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Total synthesis of (+)-piericidin A_1 and (−)-piericidin B_1

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ABSTRACT

The convergent syntheses of (+)-piericidin A_1 **1** and (−)-piericidin B_1 **2** have been achieved based on classical Julia-Lythgoe olefination between 4-hydroxy-5,6-dimethoxy-3-methyl-2-[5-oxo-3-methyl-pent-(2*E*)-enyl]-pyridine **3** corresponding to the left half of the final molecule, and chiral phenyl sulfones, (4*R*,5*R*)-2,4,6-trimethyl-5-methoxy-1-phenylsulfonyl-octa-(2*E*,6*E*)-diene **20** and (4*R*,5*R*)-5-*tert*-butyl-dimethylsiloxy-2,4,6-trimethyl-1-phenylsulfonyl-octa-(2*E*,6*E*)-diene **33**, corresponding to the right halves. The construction of the two stereogenic centers in the right half of piericidins was achieved based on lipase-catalyzed hydrolysis of methyl (2,3)-*anti*-3-acetoxy-2,4-dimethyl-hex-(4*E*)-enoate (±)-**22**.

1. Introduction

Piericidins A_1 **1** and B_1 **2** are members of an important class of biologically active natural products isolated from *Streptomyces mobaraensis* and *Streptomyces pactam*, respectively, which display a broad range of biological effects, including cytotoxicity, antimicrobial, and insecticidal activities due to inhibition of the electron-transport system in the respiratory chain.[1] The respiratory chain includes the so-called complex I, responsible for the oxidation of NADH to NAD^+, and this complex is inhibited by rotenone and barbiturates in addition to piericidins, all of which bind at the same site in mitochondria in a competitive manner.[2] Piericidins contain a 2,3,5,6-tetrasubstituted 4-pyridinol ring, whose substitution pattern is similar to that of ubiquinone (coenzyme Q), which functions as a hydrogen acceptor in the oxidation of NADH to NAD^+ in mitochondria. The piericidin side chain contains two stereogenic centers at the C(9)- and C(10)-positions and four (*E*)-olefinic linkage, two of which are isolated double bonds [C(2)- and C(11)-positions] and two of which are conjugated with each other [(C(5)- and C(7)-positions] as shown in Figure 1.

We reported previously the synthesis of a (±)-piericidin B_1 analogue possessing a benzene ring instead of pyridine ring.[3] The first syntheses of piericidins A_1 **1** and B_1 **2** were achieved based on carbon–carbon bond formation (at the dotted line a) by Stille cross-coupling and the construction of the two stereogenic centers in the side chain by use of an asymmetric *anti*-aldol reaction.[4a,b] Herein, we report a new total synthesis of piericidins A_1 **1** and B_1 **2** based on a convergent synthesis via the Julia coupling method. Our synthetic plan for piericidins A_1 **1** and B_1 **2** is based on double bond formation between the left **3** and right **4** halves (at dotted line b) as shown in Figures 1 and 2. The construction of the two stereogenic centers in the right half **4** could be achieved by lipase-catalyzed enantioselective hydrolysis of α-methyl-β-acetoxy ester.

2. Results and discussion

2.1. Synthesis of left half 3

The non-conjugated aldehyde **3** corresponding to the C(1)–C(5) unit of the piericidin side chain was prepared starting from the known allyl alcohol congener (*E*)-**5**[3a] in three steps as shown in Scheme 1.

The reaction of (*E*)-**5** and methyl chloroformate gave the corresponding carbonate (*E*)-**6** in 60% yield. Pyridyl stannane derivative **7** was prepared from the commercially available 2,3-dimethoxypyridine by the reported procedure.[5] The Stille coupling of (*E*)-**6** and **7** in the presence of tri(dibenzylideneacetone)dipalladium(0) and LiCl afforded a 2.2:1 mixture (*E*:*Z* = 2.2:1) of coupled product in 68% yield. Treatment of this mixture with 2 M aqueous HCl followed by separation gave the desired left half **3** in 65% yield. The geometry of (*E*)-**3** was confirmed by NOE as shown in Scheme 1.

2.2. Attempt synthesis of (±)-piericidin B_1 2

At first, racemic synthesis of (±)-piericidin B_1 **2** was performed as shown in Scheme 2.

The synthesis of allyl alcohol congener (±)-**9** from (±)-*anti*-**8** was carried out by the reported procedure.[3a] The reaction of (±)-**9** and 1-phenyl-1*H*-tetrazole-5-thiol (PTSH) in the presence of Ph_3P and diethyl azodicarboxylate (DEAD) to give the corresponding sulfide (±)-**10** in 89% yield. Oxidation of (±)-**10** with 30% H_2O_2 in the presence of $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ provided the corresponding sulfone

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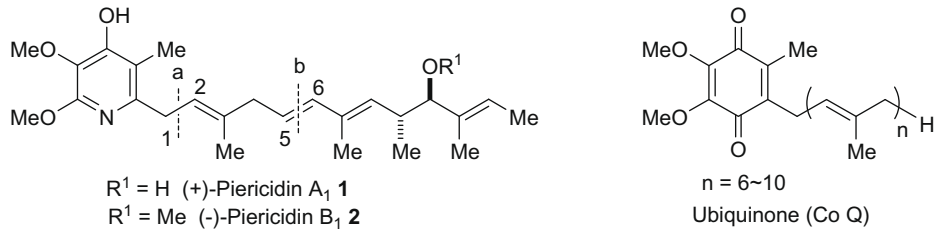


Figure 1.

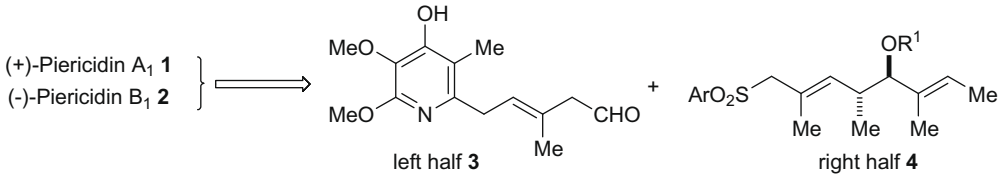
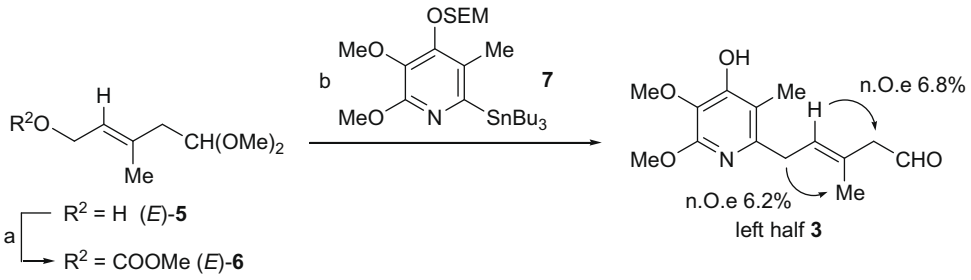
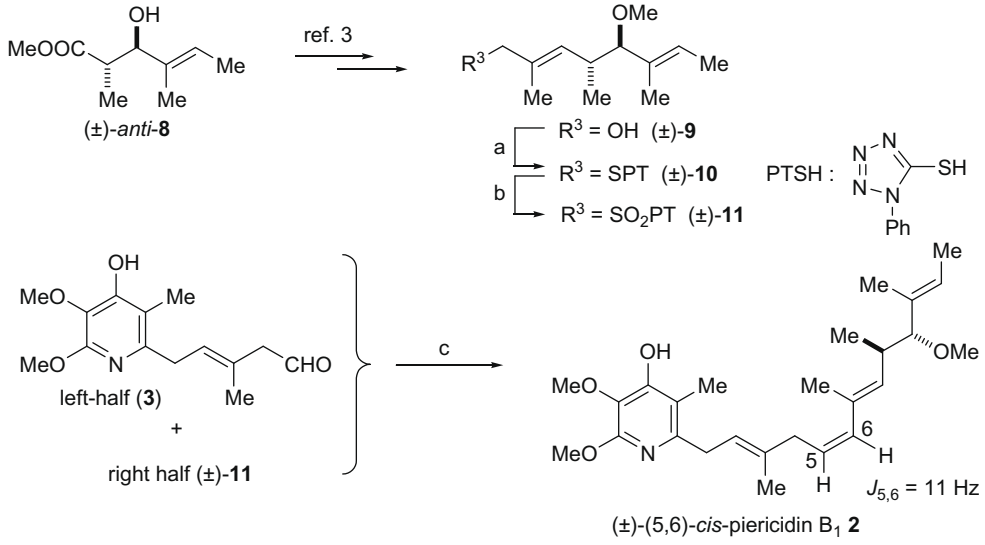


Figure 2.



Scheme 1. Reagents: (a) ClCOOMe/pyridine/toluene; (b) (1) **7**/$Pd_2(dba)_3$/LiCl/DMF; (2) 2 M-HCl aq/*i*-PrOH.



Scheme 2. Reagents: (a) PTSH/DEAD/Ph_3P/THF; (b) H_2O_2/$Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$/EtOH; (c) KHMDS/THF.

(±)-**11** in 60% yield. Modified Julia olefination of the left half **3** and (±)-**11** in the presence of potassium bis(trimethylsilyl)amide (KHMDS) gave (±)-(5,6)-*cis*-piericidin B_1 **2** in 43% yield as shown in Scheme 2. The C(5), C(6)-*cis* geometry was supported by the coupling constant $J_{5,6}$ = 11 Hz between C(5)–H and C(6)–H. Julia one-pot olefination between aldehyde **3** and PT-sulfone (±)-**11** gave (±)-(5,6)-*cis*-piericidin B_1 (**2**) with high *cis*-selectivity. This high selectivity could be explained as shown in Figure 3.

