Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Enantioselective Total Synthesis of Periconiasin A

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Table of Contents

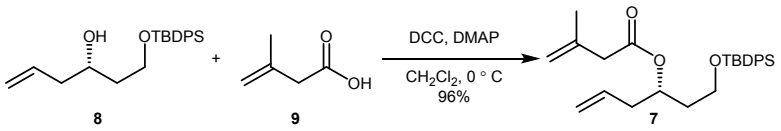
1. General Information

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise stated. All the chemicals were purchased commercially and used without further purification, unless otherwise stated. The boiling point of petroleum ether (PE) is between 60-90 ºC. Tetrahydrofuran (THF) was distilled from sodium-benzophenone. Dichloromethane (CH_2Cl_2) and diethyl ether (Et_2O) were distilled from calcium hydride under argon atmosphere. Toluene was distilled from sodium under argon atmosphere. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm Qingdao silica gel plates (60F-254) using UV lights as the visualizing agent and $KMnO_4$. Flash column chromatography was performed over Qingdao silica gel (200-300 mesh). Infrared spectra were recorded on a Nicolet AVATER FTIR380 spectrometer as thin film and are reported in reciprocal centimeter (cm^{-1}). High resolution mass spectra (HRMS) were recorded on a Micromass QTOF2 Quadrupole/Time-of-Flight Tandem mass spectrometer using electron spray ionization. NMR spectra were recorded on Bruker AV-400, Bruker AV-500 and Bruker AV-600 instruments and were calibrated using residual undeuterated solvents ($CHCl_3$, $\delta_H = 7.26$; DMSO-d_6, $\delta_H = 2.50$) and deuterated solvents ($CDCl_3$, $\delta_C = 77.0$; DMSO-d_6, $\delta_C = 39.6$) as internal references. The data for ^1H NMR are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, brs = broad singlet), coupling constants (Hz) and integration.

2. Experimental Procedure

2.1 Syntheses of (*Z*,*E*,*E*)-skipped trienaldehyde

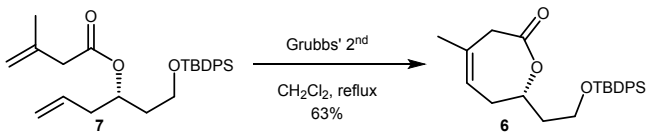
Synthesis of chiral diene ester 7



To a solution of chiral alcohol **8**[1] (51.31 g, 144.7 mmol) and 3-methyl-3-butenoic acid **9**[2] (36.22 g, 361.8 mmol) in CH_2Cl_2 (600 mL) at 0 °C were added DMAP (8.84 g, 72.36 mmol) and DCC (68.62 g, 332.8 mmol) in sequence. The reaction mixture was stirred at this temperature for 1 h and filtered through a pad of celite. The filtrate was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (PE/EtOAc = 150:1) afforded **7** (60.62 g, 96% yield) as a colorless oil.

$[\alpha]_D^{25}$ +16.0 (c 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 – 7.64 (m, 4H), 7.45 – 7.37 (m, 6H), 5.86 – 5.68 (m, 1H), 5.22 – 5.13 (m, 1H), 5.07 – 5.11 (m, 1H), 5.06 (brs, 1H), 4.88 (brs, 1H), 4.82 (brs, 1H), 3.70 (t, *J* = 6.4 Hz, 2H), 2.96 (s, 2H), 2.44 – 2.28 (m, 2H), 1.90 – 1.81 (m, 2H), 1.78 (s, 3H), 1.07 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.7, 138.6, 135.54, 135.51, 133.7, 133.6, 133.5, 129.6, 127.6, 117.8, 114.5, 70.7, 60.1, 43.7, 38.7, 36.3, 26.8, 22.4, 19.1; **IR** (KBr, cm^{-1}) □ 3072, 2958, 2930, 2857, 1734, 1112, 702; **HRMS** (ESI, m/z) calcd for $C_{27}H_{36}O_3Si$ $[M+Na]^+$: 459.2326, found: 459.2327.

