the side chain.

Key words piericidin analogue; palladium-catalyzed cross-coupling; sulfone-aldehyde Julia coupling; reductive olefin-formation

Piericidins are metabolites of *Streptomyces mobaraensis* and *pactam*[1] and have been well-known as inhibitors of the mitochondrial transport system.[2] These compounds have a 2′,3′,5′,6′-tetrasubstituted 4-pyridinol ring with a long side chain at the 2′-position (Chart 1). The side chain includes two chiral centers and an all (*E*)-tetraene structure. The structure activity relationship[3] of natural piericidins and their modified derivatives has been studied. Based on the results, a partial structure (A) (Chart 1) was proposed as being essential for piericidin-like activity on NADH oxidation. Thus, it is suggested that the unsaturation between the C_2-position and C_3-position is important for the inhibitory effect. Rotenone is a classical inhibitor of NADH-ubiquinone oxido-reductase in the respiratory chain.[4] There is no apparent structural similarity among rotenone, amytal (barbiturate), myxalamide D and piericidins as shown in Chart 1, but all of these compounds inhibit the same site in the electron transport system.[2] Therefore, we selected as synthetic targets the piericidin analogues **1** and **2** corresponding to the (*E*)- and (*Z*)-isomers at the 2-position of the side chain, respectively (Chart 2). Analogue **1** has a simple aromatic ring and the same side chain as natural piericidin B_1.

In the preceding paper[5] the preparation of the side chain of piericidin B_1 (**3**) was achieved based on coupling between the sulfone **4** and the non-conjugated aldehyde **5** (Chart 2). An attempt to combine an allylic halide **6** derived from **3** with *N*-chlorosuccinimide (NCS) and triphenylphosphine and 2-bromo-3-methyl-4-benzyloxy-5,6-dimethoxypyridine (**7a**), which was prepared according to Schmidtchen and Rapoport,[6] was unsuccessful. Reaction of the lithium anion **7b** and allylic halide **6** only afforded 3-methyl-4-benzyloxy-5,6-dimethoxypyridine. Palladium-catalyzed cross-coupling of **6** and **7a** in the presence of hexamethylditin gave the same result. Further, the reaction of 3-methoxyphenyl-tri-*n*-butyltin (**8**), prepared from 3-bromoanisole and tri-*n*-butyltin chloride, and **6** in the presence of palladium(0) catalyst did not afford the desired **1**. In this paper, we describe the synthesis of two piericidin analogues (2*E*)-**1** and (2*Z*)-**2** according to the sequence shown in Chart 3. 1) Preparation of the non-conjugated aldehyde (*E*)-**13** or (*Z*)-**14** from the arylacetal (*E*)-**11** or (*Z*)-**12** by acid hydrolysis under mild conditions. 2) Carbon–

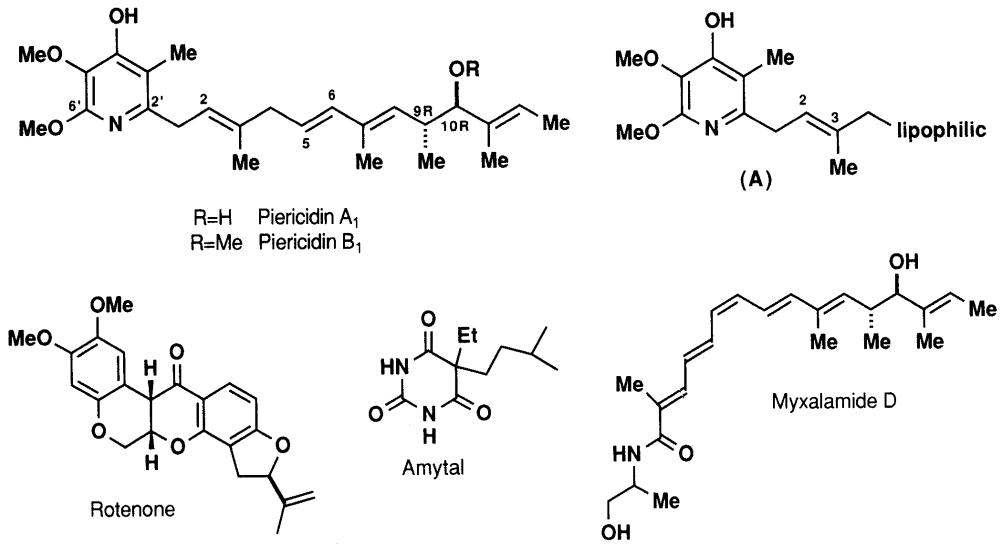


Chart 1

* To whom correspondence should be addressed.