Metallated PT-sulfone **11** condenses with aldehyde **3** to give *anti* isomer **12** and *syn* isomer **13**, which are converted to intermediates **14** and **15**, respectively. Direct loss of potassium-tetrazolone and sulfur dioxide from intermediates **14** and **15** may yield *trans* isomer **2** via **18** and *cis* isomer **2** via **19**. The energy barrier to Smiles rearrangement for the *anti* isomer **14** is presumably higher than that for the corresponding *syn* isomer **15** due to the eclipsed/gauche arrangement of R^4 and R^5 in the appropriate transition state

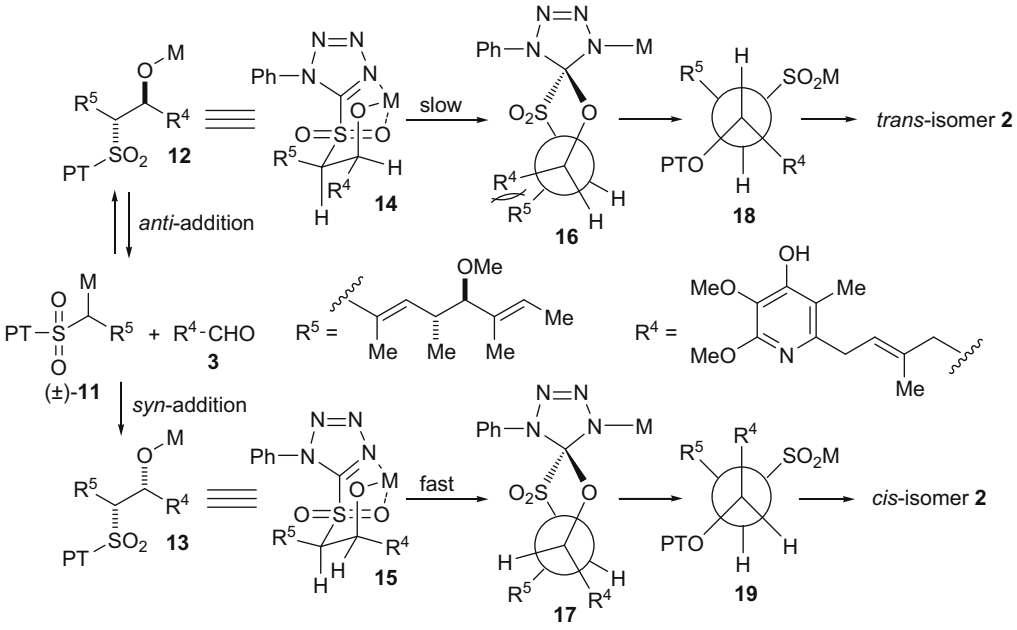


Figure 3.

for spirocyclization. Therefore, the formation rate of **16** from **14** may be slow, while that of **17** from **15** may be fast. The possibility of addition/retroaddition in the reaction of metallated PT-sulfone with aldehyde has been established experimentally.[6] Equilibration between **12** and **13** together with faster Smiles rearrangement/elimination for the latter provides a reasonable explanation for the high *cis*-selectivity. The *E*/*Z* selectivity in the modified Julia olefination depends on the structure of the used aldehyde and heterocyclic sulfone.[6] In case of using an aliphatic aldehyde possessing a bulky substituent, *cis*-selectivity is observed and the present olefination corresponds to the above-mentioned fact.

2.3. Chiral synthesis of (−)-piericidin B_1 2

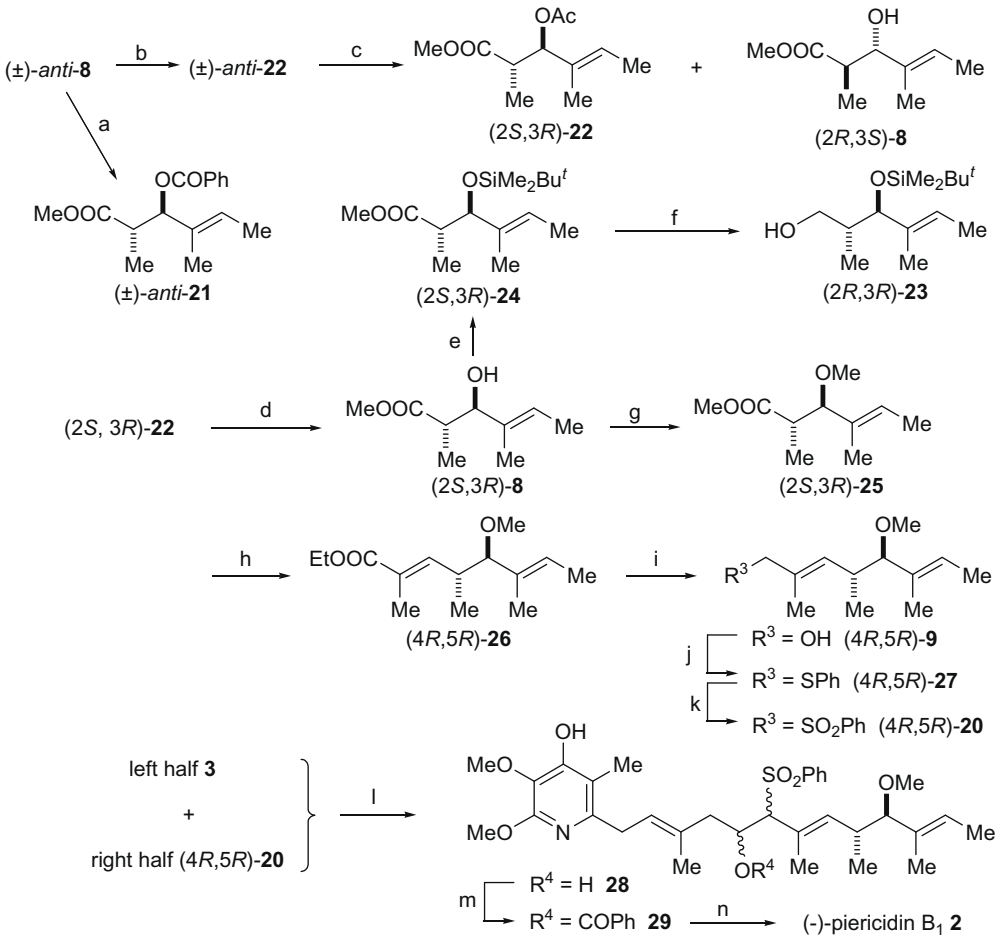
For the chiral synthesis of piericidin B_1 **2**, classical Julia-Lythgoe olefination between left half **3** and optically active phenyl sulfone (4*R*,5*R*)-**20** was carried out and a resolution of (±)-**8** was accomplished by enzyme-assisted resolution as shown in Scheme 3.

To determine the enantiomeric excess (ee) of the enzymatic reaction products, racemate (±)-**8** was converted to the corresponding benzoate (±)-**21** in 97% yield, which gave two well-separated peaks of the enantiomeric isomers in HPLC analysis (see Section 4), thus allowing the determination of the ee of the enzymatic reaction products. Acetylation of (±)-**8** gave the corresponding acetate (±)-**22** in 88% yield, which was selected as the substrate for enzyme-assisted hydrolysis by a brief screening experiment. The screening experiment for finding a suitable enzyme showed that the most effective lipase was Amano A6 from *Aspergillus niger*. When (±)-**22** was subjected to enantioselective hydrolysis in phosphate buffer using Amano A6 for 28 h, (−)-**22** {$[\alpha]_D^{23} = -12.7$ (*c* 1.0, $CHCl_3$) corresponding to >99% ee, 44% yield} and (+)-**8** {$[\alpha]_D^{24} = +8.2$ (*c* 1.0, $CHCl_3$) corresponding to 79% ee, 51% yield} were obtained. The ee for each enzymatic product was calculated by HPLC analysis after conversion of the enzymatic products to the corresponding benzoates. The *E*-value[7] of this enzymatic reaction was estimated to be 43.7. To determine the absolute structure of (−)-**22**, (−)-**22** was converted to the reported alcohol (2*R*,3*R*)-**23** {$[\alpha]_D^{25} = +17.8$ (*c* 0.69, $CHCl_3$)}[8] as follows. Deacetylation of acetate (−)-**22** gave alcohol (−)-**8** {$[\alpha]_D^{19} = -10.4$ (*c* 1.21, $CHCl_3$) corresponding to >99% ee} in 91% yield. Silylation of (−)-**8** afforded the corresponding silyl ether (−)-**24** {$[\alpha]_D^{21} = -1.6$ (*c* 1.05, $CHCl_3$)} in 86% yield, which was reduced with Dibal-H to provide alcohol (+)-**23** {$[\alpha]_D^{20} = +18.7$ (*c* 1.03, $CHCl_3$)} in 91% yield. Spectroscopic data of the present (+)-**23** were identical with those of the known (2*R*,3*R*)-**23** including the sign of the specific rotation. Thus the absolute structure of enzymatic reaction products, (−)-**22** and (+)-**8**, were found to possess the (2*S*,3*R*)- and (2*R*,3*S*)-configurations, respectively. As the desired (2*S*,3*R*)-**8** was already obtained from (2*S*,3*R*)-**22**, (2*S*,3*R*)-**8** was converted to (−)-piericidin B_1 **2** as shown in Scheme 3. Methylation of (2*S*,3*R*)-**8** afforded the β-methoxy ester (2*S*,3*R*)-**25** in 79% yield, which was reduced with Dibal-H to give the alcohol in 98% yield. Swern oxidation of this alcohol followed by Wittig condensation with [1-(ethoxycarbonyl)ethylidene]triphenylphosphorane provided (*E*)-ester (4*R*,5*R*)-**26** in 90% overall yield from (2*S*,3*R*)-**25**. Reduction of (4*R*,5*R*)-**26** with Dibal-H gave allyl alcohol (4*R*,5*R*)-**9** in 98% yield The reaction of (4*R*,5*R*)-**9** and iodine in the presence of Ph_3P and imidazole gave the corresponding iodide, which was treated with thiophenoxide to give the corresponding sulfide (4*R*,5*R*)-**27** in 85% overall yield. Oxidation of (4*R*,5*R*)-**27** with 30% H_2O_2 in the presence of $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ provided the corresponding sulfone (4*R*,5*R*)-**20** in 93% yield. The reaction of the left half **3** and (4*R*,5*R*)-**20** in the presence of *n*-BuLi gave a diastereomeric mixture of hydroxy-sulfone derivatives **28** in 69% yield, which was converted to the corresponding benzoates **29** in 81% yield. This diastereomeric mixture of benzoates **29** was treated with 5% sodium amalgam to afford (−)-piericidin B_1 **2** {$[\alpha]_D^{17} = -8.2$ (*c* 0.43, MeOH)} in 42% yield. The spectral data of the synthetic (−)-**2** were identical with those of synthetic natural (−)-piericidin B_1 (**2**)[4b] {$[\alpha]_D^{25} = -7.3$ (*c* 0.2, MeOH)} including the sign of specific rotation (Scheme 3).