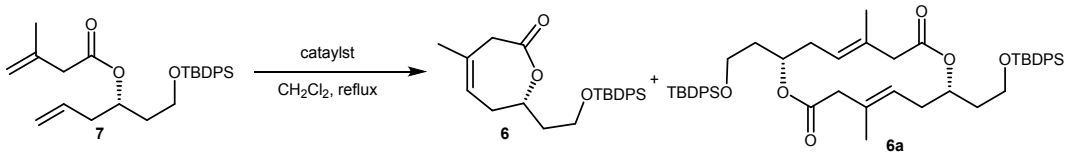
Synthesis of seven-membered lactone 6 via RCM reaction



To a solution of Grubbs' 2nd (0.194 mg, 0.229 mmol) in CH_2Cl_2 (450 mL) under argon was added a solution of diene ester **7** (2.00 g, 4.58 mmol) in CH_2Cl_2 (8 mL). The reaction mixture was degassed twice with argon, heated to reflux for 15 h then cooled to rt. The reaction mixture was concentrated *in vacuo*. Purification of the residue by flash chromatography (PE/EtOAc = 50:1) afforded **6** (1.18 g, 63% yield) as a colorless oil.

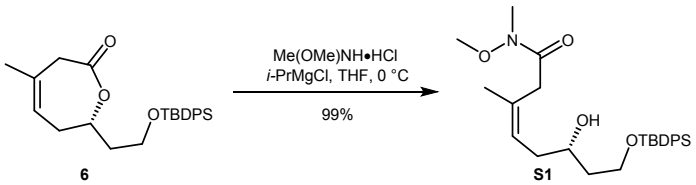
$[\alpha]_D^{25}$ +3.3 (c 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 – 7.62 (m, 4H), 7.46 – 7.36 (m, 6H), 5.45 – 5.37 (m, 1H), 5.03 – 4.94 (m, 1H), 3.96 – 3.86 (m, 1H), 3.80 – 3.67 (m, 2H), 2.83 (d, *J* = 15.9 Hz, 1H), 2.46 – 2.24 (m, 2H), 1.95 – 1.86 (m, 1H), 1.85 – 1.75 (m, 4H), 1.07 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.0, 135.4, 133.6, 133.4, 129.7, 127.71, 127.69, 126.6, 122.4, 73.3, 59.6, 38.7, 38.0, 35.3, 26.8, 26.7, 19.2; **IR** (KBr, cm^{-1}) 3070, 2957, 2856, 1739, 1274, 1112, 703, 505; **HRMS** (ESI, m/z) calcd for $C_{25}H_{32}O_3Si$ $[M+Na]^+$: 431.2013, found: 431.2016.

Table S1. Optimization of RCM reaction.



Entry	Catalyst	Yield
1	Grubbs' 1st	decomposed
2	Grubbs' 2nd	**6** (63%), **6a** (14%)
3	Grubbs' 3rd	low conversion
4	Hoveyda-Grubbs' 1st	NR
5	Hoveyda-Grubbs' 2nd	**6** (36%), **6a** (19%)

Synthesis of Weinreb amide S1

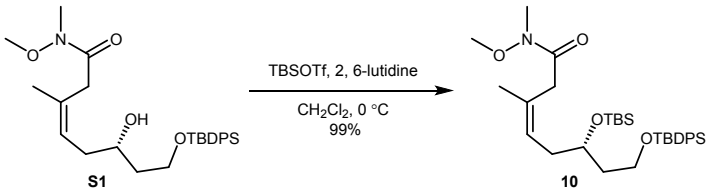


To a solution of seven-membered lactone **6** (5.00 g, 12.24 mmol) and Me(OMe)NH•HCl (2.51 g, 25.70 mmol) in THF (90 mL) at 0 °C was added *i*-PrMgCl (25.70 mL, 51.41 mmol) dropwise. The reaction mixture was stirred at this temperature for 45 min then quenched with saturated NH_4Cl solution (40 mL). The reaction mixture was diluted with water, extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (PE/EtOAc = 4:1) afforded **S1** (5.71 g, 99 % yield) as a colorless oil.