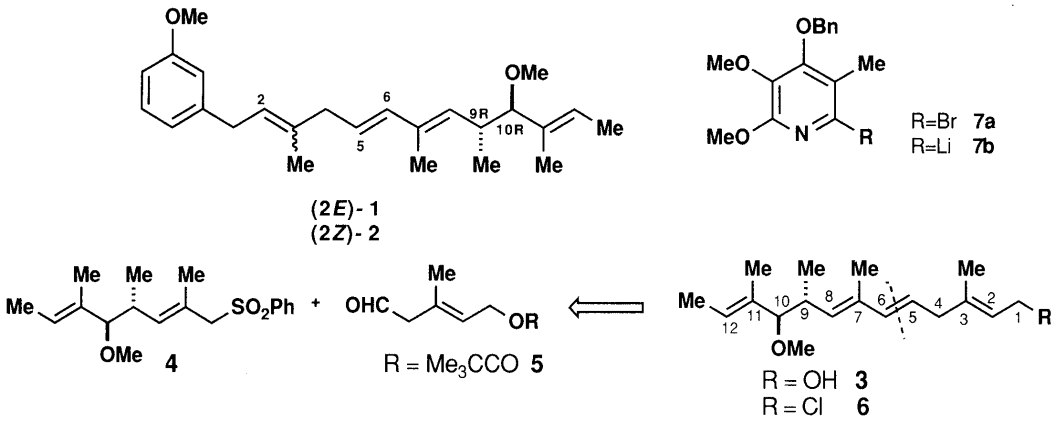


Chart 2

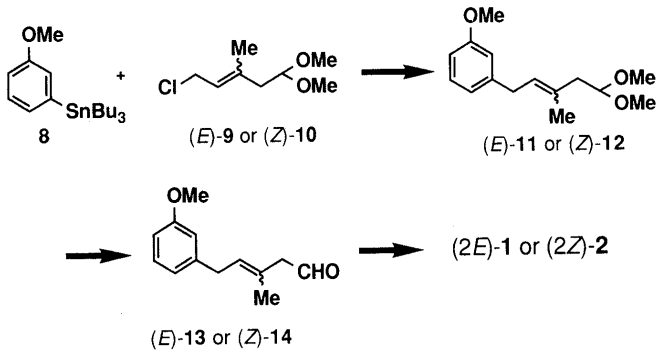


Chart 3

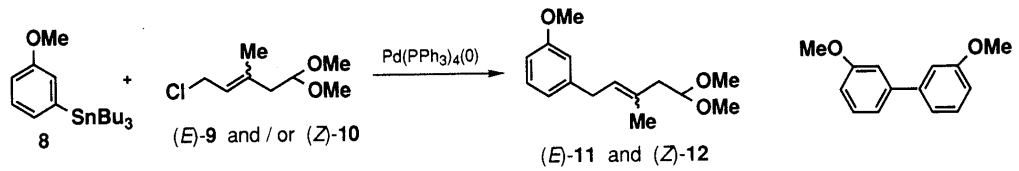
carbon double bond formation from the non-conjugated aldehyde (*E*)-**13** or (*Z*)-**14** by applying Julia's method.[7]

Palladium-Catalyzed Cross-Coupling of Aryltin and Allylic Chloride The reaction of 3-methoxyphenyl-tri-*n*-butyltin (**8**) and a mixture of acetals (*E*)-**9** and (*Z*)-**10** (70 : 30), prepared from 3-methyl-5,5-dimethoxy-2-pentenol[5] (*E* : *Z* = 70 : 30), in *N*,*N*-dimethylformamide (DMF) in the presence of tetrakis(triphenylphosphine) palladium (0) at 100 °C overnight afforded a mixture of 5-arylacetals (*E*)-**11** and (*Z*)-**12** (62 : 38) in 26% yield and 3,3′-dimethoxybiphenyl in 36% yield (entry 1 in Table 1). When the same palladium-catalyzed reaction in toluene was carried out at 100 °C overnight, a mixture of 5-arylacetals (*E*)-**11** and (*Z*)-**12** was obtained in 68% yield along with 3,3′-dimethoxybiphenyl (15% yield) (Entry 2). On the other hand, when pure (*E*)-**9** or (*Z*)-**10** was subjected to the above cross-coupling reaction, the geometry of the starting material was not retained and a mixture of (*E*)-**11** and (*Z*)-**12** with almost the same ratio (62 : 38—58 : 42) as in the previous case was obtained (entries 3, 4). Fortunately the 5-arylacetals (*E*)-**11** and (*Z*)-**12** were separable by silica gel column chromatography, and the structure of each product was determined by mean of nuclear Overhauser effect (NOE) experiments as shown in Table 1.

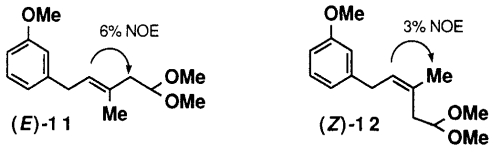
The coupling reaction of other aryltin compounds **15** and the mixture of acetals (*E*)-**9** and (*Z*)-**10** was examined under the same conditions to give corresponding 5-arylacetals **16**. The yields were as follows: 2′-methyl, 30%; 3′-methyl, 43%; 4′-methoxyl, 55%; 2′,4′-dimethoxyl, 35%. However in all cases the mixture of (*E*)- and (*Z*)-**16** could not be separated (Chart 4). The palladium-catalyzed cross-coupling reaction of organotin compound with allylic halides or acyloxy allyl compounds has been extensively studied by many chemists.[8] In the present coupling reaction, the sequence of catalytic events includes the following steps: 1) oxidative addition of the allylic compound to the palladium(0) catalyst to give an allylpalladium(II) complex (**17**), 2) transmetalation with an organotin reagent to afford an aryl-allylic organopalladium complex (**18**), and 3) reductive elimination to generate a coupled product (*E*)-**11** or (*Z*)-**12**. Generally in palladium-catalyzed reactions, the critical point is whether the geometry of the (*E*)- or (*Z*)-olefin in the starting allylic compound is retained in the coupled product. In some cases, the reaction product starting from (*E*)- or (*Z*)- geometry is single geometrical isomer.[9] In other cases, the geometry of the olefin in the starting allylic substrate is retained in the product.[10] In our case the reaction proceeded with loss of double bond geometry in the product, because of *syn-anti* isomerization in the π-allyl palladium complex, leading to loss of stereochemistry of the allylic fragment (Chart 5).