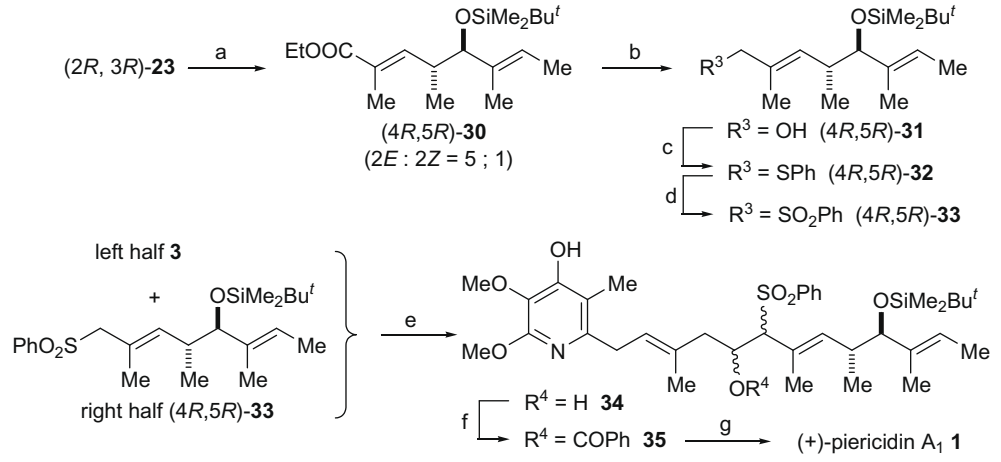
2.4. Chiral synthesis of (+)-piericidin A_1 1

As the desired (2*S*,3*R*)-**22** had already been converted to alcohol (2*R*,3*R*)-**23**, (2*R*,3*R*)-**23** was converted to (+)-piericidin A_1 **1** as shown in Scheme 4.

Swern oxidation of (2*R*,3*R*)-**23** followed by Wittig condensation with [1-(ethoxycarbonyl)-ethylidene]triphenylphosphorane provided



Scheme 3. Reagents: (a) BzCl/DMAP/pyridine; (b) Ac_2O/DMAP/pyridine; (c) lipase 'Amano A6'/phosphate buffer; (d) K_2CO_3/NaOMe/MeOH; (e) $^tBuMe_2SiCl$/imidazole/DMF; (f) Dibal-H/toluene;(g) MeI/Ag_2O/DMF; (h) (1) Dibal-H/toluene; (2) $(COCl)_2$/DMSO/Et_3N/CH_2Cl_2; (3) $Ph_3P{=}C(Me)COOEt$/DMSO; (i) Dibal-H/toluene; (j) (1) I_2/Ph_3P/imidazole/MeCN–Et_2O; (2) PhSH/NaH/DMF; (k) H_2O_2/$Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$/EtOH; (l) *n*-Buli/THF; (m) BzCl/DMAP/pyridine; (n) Na (Hg)/MeOH.



Scheme 4. Reagents: (a) (1) $(COCl)_2$/DMSO/Et_3N/CH_2Cl_2; (2) $Ph_3P{=}C(Me)COOEt$/DMSO; (b) Dibal-H/toluene; (c) (1) I_2/Ph_3P/MeCN–Et_2O; (2) PhSH/NaH/DMF; (d) H_2O_2/$Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$/EtOH; (e) *n*-Buli/THF; (f) BzCl/DMAP/pyridine; (g) (1) Na (Hg)/MeOH; (2) *n*-$Bu_4N^+F^-$/THF.

a 5:1 mixture (2*E*:2*Z* = 5:1) of (4*R*,5*R*)-**30** in 72% overall yield from (2*R*,3*R*)-**23**. Reduction of this mixture with Dibal-H gave a 5:1 mixture of allyl alcohols, which were separated to (2*E*,4*R*,5*R*)-**31** (62% yield) and (2*Z*,4*R*,5*R*)-**31** (13% yield). The reaction of (2*E*,4*R*,5*R*)-**31** and iodine in the presence of Ph_3P and imidazole gave the corresponding iodide, which was treated with thiophenoxide to give the corresponding sulfide (4*R*,5*R*)-**32** in 86% overall yield. Oxidation of (4*R*,5*R*)-**32** with 30% H_2O_2 in the presence of $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ provided the corresponding sulfone (4*R*,5*R*)-**33** in 57% yield. The reaction of the left half **3** and (4*R*,5*R*)-**33** in the presence of *n*-BuLi gave a diastereomeric mixture of hydroxysulfone derivatives **34** in 68% yield, which was converted to the corresponding benzoates

35 in 74% yield. This diastereomeric mixture of benzoates **35** was treated with 5% sodium amalgam to afford a 3:1 mixture (*E*:*Z* = 3:1) of piericidin A_1 silyl ethers in 34% yield. This 3:1 mixture was treated with tetrabutylammonium fluoride to afford a 3:1 mixture (*E*:*Z* = 3:1) of piericidins A_1 **1**, from which (+)-piericidins A_1 **1** {$[\alpha]_D^{14} = +2.1$ (*c* 0.14, MeOH), 69% yield} was isolated. The spectral data of the synthetic (+)-**1** were identical with those of synthetic natural (+)-piericidin A_1 **1**[4b] {$[\alpha]_D^{25} = +1.8$ (*c* 0.1, MeOH)} including the sign of specific rotation.

3. Conclusion

In conclusion, convergent syntheses of (+)-piericidin A_1 **1** and (−)-piericidin B_1 **2** have been achieved based on classical Julia-Lythgoe olefination between the pyridyl aldehyde derivative **3** corresponding to the left side of the final molecule, and chiral phenyl sulfones (4*R*,5*R*)-**20** and (4*R*,5*R*)-**33** corresponding to the right sides. The left half aldehyde **3** was synthesized based on the Stille cross-coupling between pyridyl stannane derivative (**7**) and allyl methyl carbonate congener (*E*)-**6** in 17% overall yield (3 steps). The construction of the two chiral centers in the right half **4** was achieved based on lipase-catalyzed hydrolysis of the (2,3)-*anti*-β-acetoxy-α-methyl ester (±)-**22**. The right half sulfones (4*R*,5*R*)-**20** and (4*R*,5*R*)-**33** were synthesized from the enzymatic reaction product (2*S*,3*R*)-**22** (>99% ee) in 37% overall yield (8 steps) and 17% overall yield (7 steps), respectively.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on JEOL AL-400 or JEOL ECP-500 NMR spectrometer in $CDCl_3$. Electron impact-mass spectrometry (EI-MS) and fast atom bombardment mass spectra (FAB-MS) were performed with JEOL JMS GC-mate II or JEOL JMS-600H (matrix; Tokyo Kasei, DDT/TG11). Electron spray ionization-mass spectrometry (ESI-MS) was performed with a JEOL JMS-T100LP mass spectrometer. IR spectra were recorded with a JASCO FT/IR-4100 spectrometer. Optical rotations were measured with a JASCO P-2200 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, Merck Silica Gel 60 was employed.