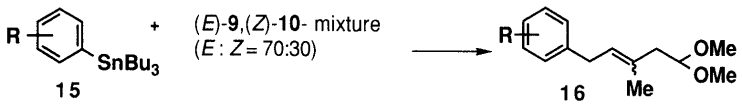
Synthesis of Piericidin Analogues The synthesis of piericidin analogues (2*E*)-**1** and (2*Z*)-**2** from the 5-arylacetal (*E*)-**11** or (*Z*)-**12** was carried out in the same way as described in a preceding paper[5] (Chart 6). A solution of (*E*)-**11** in isopropanol including 2 M hydrochloric acid was allowed to stand for 2 d in a refrigerator to give the non-conjugated aldehyde (*E*)-**13** along with a small amount of α,β-unsaturated aldehyde. Without purification, the crude aldehyde (*E*)-**13** was reacted with the sulfone **4** in the presence of *n*-butyllithium in tetrahydrofuran at −78 °C to afford a diastereomeric mixture (2*E*)-**19** in 46% yield from **4**. Then benzoylation ((2*E*)-**21**, 60% yield) of (2*E*)-**19**, followed by reductive olefin-formation[7] with sodium amalgam at −20 °C gave the piericidin analogue (2*E*)-**1** in 71% yield. The synthesis of the other piericidin analogue (2*Z*)-**2**, corresponding to the isomer of (2*E*)-**1** at the 2-position of the side chain, was performed similarly. Thus, the coupling of the non-conjugated aldehyde (*Z*)-**14** and the sulfone **4** gave a diastereomeric mixture (2*Z*)-**20** in 18% yield from **4**. Benzoylation ((2*Z*)-**22**, 58% yield) of (2*Z*)-**20** followed by reductive olefin-formation afforded (2*Z*)-**2** in 30% yield. The structures of the synthetic analogues (2*E*)-**1** and (2*Z*)-**2** were confirmed by NOE experiments as shown in

Table 1. Reaction of the Aryl-tri-*n*-butyltin **8** and (*E*)-**9** or/and (*Z*)-**10** in the Presence of $Pd(PPh_3)_4(0)$



Entry	(*E*)-**9** and (*Z*)-**10** ((*E*):(*Z*))	Condition	(*E*)-**11** and (*Z*)-**12** Yield (%)	(*E*):(*Z*)	Biphenyl deriv. Yield (%)
1	70:30	100 °C/DMF	26	62:38	36
2	70:30	100 °C/toluene	68	63:38	15
3	(*E*)-**9**	100 °C/toluene	68	62:38	—
4	(*Z*)-**10**	100 °C/toluene	52	58:42	—





Reaction of the Aryl-tri-*n*-butyl tin and (*E*)-**9**, (*Z*)-**10** in The Presence of $Pd(PPh_3)_4$ (0) in Toluene at 100°C

	2'-Me	3'-Me	4'-MeO	2',4'-diMeO
16	30 %	43 %	55 %	35 %

Chart 4

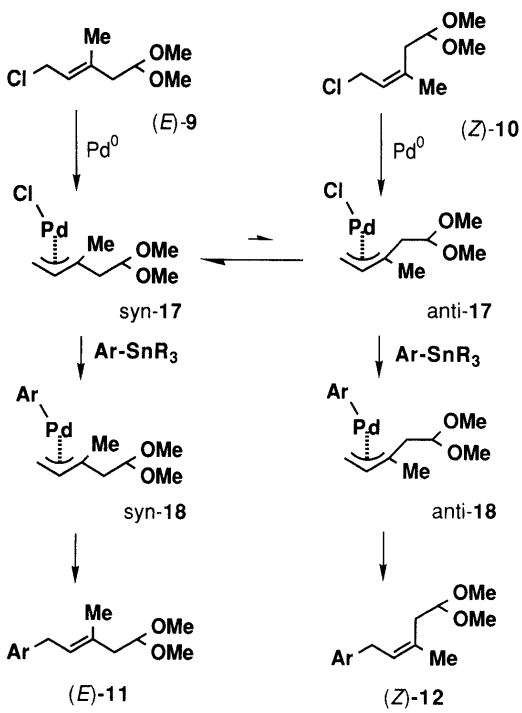


Chart 5

Chart 7. In the NOE experiments, 4% enhancement between C_1-H and C_3-Me, 25% enhancement between C_6-H and C_8-H, and 3% enhancement between C_{11}-Me and C_{12}-Me were observed for the (2*E*)-analogue **1**. In the case of the (2*Z*)-analogue **2**, NOE enhancements were observed between C_1-H and C_4-H (13%), and C_6-H and C_8-H (21%). The coupling constants (J) of C_5-H and C_6-H in both compounds are 15.0 Hz, suggesting (5*E*)-geometry.

In conclusion, we have accomplished the syntheses of two piericidin analogues based on Julia's procedure by coupling of the sulfone **4** and the non-conjugated aldehyde (*E*)-**13** or (*Z*)-**14**.

Experimental

The melting points were determined on Yanaco MP-S3 micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-300 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL EX-400 (400 MHz) spectrometer with tetramethylsilane as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), double doublet (dd), double triplet (dt), multiplet (m), and broad (br). High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-AM II 50 spectrometer. Mass spectra (MS) were recorded on a JEOL JMS-AM II 50 (electron impact (EI)) or JEOL JMS-DX303 (FAB) mass spectrometer. For column chromatography, Silica gel 60 (Merck 1.07734) was employed.

Reduction of Methyl 3-Methyl-5,5-dimethoxy-(2*Z*)-pentenoate with Diisobutylaluminium Hydride (DIBAL) Methyl 3-methyl-5,5-dimethoxy-(2*Z*)-pentenoate was prepared according to the previous paper.[5] Under an Ar atmosphere at 0 °C, a 1.5 M DIBAL toluene solution (5.90 ml, 0.009 mol) was added to a solution of methyl 3-methyl-5,5-dimethoxy-(2*Z*)-pentenoate (0.667 g, 0.0035 mol) in toluene (10.0 ml) under stirring. The whole was warmed to ambient temperature and stirred for 30 min. After ice-cooling, ether (20 ml) and 1.0 M NaOH (10 ml) were added to the reaction mixture under stirring. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was subjected to column chromatography

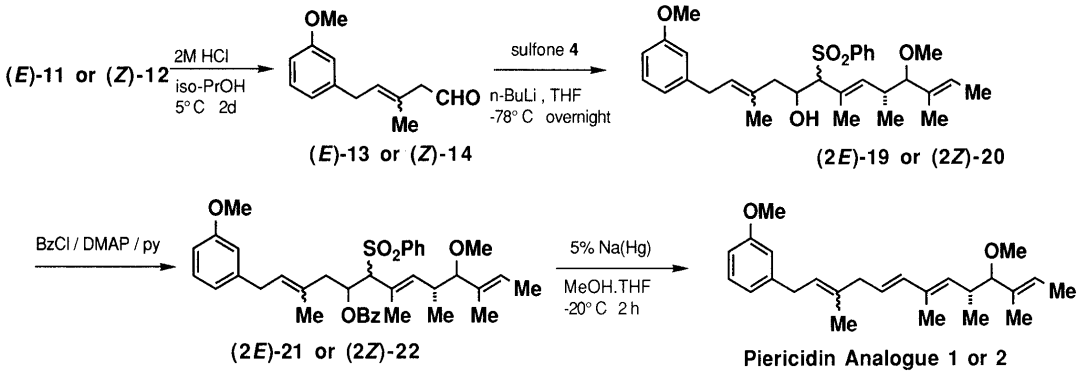


Chart 6

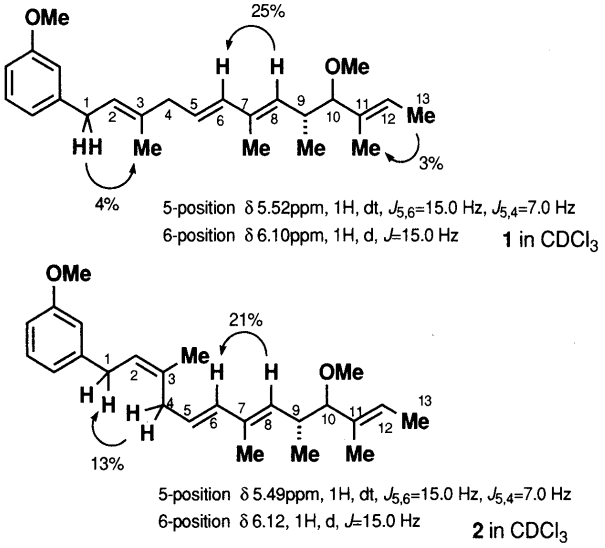


Chart 7

(hexane–AcOEt, 4:1) to give 3-methyl-5,5-dimethoxy-(2*Z*)-pentenol (0.449 g, 78.5%) as a colorless oil. *Anal.* Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.30; H, 10.56. FAB-MS *m/z*: 160 (M^+). IR (neat): 3400 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.81 (3H, s, C_3-Me), 2.33 (1H, br s, OH), 2.45 (2H, d, J=6.0 Hz, 4-H), 3.37 (6H, s, OMe), 4.03 (2H, t, J=6.0 Hz, 1-H), 4.43 (1H, d, J=6.0 Hz, 5-H), 5.70 (1H, t, J=6.0 Hz, 2-H).