4.2. 3-Methyl-5,5-dimethoxy-pent-(2*E*)-enyl methyl carbonate 6

To a solution of (2*E*)-**5** (0.50 g, 3.12 mmol) in toluene (5 mL) at 0 °C were added pyridine (1.0 mL, 12.5 mmol) and methyl chloroformate (1.0 mL, 12.5 mmol) and the reaction mixture was stirred for 3 h. The reaction mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was dried over $MgSO_4$. Concentration of the organic layer gave a crude residue, which was chromatographed on silica gel (40 g, *n*-hexane/AcOEt = 20:1) to provide (2*E*)-**7** (0.403 g, 60% yield) as a colorless oil. (2*E*)-**6**: IR (neat): 1747 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.72 (3H, s), 2.31 (2H, d, *J* = 5.8 Hz), 3.28 (6H, s), 3.73 (3H, s), 4.46 (1H, t, *J* = 5.8 Hz), 4.63 (2H, d, *J* = 7.0 Hz), 5.42 (1H, t, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 17.0, 42.5, 52.8 (2C), 54.6, 64.4, 103.2, 120.7, 138.4, 155.8. HRMS (ESI) (*m*/*z*): calcd for $C_{10}H_{18}O_5$ (M^+): 218.1154, found: 218.1114.

4.3. 4-Hydroxy-5,6-dimethoxy-3-methyl-2-[5-oxo-3-methyl-pent-(2*E*)-enyl]-pyridine 3

(1) To a solution of (2*E*)-**6** (0.25 g, 1.15 mmol) and **7** (1.20 g, 2.04 mmol) in DMF (10 mL) were added LiCl (0.15 g, 3.45 mmol) and $Pd_2(dba)_3$ (0.16 g, 0.173 mmol) and the reaction mixture was stirred for 5 h. at 100 °C under argon atmosphere. The reaction mixture was filtered off with the aid of Celite to afford the filtrate. The filtrate was evaporated to give a crude residue which was chromatographed on silica gel (130 g, *n*-hexane/AcOEt = 20:1) to provide a 2.2:1 mixture (*E*:*Z* = 2.2:1) of coupling products (0.344 g, 68% yield).

(2) To a solution of the above mentioned coupling products (0.344 g) in *iso*-PrOH (4 mL) at 0 °C was added 2 M HCl (2 mL) and the reaction mixture was stood for 12 h at 5 °C. The reaction mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was dried over $MgSO_4$. Concentration of the organic layer gave a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane/AcOEt = 10:1) to provide (2*E*)-**3** (0.135 g, 65% yield) as a colorless oil. (2*E*)-**3**: IR (neat): 3227, 1718 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.80 (3H, s), 2.08 (3H, s), 3.06 (2H, dd, *J* = 1.2, 2.4 Hz), 3.40 (2H, d, *J* = 6.8 Hz), 3.84 (3H, s), 3.92 (3H, s), 5.55 (1H, dt, *J* = 1.2, 6.8 Hz), 6.18 (1H, s), 9.61 (1H, t, *J* = 2.4 Hz). ^{13}C NMR ($CDCl_3$): δ 10.4, 17.3, 34.3, 53.0, 54.2, 60.6, 112.0, 127.1, 127.7, 127.9, 149.8, 153.6, 154.0, 200.5. HRMS (FAB) (*m*/*z*): calcd for $C_{10}H_{18}O_5$ (M^++1): 266.1392, found: 266.1406.

4.4. (±) (4,5)-*anti*-2,4,6-Trimethyl-5-methoxy-1-(1′-phenyl-1*H*-tetrazolyl-5′-sulfanyl)-octa-(2*E*,6*E*)-diene 10

To a solution of (±)-**9** (0.500 g, 2.52 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (0.540 g, 3.02 mmol), and triphenylphosphine (0.800 g, 3.0 mmol) in THF (10 mL) at 0 °C under argon atmosphere was added 2.2 M of DEAD in toluene solution (1.7 mL, 3.78 mmol). After stirring for 2 h at room temperature, the reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Concentration of the organic layer gave a residue which was chromatographed on silica gel (30 g, *n*-hexane/AcOEt = 30:1) to provide (±)-**10** (0.807 g, 89%) as a colorless oil. (±)-**10**: IR (neat): 1597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.68 (3H, d, *J* = 6.8 Hz), 1.46 (3H, s), 1.61 (3H, d, *J* = 6.4 Hz), 1.69 (3H, s), 2.40–2.50 (1H, m), 3.04 (3H, s), 3.08 (1H, d, *J* = 9.0 Hz), 4.00 (2H, s), 5.36 (1H, q, *J* = 6.4 Hz), 5.43 (1H, d, *J* = 9.0 Hz), 7.49–7.57 (5H, m). ^{13}C NMR ($CDCl_3$): δ 10.3, 13.0, 15.5, 17.1, 35.5, 43.3, 56.1, 92.2, 124.0 (2C), 124.4, 128.2, 129.7 (2C), 130.0, 133.5, 133.8, 135.9, 154.2. HRMS (EI) (*m*/*z*): calcd for $C_{19}H_{26}N_4OS$ (M^+): 358.1827, found: 358.1829.

4.5. (±) (4,5)-*anti*-2,4,6-Trimethyl-5-methoxy-1-(1′-phenyl-1*H*-tetrazolyl-5′-sulfonyl)-octa-(2*E*,6*E*)-diene 11

To a mixture of (±)-**10** (0.150 g, 0.42 mmol) and $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (0.105 g, 0.084 mmol) in EtOH (2 mL) at 0 °C was added 30% H_2O_2 (0.4 mL, 3.36 mmol), and the mixture was stirred for 2.5 h at room temperature. The reaction mixture was diluted with EtOAc and washed with H_2O, 10% aqueous $Na_2S_2O_3$, and brine. The organic layer was dried over $MgSO_4$. Concentration of the organic layer gave a residue which was chromatographed on silica gel (25 g, *n*-hexane/AcOEt = 20:1) to provide (±)-**11** (0.098 g, 60%) as a colorless crystal. (±)-**11**: IR (neat): 1597, 1347, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.66 (3H, d, *J* = 6.8 Hz), 1.46 (3H, s), 1.61 (3H, d, *J* = 6.8 Hz), 1.75 (3H, s), 2.43–2.53 (1H, m), 2.99 (3H, s), 3.03 (1H, d, *J* = 9.0 Hz), 4.27 (2H, q, *J* = 14.4 Hz), 5.35–5.41 (2H, m), 7.52–7.63 (5H, m). ^{13}C NMR ($CDCl_3$): δ 10.1, 13.0, 16.7, 16.9, 35.8, 55.9, 65.9, 91.9, 120.0, 125.1, 125.7 (2C), 129.4 (2C), 131.3, 133.0, 133.2, 143.9, 153.1. HRMS (EI) (*m*/*z*): calcd for $C_{19}H_{26}N_4O_3S$ (M^+): 390.1726, found: 390.1726.

4.6. (±) (5,6)-*cis*-Piericidin B_1 2

To a solution of **3** (0.025 g, 0.094 mmol) and (±)-**11** (0.037 g) in THF (2 mL) at −78 °C under argon atmosphere was added KHMDS

(0.5 M in toluene, 0.4 mL, 0.198 mmol) and the reaction mixture was stirred for 12 h at the same temperature. The mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$. Evaporation of the organic layer gave a residue which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt = 25:1) to provide (±)-*cis*-**2** (0.017 g, 43%) as a colorless and starting (±)-**11** (0.018 g, 48% recovery). (±)-*cis*-**2** IR (neat): 3364, 1587, 1473 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.73 (3H, d, J = 6.8 Hz), 1.50 (3H, s), 1.62 (3H, d, J = 6.8 Hz), 1.72 (3H, s), 1.74 (3H, s), 2.07 (3H, s), 2.50–2.60 (1H, m), 2.89–2.94 (2H, m), 3.07 (3H, s), 3.14 (1H, d, J = 8.9 Hz), 3.35 (2H, d, J = 6.8 Hz), 3.84 (3H, s), 3.93 (3H, s), 5.20 (1H, d, J = 8.8 Hz), 5.27–5.40 (3H, m), 5.89 (1H, d, J = 11.6 Hz), 6.12 (1H, s). ^{13}C NMR ($CDCl_3$): δ 10.37, 10.44, 13.0, 16.8, 17.0, 17.4, 34.6, 35.3, 38.5, 53.0, 56.1, 60.6, 92.8, 111.9, 121.4, 124.2, 127.0, 127.8, 131.7, 133.9, 134.3, 134.4, 135.5, 151.1, 153.4, 153.9. HRMS (EI) (*m/z*): calcd for $C_{26}H_{39}NO_4$ (M^+): 429.2879, found: 429.2876.

4.7. (±) Methyl (2,3)-*anti*-3-benzoyloxy-2,4-dimethyl-hex-(4*E*)-enoate 21

To a solution of (±)-*anti*-**8** (0.05 g, 0.29 mmol) in pyridine (1 mL) at 0 °C were added benzoyl chloride (0.05 mL, 0.35 mmol) and 4-*N*,*N*-dimethylamino pyridine (0.005 g) and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with 7% aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt = 50:1) to provide (±)-*anti*-**21** (0.077 g, 97% yield) as a colorless oil (±)-*anti*-**21**: IR (neat): 1741, 1723, 1270 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.09 (3H, d, J = 6.8 Hz), 1.617 (3H, s), 1.623 (3H, d, J = 7.2 Hz), 2.96 (1H, dq, J = 6.8, 10.2 Hz), 3.60 (3H, s), 5.47 (1H, d, J = 10.2 Hz), 5.74 (1H, q, J = 7.2 Hz), 7.38–7.42 (2H, m), 7.49–7.54 (1H, m), 7.97–8.00 (2H, m). ^{13}C NMR ($CDCl_3$): δ 10.9, 13.2, 14.0, 42.3, 51.8, 81.7, 126.8, 128.3 (2C), 129.6 (2C), 130.4, 130.8, 132.8, 165.1, 174.7. HRMS (EI) (*m/z*): calcd for $C_{16}H_{20}O_4$ (M^+): 276.1362, found: 276.1363. HPLC (column; CHIRALPAK AD-H (4.6 × 250 mm), *n*-hexane/EtOH = 100:1, flow rate: 1.0 mL/min, UV detection: 254 nm): t_R = 8.5, 14.8 min.