Preparation of 1-Chloro-3-methyl-5,5-dimethoxy-(2*Z*)-pentene 10 Under ice-cooling, triphenylphosphine (2.92 g, 0.011 mol) and NCS (1.49 g, 0.011 mol) were added to a solution of 3-methyl-5,5-dimethoxy-(2*Z*)-pentenol (1.00 g, 0.006 mol) in CH_2Cl_2 (5.0 ml). The whole was stirred for 30 min. Brine (5 ml) and CH_2Cl_2 (10 ml) were added. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane–AcOEt, 10:1) to afford the (2*Z*)-acetal **10** (0.80 g, 72.3%) as a colorless oil, which was used immediately after preparation. ^{1}H-NMR ($CDCl_3$) δ: 1.83 (3H, s, C_3-Me), 2.43 (2H, d, J=6.0 Hz, 4-H), 3.35 (6H, s, OMe), 4.11 (2H, d, J=8.0 Hz, 1-H), 4.44 (1H, t, J=6.0 Hz, 5-H), 5.55 (1H, br t, J=8.0 Hz, 2-H).

Preparation of 1-Chloro-3-methyl-5,5-dimethoxy-(2*E*)-pentene 9 3-Methyl-5,5-dimethoxy-(2*E*)-pentenol[5] (1.00 g, 0.006 mol) was treated in the same manner as described for the preparation of the (2*Z*)-acetal **10** to give the (2*E*)-acetal **9** (0.80 g, 72.3%), which was used immediately after preparation. ^{1}H-NMR ($CDCl_3$) δ: 1.77 (3H, s, C_3-Me), 2.36 (2H, d, J=6.0 Hz, 4-H), 3.33 (6H, s, OMe), 4.10 (2H, d, J=8.0 Hz, 1-H), 4.48 (1H, t, J=6.0 Hz, 5-H), 5.53 (1H, t, J=8.0 Hz, 2-H).

Preparation of a Mixture of (2*E*)-Acetal 9 and (2*Z*)-Acetal 10 The reaction of 4,4-dimethoxy-2-butanone and trimethoxyphosphonoacetate gave a mixture of (*E*)- and (*Z*)-esters (70:30) as described in the preceding paper.[5] Reduction of the mixture of (*E*)- and (*Z*)-ester (70:30), followed by chlorination with NCS and triphenylphosphine afforded a mixture of (*E*)-**9** and (*Z*)-**10** acetal (70:30).

Preparation of 3-Methoxyphenyl-tri-(*n*-butyl)tin (8) Under an Ar atmosphere, a 1.6 M *n*-BuLi hexane solution (6.6 ml, 0.010 mol) was added to a solution of 3-bromoanisole (1.30 g, 0.007 mol) in anhydrous tetrahydrofuran (THF, 5.0 ml) under stirring at −78 °C. After 1.0 h, a solution of tri-*n*-butyltin chloride (2.26 g, 0.007 mol) in anhydrous THF (2.0 ml) was added dropwise *via* a syringe to the above reaction mixture and the whole was allowed to stand for 2.0 h at −78 °C. It was then warmed to −20 °C. Et_2O (50 ml) and brine (10 ml) were added under stirring. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue (2.96 g) was subjected to column chromatography (hexane–AcOEt, 100:1) to give 3-methoxyphenyl-tri-*n*-butyltin (**8**) (1.79 g, 64.8%) as a colorless oil. *Anal.* Calcd for $C_{19}H_{34}OSn$: C, 57.46: H, 8.63. Found: C, 57.19; H, 9.19. ^{1}H-NMR ($CDCl_3$) δ: 0.86—1.65 (27H, m, butyl group), 3.81 (3H, s, OMe), 6.80—7.30 (4H, m, aryl).

Reaction of 3-Methoxyphenyl-tri-*n*-butyltin (8) and a Mixture of (*E*)-Acetal 9 and (*Z*)-Acetal 10 in DMF Under an Ar atmosphere, a solution of 3-methoxyphenyl-tri-*n*-butyltin (373 mg, 0.9 mmol) and a mixture of (*E*)-acetal **9** and (*Z*)-acetal **10** (70:30) (140 mg, 0.8 mmol) in DMF (1.0 ml) was heated in the presence of tetrakis(triphenylphosphine) palladium (0) (5% mol) at 100 °C overnight. Ether (50 ml) and brine (10 ml) were added to the reaction mixture under stirring. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane–AcOEt, 50:1—20:1) to afford 3,3′-dimethoxybiphenyl (70.7 mg, 36.0%) from the first eluate and a mixture of (*E*)-5-arylacetal **11** and (*Z*)-5-arylacetal **12** (34.5 mg, 26.0%) from the second eluate. The mixture of (*E*)-**11** and (*Z*)-**12** was subjected again to column chromatography with hexane–benzene (3:1) to give pure (*Z*)-**12** and pure (*E*)-**11**.

3,3′-Dimethoxy-biphenyl: EI-MS *m/z*: 214 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 3.85 (6H, s, OMe), 6.89 (2H, d, J=8.0 Hz, 6-H), 7.11 (2H, br s, 2-H), 7.17 (2H, d, J=8.0 Hz, 4-H), 7.34 (2H, t, J=8.0 Hz, 5-H).

5-(3′-Methoxyphenyl)-3-methyl-(3*Z*)-pentenal Dimethylacetal **12**: *Anal.* Calcd for $C_{15}H_{22}O_3 \cdot 1/4H_2O$: C, 70.70; H, 8.90. Found: C, 70.77, H, 8.91. FAB-MS *m/z*: 250 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.80 (3H, s, C_3-Me), 2.47 (2H, d, J=6.0 Hz, 2-H), 3.35 (6H,s, OMe), 3.37 (2H, d, J=7.5 Hz, 5-H), 3.79 (3H, s, aryl-OMe), 4.49 (1H,t, J=6.0 Hz, 1-H), 5.45 (1H, t, J=7.5 Hz, 4-H), 6.73 (1H, br d, J=8.0 Hz, 4′-H), 6.74, (1H, br s, 2′-H), 6.78 (1H, br d, J=8.0 Hz, 6′-H), 7.19 (1H, t, J=8.0 Hz, 5′-H).

5-(3′-Methoxyphenyl)-3-methyl-(3*E*)-pentenal Dimethylacetal **11**: *Anal.* Calcd for $C_{15}H_{22}O_3 \cdot 1/2H_2O$: C, 69.47; H, 8.94. Found: C, 69.32, H, 9.36. FAB-MS *m/z*: 250 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.76 (3H, s, C3-Me), 2.36 (2H, d, J=6.0 Hz, 2-H), 3.33 (6H, s, OMe), 3.36 (2H, d, J=7.5 Hz, 5-H), 3.79 (3H, s, aryl-OMe), 4.53 (1H,t, J=6.0 Hz, 1-H), 5.43 (1H, t, J=7.5 Hz, 4-H), 6.73 (1H, br d, J=8.0 Hz, 4′-H), 6.74, (1H, br s, 2′-H), 6.78 (1H, br d, J=8.0 Hz, 6′-H), 7.19 (1H, t, J=8.0 Hz, 5′-H).

Reaction of 3-Methoxyphenyl-tri-*n*-butyltin (8) and a Mixture of (*E*)-Acetal 9 and (*Z*)-Acetal 10 in Toluene A solution of 3-methoxyphenyl-tri-*n*-butyltin (**8**) (387 mg, 0.97 mmol) and a mixture of (*E*)-acetal **9** and (*Z*)-acetal **10** (70:30, 174 mg, 0.97 mmol) in toluene (2.0 ml) was heated in the presence of tetrakis(triphenylphosphine) palladium(0) (5% mol) at 100 °C overnight. The reaction mixture was treated in the same manner as in the case of the reaction in DMF to give 3,3′-dimethoxybiphenyl (31 mg, 15.0%) and a mixture of (*E*)-5-arylacetal **11** and (*Z*)-5-arylacetal **12** (62:38, 165 mg, 67.7%).

Reaction of Aryl-tri-*n*-butyltin (15) and a Mixture of (*E*)-Acetal 9 and (*Z*)-Acetal 10 in Toluene Aryl-tri-*n*-butyltins (**15**) were prepared from

bromobenzene derivatives and tri-*n*-butyltin chloride in the same manner as described in the case of 3-methoxyphenyl-tri-*n*-butyltin. Aryl-tri-*n*-butyltins were used without purification. Aryl-tri-*n*-butyltin (**15**) (2.0 g, 0.005 mol) and a mixture of (*E*)-acetal **9** and (*Z*)-acetal **10** (70 : 30, 0.89 g, 0.005 mol) were reacted in the same manner as in the case of the reaction in DMF. The results (yield of 5-arylacetal **16**) were as follows: 2′-Me, 0.35 g (30.0%); 3′-Me, 0.50 g (43.0%); 3′-MeO, 0.85 g (68.0%); 4′-MeO, 0.69 g (55.0%); 2′,4′-di-MeO, 0.49 g (35.0%).

A Mixture of (3*E*)- and (3*Z*)-5-(2′-Methylphenyl)-3-methylpentenal Dimethylacetal (**16**): FAB-MS *m/z*: 234 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.76, 1.80 (each 3H, s, C_3-Me), 2.27, 2.28 (each 3H, s, Ar-Me), 2.37, 2.47 (each 2H, d, J=6.0 Hz, 2-H), 3.34 (d, J=7.0 Hz, 5-H), 3.31, 3.34 (each 6H, s, OMe), 4.48, 4.51 (each 1H, t, J=6.0 Hz, 1-H), 5.35, 5.36 (each 1H, br t, J=7.0 Hz, 4-H), 7.07—7.17 (m, aryl).

A Mixture of (3*E*)- and (3*Z*)-5-(3′-Methylphenyl)-3-methylpentenal Dimethylacetal (**16**): FAB-MS *m/z*: 234 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.76, 1.80 (each 3H, s, C_3-Me), 2.32 (s, Ar-Me), 2.35, 2.46 (each 2H, d, J=6.0 Hz, 2-H), 3.32, 3.35 (each 6H, s, OMe), 3.34 (d, J=7.0 Hz, 5-H), 4.49, 4.52 (each 1H, t, J=6.0 Hz, 1-H), 5.43 (br t, J=7.0 Hz, 4-H), 6.50—7.20, 7.13—7.19 (m, aryl).