4.8. (±) Methyl (2,3)-*anti*-3-acetoxy-2,4-dimethyl-hex-(4*E*)-enoate 22

To a solution of (±)-*anti*-**8** (10.0 g, 58 mmol) in pyridine (50 mL) at 0 °C were added Ac_2O (8.2 mL, 87 mmol) and 4-*N*,*N*-dimethylamino pyridine (0.005 g) and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with 7% aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (150 g, *n*-hexane/AcOEt = 30:1) to provide (±)-*anti*-**22** (10.9 g, 88% yield) as a colorless oil (±)-*anti*-**22**: IR (neat): 1739, 1230 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.99 (3H, d, J = 7.2 Hz), 1.53 (3H, d, J = 1.0 Hz), 1.59 (1H, d, J = 6.8 Hz), 1.95 (3H, s), 2.75 (1H, dq, J = 7.2, 10.4 Hz),3.64 (3H, s), 5.23 (1H, d, J = 10.4 Hz), 5.62 (1H, dq, J = 1.0, 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 10.7, 13.1, 13.9, 21.0, 42.0, 51.7, 81.0, 126.8, 130.7 169.6, 174.7. HRMS (EI) (*m/z*): calcd for $C_{11}H_{18}O_4$ (M^+): 214.1205, found: 214.1215.

4.9. Lipase-catalyzed hydrolysis of (±)-*anti*-22

A suspension of (±)-*anti*-**22** (3.00 g, 14 mmol) and lipase A6 (1.5 g) in 0.1 M phosphate buffer (pH 7.2; 600 mL) was stirred for 28 at 33 °C. After the reaction mixture was filtered, the precipitate was washed with AcOEt. The combined organic layer was dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (50 g, *n*-hexane/AcOEt = 30:1) to provide (−)-(2*S*,3*R*)-**22** (1.32 g, 44% yield) and (+)-(2*R*,3*S*)-**8** (1.23 g, 51% yield) as a colorless oil, respectively, in elution order. NMR data of (−)-(2*S*,3*R*)-**22** and (+)-(2*R*,3*S*)-**8** were identical with those of (±)-*anti*-**22** and (±)-*anti*-**8**, respectively. Small amount of (−)-(2*S*,3*R*)-**22** (ca. 0.02 g) in MeOH was treated with K_2CO_3 and NaOMe to give (2*S*,3*R*)-**8**, which was converted to the corresponding (2*S*,3*R*)-benzoate **21**. HPLC analysis of (2*S*,3*R*)-benzoate **21** indicated almost single peak (t_R = 8.5 min). Small amount of (+)-(2*R*,3*S*)-**8** (ca. 0.02 g) was converted to the corresponding (2*S*,3*R*)-benzoate **21**, which was subjected to HPLC analysis to give two peaks (8.5 min:14.8 min = 10.5:89.5). (−)-(2*S*,3*R*)-**22** {$[\alpha]_D^{23} = -12.7$ (c 1.0, $CHCl_3$) corresponding to >99% ee}, (+)-(2*R*,3*S*)-**8** {$[\alpha]_D^{24} = +8.2$ (c 1.0, $CHCl_3$) corresponding to 79% ee}, IR (neat): 3454, 1738 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.98 (3H, d, J = 7.2 Hz), 1.56 (3H, s), 1.59 (3H, d, J = 6.4 Hz), 2.44 (1H, br s), 2.62 (1H, dq, J = 9.2, 7.2 Hz), 3.68 (3H, s), 4.05 (1H, d, J = 9.2 Hz), 5.49 (1H, q, J = 6.4 Hz). ^{13}C NMR ($CDCl_3$): δ 10.3, 13.1, 14.3, 43.2, 51.8, 80.0, 123.9, 134.8, 176.5. HRMS (EI) (*m/z*): calcd for $C_9H_{16}O_3$ (M^+): 172.1100, found: 172.1099.

4.10. Methyl (2*S*,3*R*)-3-*tert*-butyldimethylsiloxy-2,4-dimethyl-hex-(4*E*)-enoate 24

(1) To a solution of (2*S*,3*R*)-**22** (4.5 g, 21 mmol) in MeOH (100 mL) were added K_2CO_3 (1.0 g) and NaOMe (0.005 g, catalytic amount) and the reaction mixture was stirred for 4 h at room temperature. After 10% aqueous NH_4Cl was added to the reaction mixture, whole mixture was condensed under reduced pressure to give a residue. The residue was diluted with H_2O and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (70 g, *n*-hexane/AcOEt = 7:1) to provide (2*S*,3*R*)-**8** (3.29 g, 91% yield) as a colorless oil. (−)-(2*S*,3*R*)-**8** {$[\alpha]_D^{19} = -10.4$ (c 1.21, $CHCl_3$) corresponding to >99% ee}. NMR data of (+)-(2*S*,3*R*)-**8** were identical with those of (±)-*anti*-**8**.

(2) To a solution of (2*S*,3*R*)-**8** (0.800 g, 4.65 mmol) in DMF (10 mL) was added imidazole (0.95 g, 14 mmol) and ^{t}butyldimethylsilyl chloride (TBDMSCl, 2.10 g, 14 mmol) and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was diluted with brine and extracted with AcOEt/*n*-hexane (1:1). The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (40 g, *n*-hexane/AcOEt = 50:1) to afford (2*S*,3*R*)-**24** (1.14 g, 86% yield) as a colorless oil. (−)-(2*S*,3*R*)-**24** {$[\alpha]_D^{21} = -1.6$ (c 1.05, $CHCl_3$)}; IR (neat): 1741 cm^{-1}; ^1H NMR: δ −0.08 (3H, s), −0.04 (3H, s), 0.80 (9H, s), 0.87 (3H, d, J = 7.0 Hz), 1.50 (3H, s), 1.58 (3H, d, J = 6.6 Hz), 2.58 (1H, dq, J = 7.0, 9.8 Hz), 3.64 (3H, s), 4.05 (1H, d, J = 9.8 Hz), 5.04 (1H, q, J = 6.6 Hz). ^{13}C NMR: δ −5.5, −4.8, 9.9, 13.0, 14.1, 17.9, 25.6 (3C), 44.8, 51.4, 81.7, 123.6, 135.3, 176.4. HRMS (FAB) (*m/z*): calcd for $C_{15}H_{31}O_3Si$ (M^++1): 287.2042, found: 287.2048.

4.11. (2*R*,3*R*)-3-*tert*-Butyldimethylsiloxy-2,4-dimethyl-hex-(4*E*)-en-1-ol 23

To a solution of (2*S*,3*R*)-**22** (1.10 g, 3.84 mmol) in toluene (15 mL) at 0 °C under argon atmosphere was added 1.5 M solution of Dibal-H in toluene (5.7 mL, 8.5 mmol) and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with MeOH (2 mL), H_2O (10 mL) and the whole mixture was stirred for 12 h at the same temperature. The generated precipitate was filtered off with the aid of Celite to afford the filtrate. The filtrate was separated and the organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave (2*R*,3*R*)-**23** (0.903 g, 91% yield)

as a homogeneous oil. (+)-(2*R*,3*R*)-**23** {$[\alpha]_D^{20} = +18.7$ (*c*=1.03, $CHCl_3$)}, IR (neat): 3412 cm^{-1}; ^1H NMR: δ −0.04 (3H, s), 0.05 (3H, s), 0.71 (3H, d, *J* = 6.8 Hz), 0.86 (9H, s), 1.53 (3H, s), 1.57 (3H, d, *J* = 6.4 Hz), 1.76–1.86 (1H, m), 2.99 (1H, br s), 3.58 (2H, d, *J* = 5.2 Hz), 3.79 (1H, d, *J* = 8.4 Hz), 5.37 (1H, q, *J* = 6.4 Hz). ^{13}C NMR: δ −5.3, −4.5, 11.0, 12.9, 14.2, 18.1, 25.8 (3C), 38.3, 67.3, 85.2, 122.1, 136.5. HRMS (EI) (*m/z*): calcd for $C_{14}H_{30}O_2Si$ (M^+): 258.2015, found: 258.2020.

4.12. Methyl (2*S*,3*R*)-3-methoxy 2,4-dimethyl-hex-(4*E*)-enoate 25

To a solution of (2*S*,3*R*)-**8** (3.44 g, 20 mmol) and Ag_2O (6.95 g, 30 mmol) in DMF (40 mL) at 0 °C was added methyl iodide (3.74 mL, 60 mL) and the reaction mixture covered with aluminum foil was stirred for 48 h at room temperature. The reaction mixture was filtered off with the aid of Celite. The filtrate was diluted with H_2O and extracted with a mixed solvent (*n*-hexane/AcOEt = 5:1). The organic layer was dried over $MgSO_4$. Concentration of the organic layer gave a crude residue, which was chromatographed on silica gel (120 g, *n*-hexane/AcOEt = 30:1) to provide (2*S*,3*R*)-**25** (2.939 g, 79% yield) as a colorless oil. (2*S*,3*R*)-**25**: {$[\alpha]_D^{20} = -21.4$ (*c* 1.1, $CHCl_3$)}, IR (neat): 1738 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.90 (3H, t, *J* = 7.1 Hz), 1.47 (3H, s), 1.63 (3H, d, *J* = 6.7 Hz), 2.58 (1H, dq, *J* = 7.1, 10.3 Hz), 3.09 (3H, s), 3.54 (1H, d, *J* = 10.3 Hz), 3.68 (3H, s), 5.49 (1H, q, *J* = 6.7 Hz). ^{13}C NMR ($CDCl_3$): δ 9.6, 13.1, 14.2, 42.7, 51.7, 55.9, 89.7, 126.3, 131.9, 176.4. HRMS (EI) (*m/z*): calcd for $C_{10}H_{18}O_3$ (M^+): 186.1256, found: 186.1256.