A Mixture of (3*E*)- and (3*Z*)-5-(4′-Methylphenyl)-3-methylpentenal Dimethylacetal (**16**): FAB-MS *m/z*: 250 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.75, 1.80 (each 3H, s, C_3-Me), 2.35, 2.46 (each 2H, d, J=6.0 Hz, 2-H), 3.31 (d, J=7.0 Hz, 5-H), 3.32, 3.34 (each 6H, s, OMe), 3.77 (s, aryl-OMe), 4.48, 4.52 (each 1H, t, J=6.0 Hz, 1-H), 5.42 (br t, J=7.0 Hz, 4-H), 6.82 (d, J=8.0 Hz, 3′ and 5′-positions), 7.08, 7.09 (each 2H, d, J=8.0 Hz, 2′ and 6′-positions).

A Mixture of (3*E*)- and (3*Z*)-5-(2′,4′-Dimethoxyphenyl)-3-methylpentenal Dimethylacetal (**16**): FAB-MS *m/z*: 280 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.74, 1.78 (each 3H, s, C_3-Me), 2.34, 2.47 (each 2H, d, J=6.0 Hz, 2-H), 3.26, 3.28 (each 2H, d, J=7.0 Hz, 5-H), 3.32, 3.34 (each 6H, s, OMe), 3.79, 3.80 (s, aryl-OMe), 4.49, 4.51 (each 1H, t, J=6.0 Hz, 1-H), 5.39, 5.40 (each 1H, br t, J=7.0 Hz, 4-H), 6.37—6.49 (m, 5′- and 6′-positions), 6.82, 7.03 (each 1H, d, J=8.0 Hz, 6′-position).

Reaction of the Sulfone 4 and the Non-conjugated Aldehyde (*E*)-13 1) Preparation of 5-(3′-Methoxyphenyl)-3-methyl-(3*E*)-pentenal **13**: Under ice-cooling, cold 2.0 M HCl (2.0 ml) was added slowly to a solution of the (*E*)-5-arylacetal **11** (320 mg, 1.27 mmol) in isopropanol (4.0 ml). The whole was kept in a refrigerator at −5 °C for 2 d. Cold 7% $NaHCO_3$ (10 ml) was introduced into the reaction mixture under stirring. The whole was extracted with ether (10 ml × 3). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a colorless oil (*E*)-**13** (260 mg), which was used without purification. ^{1}H-NMR ($CDCl_3$) δ: 1.78 (3H, s, C_3-Me), 3.10 (2H, d, J=2.5 Hz, 2-H), 3.40 (2H, d, J=7.5 Hz, 5-H), 5.52 (1H, d, J=7.5 Hz, 4-H), 9.65 (1H, t, J=2.5 Hz, CHO).

2) Coupling Reaction of the Sulfone **4** and 5-(3′-Methoxyphenyl)-3-methyl-(3*E*)-pentenal (**13**): Under an Ar atmosphere at −20 °C, a 1.6 M *n*-BuLi hexane solution (0.95 ml, 1.53 mmol) was added to a solution of the sulfone **4** (410 mg, 1.27 mmol) in anhydrous THF (3.0 ml) *via* a syringe under stirring. After 1.0 h, the mixture was cooled to −78 °C, then a solution of crude aldehyde (*E*)-**13** (260 mg) in anhydrous THF (1.0 ml) was introduced. The whole was warmed to −20 °C and allowed to stand overnight. Ether (30 ml) and 10% aqueous NH_4Cl (10 ml) were added under stirring. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane–AcOEt, 20 : 1) to give a diastereomeric mixture (2*E*)-**19** (311 mg, 46.4% from **11**). The hydroxyl group absorption was detected in the IR spectrum (3400 cm^{-1}). ^{1}H-NMR ($CDCl_3$) δ: 0.24, 0.36, 0.67, 0.70 (d, J=7.0 Hz, C_9-Me), 6.68—6.80, 7.15—7.22 (m, aryl of methoxyphenyl group), 7.46—7.64, 7.77—7.88 (m, $-SO_2Ph$). Not all of the signals could be assigned.

Reaction of the Sulfone 4 and the Non-conjugated Aldehyde (*Z*)-14 1) Preparation of 5-(3′-Methoxyphenyl)-3-methyl-(3*Z*)-pentenal (**14**): Acid hydrolysis of the (*Z*)-5-arylacetal **12** (330 mg, 1.30 mmol) was carried out in the same manner as in the case of the (*E*)-5-arylacetal **11** to give (*Z*)-**14** (260 mg) as a colorless oil, which was used without purification. ^{1}H-NMR ($CDCl_3$) δ: 1.82 (3H, s, C_3-Me), 3.23 (2H, d, J=2.5 Hz, 2-H),3.34 (2H, d, J=7.5 Hz, 5-H), 5.67 (1H, t, J=7.5 Hz, 4-H), 9.62 (1H, t, J=2.5 Hz, CHO).

2) Coupling Reaction of the Sulfone **4** and 5-(3′-Methoxyphenyl)-3-methyl-(3*Z*)-pentenal (**14**): A reaction of the sulfone **4** (420 mg, 1.30 mmol) and (*Z*)-**14** (260 mg) was carried out in the same manner as in the case of (*E*)-**13** to give a diasteromeric mixture (2*Z*)-**20** (100 mg, 18.4% from **12**). The hydroxyl group absorption was detected in the IR spectrum (3400 cm^{-1}). ^{1}H-NMR ($CDCl_3$) δ: 0.38, 0.54, 0.66, 0.73 (d, J=7.0 Hz, C_9-Me). 6.67—6.80, 7.13—7.21 (m, aryl of methoxyphenyl group), 7.46—7.64, 7.83—7.90 (m, $-SO_2Ph$). Not all of the signals could be assigned.