4.13. Ethyl (4*R*,5*R*)-5-methoxy-2,4,6-trimethyl-octa-(2*E*,6*E*)-dienoate 26

(1) To a solution of (2*S*,3*R*)-**25** (3.00 g, 16 mmol) in toluene (25 mL) at 0 °C under argon atmosphere was added 1.5 M solution of Dibal-H in toluene (24 mL, 36 mmol) and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with MeOH (2 mL), H_2O (10 mL) and the whole mixture was stirred for 12 h at the same temperature. The generated precipitate was filtered off with the aid of Celite to afford the filtrate. The filtrate was separated and the organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave (2,3)-*anti*-3-methoxy-2,4-dimethyl-hex-(4*E*)-en-1-ol (2.50 g, 98% yield). IR (neat): 3407 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.62 (3H, d, *J* = 7.0 Hz), 1.49 (3H, s), 1.62 (3H, d, *J* = 6.7 Hz), 1.84–1.93 (1H, m), 3.13 (3H, s), 3.26 (1H, d, *J* = 9.6 Hz), 3.50–3.60 (3H, m), 5.49 (1H, q, *J* = 6.7 Hz). ^{13}C NMR ($CDCl_3$): δ 9.9, 12.9, 13.7, 37.0, 55.5, 68.8, 94.9, 125.0, 133.2. MS (EI) (*m/z*): calcd for $C_9H_{18}O_2$ (M^+): 158.1307, found: 158.1301.

(2) To a solution of oxalyl chloride (3.4 mL, 40 mmol) in CH_2Cl_2 (40 mL) at −78 °C under argon atmosphere was added a solution of DMSO (5.00 g, 64 mmol) in CH_2Cl_2 (10 mL) and the whole mixture was stirred for 15 min at the same temperature. To the above mixture was added a solution of the above alcohol (2.50 g) in CH_2Cl_2 (10 mL) and the reaction mixture was warmed to −20 °C. Et_3N (14 mL, 104 mmol) was added to the above reaction mixture and the whole mixture was warmed to 0 °C. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. Concentration of the organic layer gave quantitatively a crude corresponding aldehyde (2.452 g), which was used for the next reaction without further purification. To a solution of the above aldehyde in DMSO (40 mL) was added [1-(ethoxycarbonyl)ethylidene]triphenylphosphorane (17.4 g, 48 mmol) and the whole mixture was stirred for 48 h at 40 °C under argon atmosphere. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Concentration of the organic layer gave a residue which was chromatographed on silica gel (120 g, *n*-hexane/AcOEt = 50:1) to provide (4*R*,5*R*)-**26** (3.32 g, 90% overall yield from (2*S*,3*R*)-**25** as a colorless oil. (4*R*,5*R*)-**26** {$[\alpha]_D^{19} = +0.8$ (*c* 1.28, $CHCl_3$)}, IR (neat): 1708 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.78 (3H, d, *J* = 6.8 Hz), 1.27 (3H, t, *J* = 7.0 Hz), 1.51 (3H, s), 1.63 (3H, d, *J* = 6.8 Hz), 1.83 (3H, d, *J* = 1.4 Hz), 2.59–2.69 (1H, m), 3.09 (3H, s), 3.23 (1H, d, *J* = 9.2 Hz), 4.16 (2H, q, *J* = 7.0 Hz), 5.43 (1H, q, *J* = 6.8 Hz), 6.66 (1H, dq, *J* = 1.4, 9.6 Hz). ^{13}C NMR ($CDCl_3$): δ 10.2, 12.6, 13.0, 14.3, 16.4, 36.0, 56.1, 60.3, 92.1, 125.0, 127.6, 133.3, 146.0, 168.4. HRMS (ESI) (*m/z*): calcd for $C_{14}H_{24}O_3$ (M^+): 240.1725, found: 240.1702.

4.14. (4*R*,5*R*)-5-Methoxy-2,4,6-trimethyl-octa-(2*E*,6*E*)-dien-1-ol 9

To a solution of (4*R*,5*R*)-**26** (3.00 g, 13 mmol) in toluene (50 mL) at 0 °C under argon atmosphere was added 1.5 M solution of Dibal-H in toluene (19 mL, 29 mmol) and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with MeOH (2 mL), H_2O (10 mL) and the whole mixture was stirred for 12 h at the same temperature. The generated precipitate was filtered off with the aid of Celite to afford the filtrate. The filtrate was separated and the organic layer was dried over $MgSO_4$. Concentration of the organic layer gave a residue which was chromatographed on silica gel (70 g, *n*-hexane/AcOEt = 7:1) to provide (4*R*,5*R*)-**9** (2.553 g, 98% yield) as a colorless oil. (4*R*,5*R*)-**9** {$[\alpha]_D^{20} = -1.0$ (*c* 1.28, $CHCl_3$)}, IR (neat): 3404 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.73 (3H, d, *J* = 7.2 Hz), 1.50 (3H, s), 1.62 (3H, d, *J* = 6.8 Hz), 1.65 (3H, s), 1.81 (1H, br s), 2.48–2.59 (1H, m), 3.09 (3H, s), 3.14 (1H, d, *J* = 8.8 Hz), 3.97 (2H, s), 5.29 (1H, d, *J* = 8.8 Hz), 5.39 (1H, q, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 10.3, 13.0, 13.9, 17.5, 34.8, 56.0, 69.0, 92.7, 124.4, 130.2, 133.7, 134.7. HRMS (EI) (*m/z*): calcd for $C_{12}H_{22}O_2$ (M^+): 198.1620, found: 198.1592.

4.15. (4*R*,5*R*)-2,4,6-Trimethyl-5-methoxy-1-phenylsulfanyl-octa-(2*E*,6*E*)-diene 27

(1) To a solution of (4*R*,5*R*)-**9** (0.500 g, 2.52 mmol), imidazole (0.43 g, 5.63 mmol), and triphenylphosphine (1.32 g, 4.5 mmol) in a mixed solvent (Et_2O/CH_3CN = 1:1, 15 mL) at 0 °C was added I_2 (1.60 g, 6.30 mmol). After stirring for 30 min at room temperature, the reaction mixture was diluted with 10% aqueous $Na_2S_2O_3$ and extracted with *n*-hexane. The organic layer was washed with brine and dried over $MgSO_4$. Concentration of the organic layer gave quantitatively a crude iodide which was used for next reaction without further purification.

(2) To a suspension of 55% NaH in oil (110 mg, 2.5 mmol) in DMF (5 mL) at 0 °C was added thiophenol (0.3 mL, 2.7 mmol), and a solution of the above crude iodide in DMF (2 mL) was added to the above reaction mixture. After stirring for 1 h at 55 °C, the reaction mixture was diluted with 2 M aqueous NaOH and extracted with Ether. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic layer gave a residue which was chromatographed on silica gel (40 g, *n*-hexane/AcOEt = 100:1) to provide (4*R*,5*R*)-**27** (0.622 g, 85% yield from (4*R*,5*R*)-**9**) as a colorless oil. (4*R*,5*R*)-**27**: {$[\alpha]_D^{18} = -18.4$ (*c* 0.98, $CHCl_3$)}, IR (neat): 1584, 1480 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.62 (3H, d, *J* = 7.0 Hz), 1.49 (3H, s), 1.62 (3H, d, *J* = 6.6 Hz), 1.76 (3H, s), 2.44–2.54 (1H, m), 3.07 (3H, s), 3.51 (2H, q, *J* = 13.1 Hz), 5.15 (1H, d, *J* = 8.8 Hz), 5.35 (1H, q, *J* = 6.6 Hz), 7.13–7.17 (1H, m), 7.22–7.26 (2H, m), 7.33–7.36 (2H, m). ^{13}C NMR ($CDCl_3$): δ 10.4, 13.0, 15.6, 17.3, 35.5, 44.5, 56.1, 92.5, 124.2, 126.1, 128.6 (2C), 130.1, 130.6 (2C), 133.4, 133.9, 136.7. HRMS (EI) (*m/z*): calcd for $C_{18}H_{26}OS$ (M^+): 290.1704, found: 290.1703.

4.16. (4*R*,5*R*)-2,4,6-Trimethyl-5-methoxy-1-phenylsulfonyl-octa-(2*E*,6*E*)-diene 20

To a mixture of (4*R*,5*R*)-**27** (0.500 g, 1.72 mmol) and $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (0.430 g, 0.34 mmol) in EtOH (8 mL) at 0 °C was added 30% H_2O_2 (1.6 mL, 13.8 mmol), and the mixture was stirred for 3 h at room temperature. The reaction mixture was diluted with EtOAc and washed with H_2O, 10% aqueous $Na_2S_2O_3$ and brine. The organic layer was dried over $MgSO_4$. Evaporation of the organic layer gave a residue which was chromatographed on silica gel (30 g, *n*-hexane/AcOEt = 10:1) to provide (4*R*,5*R*)-**20** (0.516 g, 93%) as a colorless crystal. (4*R*,5*R*)-**20**: $\{[\alpha]_D^{16} = +24.0$ (*c* 1.04, $CHCl_3$)}, IR (neat): 1586, 1498, 1308, 1149, 1138 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.52 (3H, d, *J* = 6.8 Hz), 1.44 (3H, s), 1.59 (3H, d, *J* = 6.4 Hz), 1.72 (3H, s), 2.38–2.47 (1H, m), 3.02 (3H, s), 3.74 (2H, s), 4.94 (1H, d, *J* = 9.2 Hz), 5.31 (1H, q, *J* = 6.4 Hz), 7.48–7.53 (2H, m), 7.58–7.62 (1H, m), 7.83–7.86 (2H, m). ^{13}C NMR ($CDCl_3$): δ 10.2, 13.0, 16.8, 17.0, 35.6, 55.9, 66.3, 92.0, 123.1, 124.7, 128.7, 128.8, 133.35 (2C), 133.39 (2C), 138.5, 140.4. HRMS (EI) (*m*/*z*): calcd for $C_{18}H_{26}O_3S$ (M^+): 322.1603, found: 322.1404.

4.17. (−)-Piericidin B_1 2

(1) To a solution of (4*R*,5*R*)-**20** (0.100 g, 0.31 mmol) in THF (5 mL) at −20 °C under argon atmosphere was added *n*-BuLi (2.6 M in *n*-hexane, 0.26 mL, 0.68 mmol) and the reaction mixture was stirred for 1 h at the same temperature. A solution of **3** (0.165 g, 0.62 mmol) in THF (1 mL) was added to the above reaction mixture at −78 °C under argon atmosphere and the reaction mixture was stirred for 12 h at the same temperature. The mixture was diluted with 10% aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$. Evaporation of the organic layer gave a residue which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt = 4:1) to provide a diastereomeric mixture of **28** (0.127 g, 69%) as a colorless oil, which was used for the next reaction without further purification. **28**; IR (neat): 3414, 1586, 1358, 1302, 1125 cm^{-1}; HRMS (EI) (*m*/*z*): calcd for $C_{32}H_{45}NO_7S$ (M^+): 589.2917, found: 587.2917.

(2) To a solution of a diastereomeric mixture of **28** (0.110 g, 0.19 mmol) in pyridine (3 mL) at 0 °C were added 4-dimethylaminopyridine (0.115 g, 0.94 mmol) and benzoyl chloride (0.09 mL, 0.75 mmol) and the reaction mixture was stirred for 1 h at room temperature. The mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic layer gave a residue which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt = 5:1) to provide a diastereomeric mixture of **29** (0.105 g, 81%) as a colorless oil, which was used for the next reaction without further purification. **29**; IR (neat): 3519, 1743, 1584, 1266 cm^{-1}; HRMS (EI) (*m*/*z*): calcd for $C_{39}H_{49}NO_8S$ (M^+): 691.3179, found: 691.3183.

(3) To a solution of a diastereomeric mixture of **29** (0.024 g, 0.035 mmol) in MeOH (2 mL) at 0 °C was added 5% sodium amalgam (0.08 g, 0.17 mmol) and the reaction mixture was stirred for 12 h at the same temperature. The mixture was diluted with brine at 0 °C and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic layer gave a residue which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt = 20:1) to provide (−)-**2** (0.0062 g, 42%) as a colorless oil. (−)-**2**; $\{[\alpha]_D^{17} = -8.2$ (*c* 0.43, MeOH)}, IR (neat): 3403, 1586, 1469 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.75 (3H, d, *J* = 6.9 Hz), 1.50 (3H, s), 1.53 (3H, s), 1.63 (3H, d, *J* = 6.7 Hz), 1.72 (3H, s), 2.07 (3H, s), 2.57–2.67 (1H, m), 2.75 (2H, d, *J* = 7.0 Hz), 3.10 (3H, s), 3.14 (1H, d, *J* = 8.9 Hz), 3.34 (2H, d, *J* = 6.8 Hz), 3.84 (3H, s), 3.93 (3H, s), 5.27 (1H, d, *J* = 9.0 Hz), 5.36–5.42 (2H, m), 5.49 (1H, dt, *J* = 7.1, 15.5 Hz), 6.06 (1H, d, *J* = 15.5 Hz), 6.12 (1H, s). ^{13}C NMR ($CDCl_3$): δ 10.40, 10.43, 12.9, 13.0, 16.6, 17.7, 34.4, 35.4, 43.1, 53.1, 56.2, 60.6, 92.7, 112.0, 121.9, 124.2, 125.1, 127.8, 133.3, 134.0, 135.0, 135.3, 136.4, 150.9, 153.5, 154.0. HRMS (EI) (*m*/*z*): calcd for $C_{26}H_{39}NO_4$ (M^+): 429.2879, found: 429.2885.

4.18. Ethyl (4*R*,5*R*)-5-*tert*-butyldimethylsiloxy-2–2,4,6-trimethyl-octa-(2*E*,6*E*)-dienoate 30

To a solution of oxalyl chloride (0.85 mL, 9.6 mmol) in CH_2Cl_2 (10 mL) at −78 °C under argon atmosphere was added a solution of DMSO (1.20 g, 15 mmol) in CH_2Cl_2 (2 mL) and the whole mixture was stirred for 15 min at the same temperature. To the above mixture was added a solution of (2*R*,3*R*)-**23** (0.903 g, 3.5 mmol) in CH_2Cl_2 (2 mL) and the reaction mixture was warmed to −20 °C. Et_3N (3.2 mL, 23 mmol) was added to the above reaction mixture and the whole mixture was warmed to 0 °C**.** The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. Concentration of the organic layer gave quantitatively a crude corresponding aldehyde, which was used for the next reaction without further purification. To a solution of the above aldehyde in DMSO (10 mL) was added [1-(ethoxycarbonyl)ethylidene]triphenylphosphorane (4.17 g, 11.5 mmol) and the whole mixture was stirred for 48 h at 40 °C under argon atmosphere. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Concentration of the organic layer gave a residue which was chromatographed on silica gel (40 g, *n*-hexane/AcOEt = 70:1) to provide a 5:1 (*E*:*Z* = 5:1) mixture of (2*E*)-**30** and (2*Z*)-**30** (0.859 g, 72% overall yield from (2*S*,3*R*)-**30**) as a colorless oil. **30** IR (neat): 1712 cm^{-1}; HRMS (FAB) (*m*/*z*): calcd for $C_{19}H_{37}O_3Si$ (M^++1): 341.2512, found: 341.2524.

4.19. (4*R*,5*R*)-5-*tert*-Butyldimethylsiloxy-2,4,6-trimethyl-octa-(2*E*,6*E*)-dien-1-ol 31

To a solution of 5:1 mixture of (2*E*)-**30** and (2*Z*)-**30** (0.800 g, 2.35 mmol) in toluene (10 mL) at 0 °C under argon atmosphere was added 1.5 M solution of Dibal-H in toluene (3.4 mL, 5.2 mmol) and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with MeOH (2 mL), H_2O (10 mL) and the whole mixture was stirred for 12 h at the same temperature. The generated precipitate was filtered off with the aid of Celite to afford the filtrate. The filtrate was separated and the organic layer was dried over $MgSO_4$. Concentration of the organic layer gave a residue which was chromatographed on silica gel (40 g, *n*-hexane/AcOEt = 30:1) to provide (2*Z*)-**31** (0.09 g, 13% yield) and (2*E*)-**31** (0.434 g, 62% yield) as a colorless oil, respectively, in elution order. (2*Z*)-**31** (minor product); IR (neat): 3362 cm^{-1}; ^1H NMR ($CDCl_3$): δ −0.04 (3H, s), −0.03 (3H, s), 0.71 (3H, d, *J* = 6.8 Hz), 0.82 (9H, s), 1.55 (3H, s), 1.58 (3H, d, *J* = 6.8 Hz), 1.76 (3H, s), 2.65–2.75 (1H, m), 2.84–2.86 (1H, m), 3.54 (1H, d, *J* = 9.2 Hz), 3.79 (1H, dd, *J* = 7.6, 12.2 Hz), 4.23 (1H, dd, *J* = 2.0, 12.2 Hz), 5.00 (1H, d, *J* = 10.4 Hz), 5.31 (1H, q, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ −4.8, −4.7, 10.4, 12.9, 17.8, 18.3, 22.8, 25.8 (3C), 36.5, 62.8, 83.8, 122.6, 132.5, 135.7, 136.4. HRMS (FAB) (*m*/*z*): calcd for $C_{17}H_{35}O_2Si$ (M^++1): 299.2406, found: 299.2385. (2*E*)-**31** (major product); $\{[\alpha]_D^{18} = -2.1$ (*c* 0.94, $CHCl_3$)}, IR (neat): 3320 cm^{-1}; ^1H NMR ($CDCl_3$): δ −0.10 (3H, s), −0.06 (3H, s), 0.73 (3H, d, *J* = 6.9 Hz), 0.81 (9H, s), 1.53 (3H, s), 1.56 (3H, d, *J* = 6.8 Hz), 1.65 (3H, s), 2.46–2.56 (1H, m), 3.61 (1H, d, *J* = 8.1 Hz), 3.96 (2H, d, *J* = 5.9 Hz), 5.19 (1H, d, *J* = 9.6 Hz), 5.30 (1H, q, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ −5.1, −4.7, 10.9, 12.9, 14.1, 17.4, 18.1, 25.7 (3C), 36.8, 69.3, 83.4, 121.3, 130.8, 134.1, 137.1. HRMS (FAB) (*m*/*z*): calcd for $C_{17}H_{35}O_2Si$ (M^++1): 299.2406, found: 299.2423.