Benzoylation of the Hydroxy Sulfone (2*E*)-19 A solution of (2*E*)-**19** (311 mg, 0.59 mmol), BzCl (330 mg, 2.35 mmol) and 4-(dimethylamino)-pyridine (360 mg, 2.94 mmol) in pyridine (5.0 ml) was allowed to stand overnight at ambient temperature. Ether (50 ml) and 7% $NaHCO_3$ (15 ml) were added. Extraction with ether (50 ml × 3) afforded an organic layer, which was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane–AcOEt, 20 : 1) to give a diastereomeric mixture of (2*E*)-**21** (233 mg, 60.0%), which was employed without identification.

Benzoylation of the Hydroxy Sulfone (2*Z*)-20 Benzoylation of (2*Z*)-**20** (100 mg, 0.19 mmol) was carried out in the same manner as in the case of (2*E*)-**19** to give (2*Z*)-**22** (70.0 mg, 57.9%), which was employed without identification.

Reaction of the Diastereomeric (2*E*)-21 with 5% Na(Hg) At −20 °C, 5% Na(Hg) (800 mg, 1.74 mmol) was added to a solution of the diastereomeric benzoyloxy sulfone (2*E*)-**21** (233 mg, 0.35 mmol) in THF–MeOH (1 : 5) (30 ml) in portions under vigorously stirring. After 1.0 h, the same amount of 5% Na(Hg) was added again, and the reaction mixture was stirried for 2.0 h at −20 °C. Brine (50 ml) was added and the whole was concentrated to about 1/2 volume at low temperature, then extracted with ether (30 ml × 3). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane–AcOEt, 50 : 1) to give the piericidin analogue (2*E*)-**1** (91.7 mg, 71.3%) as a colorless oil, which can be stored in a refrigerator. FAB-MS *m/z*: 369 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 0.78 (3H, d, J=7.0 Hz, C_9-Me), 1.52 (3H, br s, C_{11}-Me), 1.65 (3H, br d, J=7.0 Hz, 13-H), 1.70 (3H, br s, C_3-Me), 1.74 (3H, s, C_7-Me), 2.59—2.70 (1H, m, 9-H), 2.80 (2H, d, J=7.0 Hz, 4-H), 3.12 (3H, s, C_{10}-OMe), 3.17 (1H, d, J=8.0 Hz, 10-H), 3.34 (2H, br d, J=7.0 Hz, 1-H), 3.79 (3H, s, Ar-OMe), 5.30 (1H, br d, J=9.0 Hz, 8-H), 5.38 (1H, br t, J=7.0 Hz, 2-H), 5.41 (1H, br q, J=7.0 Hz, 12-H), 5.52 (1H, dt, J=15.0, 7.0 Hz, 5-H), 6.10 (1H, br d, J=15.0 Hz, 6-H), 6.71 (1H, dd, J=2.0, 8.0 Hz, 4′-H), 6.73 (1H, br s, 2′-H), 6.78 (1H, br d, J=8.0 Hz, 6′-H), 7.19 (1H, t, J=8.0 Hz, 5′-H). NOE data are given in the text.

Reaction of the Diastereomeric (2*Z*)-22 with 5% Na(Hg) The diastereomeric benzoyloxy sulfone (2*Z*)-**22** (70.0 mg, 0.11 mmol) was treated in the same manner as in the case of (2*E*)-**21** to give the other piericidin analogue (2*Z*)-**2** (12.1 mg, 29.8%) as a colorless oil, which can be stored in a refrigerator. Formation of other products was recognized on TLC, but they were not isolated. FAB-MS *m/z*: 369 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 0.78 (3H, d, J=7.0 Hz, C_9-Me), 1.53 (3H, br s, C_{11}-Me), 1.65 (3H, br d, J=7.0 Hz, 13-H), 1.74 (3H, br s, C_3-Me), 1.75 (3H, s, C_7-Me), 2.59—2.71 (1H, m, 9-H), 2.90 (2H, d, J=7.0 Hz, 4-H), 3.13 (3H, s, C_{10}-OMe), 3.17 (1H, d, J=9.0 Hz, 10-H), 3.36 (2H, br d, J=7.0 Hz, 1-H), 3.79 (3H, s, Ar-OMe), 5.31 (1H, br d, J=9.0 Hz, 8-H), 5.37 (1H, br t, J=8.0 Hz, 2-H), 5.42 (1H, br q, J=7.0 Hz, 12-H), 5.49 (1H, dt, J=15.0, 7.0 Hz, 5-H), 6.12 (1H, br d, J=15.0 Hz, 6-H), 6.73 (1H, dd, J=2.0, 8.0 Hz, 4′-H), 6.74 (1H, br s, 2′-H), 6.79 (1H, br d, J=8.0 Hz, 6′-H), 7.20 (1H, t, J=8.0 Hz, 5′-H). NOE date are given in the text.

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