4.20. (4*R*,5*R*)-5-*tert*-Butyldimethylsiloxy-2,4,6-trimethyl-1-phenylsulfanyl-octa-(2*E*,6*E*)- diene 32

(1) To a solution of (2*E*)-**31** (0.200 g, 0.67 mmol), imidazole (0.115 g, 1.68 mmol), and triphenylphosphine (0.355 g, 1.34 mmol) in a mixed solvent (Et_2O/CH_3CN = 1:1, 5 mL) at 0 °C was added I_2 (0.425 g, 1.68 mmol). After stirring for 30 min at room temperature, the reaction mixture was diluted with 10% aqueous $Na_2S_2O_3$ and extracted with *n*-hexane. The organic layer was washed with brine and dried over $MgSO_4$. Concentration of the organic layer gave quantitatively a crude iodide which was used for next reaction without further purification.

(2) To a suspension of 55% NaH in oil (0.035 g, 0.74 mmol) in DMF (2 mL) at 0 °C was added thiophenol (0.08 mL, 0.8 mmol) and a solution of the above crude iodide in DMF (1 mL) was added to the above reaction mixture. After stirring for 1 h at 55 °C, the reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic layer gave a residue which was chromatographed on silica gel (30 g, *n*-hexane/AcOEt = 100:1) to provide (4*R*,5*R*)-**32** (0.226 g, 86% overall yield from (2*E*)-**31**) as a colorless oil. (4*R*,5*R*)-**32**: {$[\alpha]_D^{15} = -6.9$ (*c* 0.97, $CHCl_3$)}, IR (neat): 1585, 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ −0.10 (3H, s), −0.06 (3H, s), 0.61 (3H, d, *J* = 7.2 Hz), 0.82 (9H, s), 1.50 (3H, s), 1.54 (3H, d, *J* = 6.6 Hz), 1.72 (3H, s), 2.39–2.48 (1H, m), 3.47 (2H, q, *J* = 12.8 Hz), 3.57 (1H, d, *J* = 7.2 Hz), 5.06 (1H, d, *J* = 9.6 Hz), 5.25 (1H, q, *J* = 6.6 Hz), 7.12–7.17 (1H, m), 7.21–7.27 (2H, m), 7.31–7.37 (2H, m). ^{13}C NMR ($CDCl_3$): δ -5.0, -4.7, 11.0, 12.9, 15.7, 17.4, 18.1, 25.8 (3C), 37.4, 44.5, 83.1, 121.0, 126.0, 128.6 (2C), 129.4, 130.4 (2C), 133.5, 136.9, 137.1. HRMS (FAB) (*m/z*): calcd for $C_{23}H_{39}OSSi$ (M^++1): 391.2491, found: 391.2498.

4.21. (4*R*,5*R*)-5-*tert*-Butyldimethylsiloxy-2,4,6-trimethyl-1-phenylsulfonyl-octa-(2*E*,6*E*)-diene 33

To a mixture of (4*R*,5*R*)-**32** (0.200 g, 0.51 mmol) and $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (0.130 g, 0.10 mmol) in EtOH (2 mL) at 0 °C was added 30% H_2O_2 (0.6 mL, 5.1 mmol), and the mixture was stirred for 12 h at room temperature. The reaction mixture was diluted with EtOAc and the organic layer was washed with 10% aqueous $Na_2S_2O_3$ and brine. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (30 g, *n*-hexane/AcOEt = 30:1) to provide (4*R*,5*R*)-**33** (0.124 g, 57%) as a colorless oil. (4*R*,5*R*)-**33**: {$[\alpha]_D^{13} = +49.5$ (*c* 1.03, $CHCl_3$)}, IR (neat): 1586, 1462, 1318, 1150, 1129 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ −0.15 (3H, s), −0.13 (3H, s), 0.47 (3H, d, *J* = 6.8 Hz), 0.76 (9H, s), 1.45 (3H, s), 1.52 (3H, d, *J* = 6.8 Hz), 1.73 (3H, s), 2.35–2.44 (1H, m), 3.47 (1H, d, *J* = 7.6 Hz), 3.69 (2H, s), 4.82 (1H, d, *J* = 10.0 Hz), 5.21 (1H, q, *J* = 6.8 Hz), 7.48–7.52 (2H, m), 7.57–7.61 (1H, m), 7.81–7.83 (2H, m). ^{13}C NMR ($CDCl_3$): δ −5.0, −4.7, 11.0, 12.9, 15.7, 17.4, 18.1, 25.8 (3C), 37.4, 44.5, 83.1, 121.0, 126.0, 128.6 (2C), 129.4, 130.4 (2C), 133.5, 136.9, 137.1.HRMS (FAB) (*m/z*): calcd for $C_{23}H_{39}O_3SSi$ (M^++1): 423.2389, found:423.2366.

4.22. (+)-Piericidin A_1 1

(1) To a solution of (4*R*,5*R*)-**33** (0.110 g, 0.26 mmol) in THF (5 mL) at −20 °C under argon atmosphere was added *n*-BuLi (2.6 M in *n*-hexane, 0.22 mL, 0.57 mmol) and the reaction mixture was stirred for 1 h at the same temperature. A solution of **3** (0.105 g, 0.39 mmol) in THF (1 mL) was added to the above reaction mixture at −78 °C under argon atmosphere and the reaction mixture was stirred for 12 h at the same temperature. The mixture was diluted with 10% aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic layer gave a residue which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt = 4:1) to provide a diastereomeric mixture of **34** (0.121 g, 68%) as a pale yellow oil, which was used for the next reaction without further purification. **34**; IR (neat): 3421, 1586, 14727 1125 cm^{-1}; HRMS (EI) (*m/z*): calcd for $C_{37}H_{57}NO_7SSi$ (M^+): 687.3625, found: 687.3631.

(2) To a solution of a diastereomeric mixture of **34** (0.110 g, 0.16 mmol) in pyridine (3 mL) at 0 °C were added 4-dimethylaminopyridine (0.10 g, 0.8 mmol) and benzoyl chloride (0.06 mL, 0.48 mmol) and the reaction mixture was stirred for 1 h at room temperature. The mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt = 5:1) to provide a diastereomeric mixture of **35** (0.092 g, 74%) as a pale yellow oil, which was used for the next reaction without further purification. **35**; IR (neat): 3518, 1743, 1578, 1471, 1265, 1121 cm^{-1}; HRMS (EI) (*m/z*): calcd for $C_{44}H_{61}NO_8SSi$ (M^+): 791.3887, found:791.3888.

(3) To a solution of a diastereomeric mixture of **35** (0.090 g, 0.11 mmol) in MeOH (3 mL) at 0 °C was added 5% sodium amalgam (0.525 g, 1.14 mmol) and the reaction mixture was stirred for 12 h at the same temperature. The mixture was diluted with brine at 0 °C and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt = 15:1) to provide a 3:1 mixture of olefin compound (*E*:*Z* = 3:1, 0.021 g, 34%) as a colorless oil. olefin compound; IR (neat): 3516, 3416, 1587, 1471 cm^{-1}; HRMS (FAB) (*m/z*): calcd for $C_{31}H_{52}NO_4SSi$ (M^++1): 530.3666, found:530.3668.

(4) To a solution of a 3:1 mixture of the above olefin compound (0.015 g, 0.028 mmol) in THF (1 mL) under argon atmosphere were added molecular sieves (3A, 0.15 g) and 1.0 M tetrabutylammonium fluoride in THF solution (0.09 mL, 0.05 mmol) and the reaction mixture was heated at 50 °C with stirring for 12 h. The mixture was diluted with 10% aqueous NH_4Cl at 0 °C and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt = 10:1) to provide (+)-piericidin A_1 **1** (0.0081 g, 69% yield) as a pale yellow oil. (+)-piericidin A_1 (**1**); {$[\alpha]_D^{14} = +2.1$ (*c* 0.14, MeOH)}, IR (neat): 3396, 1587, 1472 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.79 (3H, d, *J* = 6.8 Hz), 1.61 (3H, d, *J* = 5.0 Hz), 1.62 (3H, s), 1.73 (3H, s), 1.79 (3H, s), 2.07 (3H, s), 2.61–2.70 (1H, m), 2.77 (2H, d, *J* = 7.3 Hz), 3.35 (2H, d, *J* = 6.8 Hz), 3.60 (1H, d, *J* = 9.2 Hz), 3.84 (3H, s), 3.93 (3H, s), 5.19 (1H, d, *J* = 9.9 Hz), 5.39 (1H, t, *J* = 7.0 Hz), 5.44–5.49 (1H, m), 5.59 (1H, dt, *J* = 6.9, 15.5 Hz), 6.07 (1H, d, *J* = 15.5 Hz). ^{13}C NMR ($CDCl_3$): δ 10.45, 10.52, 13.1, 13.2, 16.6, 17.4, 34.4, 36.9, 43.1, 53.0, 60.6, 82.8, 111.9, 122.2, 123.6, 126.8, 127.8, 133.1, 134.8, 135.5, 135.7, 136.1, 150.8, 153.5, 153.9. HRMS (FAB) (*m/z*): calcd for $C_{25}H_{38}NO_4$ (M^++1): 416.2801, found:416.2792.

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