$[\alpha]_D^{25}$ –11.8 (c 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 – 7.64 (m, 4H), 7.47 – 7.35 (m, 6H), 5.46 (t, *J* = 7.1 Hz, 1H), 3.96 – 3.78 (m, 3H), 3.69 (s, 3H), 3.61 (brs,

1H), 3.23 (brs, 2H), 3.19 (s, 3H), 2.22 (t, J = 7.1 Hz, 2H), 1.77 (s, 3H), 1.75 – 1.65 (m, 2H), 1.05 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.3, 135.4, 135.3, 133.4, 133.3, 131.4, 129.5, 127.5, 124.9, 69.5, 62.3, 61.0, 38.8, 36.3, 34.7, 32.1, 26.7, 24.0, 18.9; **IR** (KBr, cm^{-1}) 2930, 2856, 2360, 1650, 1427, 1005, 703, 505; **HRMS** (ESI, m/z) calcd for $C_{27}H_{39}NO_4Si$ $[M+Na]^+$: 492.2541, found: 492.2545.

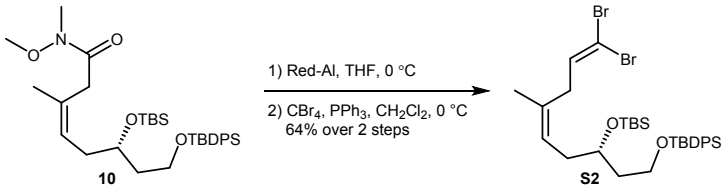
Synthesis of Weinreb amide 10



To a solution of secondary alcohol **S1** (500 mg, 1.06 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added 2, 6-lutidine (0.24 mL, 2.12 mmol) and TBSOTf (0.36 mL, 1.59 mmol) in sequence. The reaction mixture was stirred at this temperature for 30 min then quenched with water (5 mL), extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (PE/EtOAc = 15:1) afforded **10** (615 mg, 99% yield) as a colorless oil.

$[\alpha]_D^{25}$ +4.12 (c 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 4H), 7.45 – 7.33 (m, 6H), 5.37 (t, J = 6.7 Hz, 1H), 3.96 – 3.86 (m, 1H), 3.78 – 3.68 (m, 2H), 3.64 (s, 3H), 3.20 (d, J = 15.4 Hz, 1H), 3.16 (s, 3H), 3.12 (d, J = 15.4 Hz, 1H), 2.18 (t, J = 6.7 Hz, 2H), 1.78 (s, 3H), 1.75 – 1.61 (m, 2H), 1.05 (s, 9H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.2, 135.47, 135.46, 133.9, 130.2, 129.44, 129.43, 127.5, 124.8, 69.2, 60.9, 60.8, 39.9, 36.3, 35.5, 32.2, 26.8, 25.80, 23.9, 19.1, 18.0, –4.5, –4.8; **IR** (KBr, cm^{-1}) 2927, 2854, 1661, 1427, 1255, 1111, 702; **HRMS** (ESI, m/z) calcd for $C_{33}H_{53}NO_4Si_2$ $[M+Na]^+$: 606.3405, found: 606.3411.

Synthesis of dibromide S2



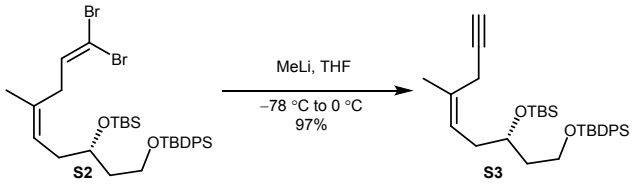
To a solution of Weinreb amide **10** (200 mg, 0.342 mmol) in THF (6 mL) at 0 °C was added Red-Al (0.11 mL, 70 wt% in toluene ca. 3.5 M, 0.376 mmol) dropwise. The reaction mixture was stirred at this temperature for 15 min then quenched with water

carefully. The reaction mixture was washed with saturated Rochelle salt solution, extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product aldehyde was used in next step without further purification.

To a solution of CBr_4 (249 mg, 0.752 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added PPh_3 (395 mg, 1.505 mmol) in CH_2Cl_2 (2 mL), the reaction mixture was stirred at this temperature for 30 min. Then to the reaction mixture at 0 °C was added a solution of aldehyde (from previous step) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at this temperature for 1 h then quenched with saturated $NaHCO_3$ solution, extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (PE/EtOAc = 100:1) afforded **S2** (150 mg, 64% from **10**) as a colorless oil.

$[\alpha]_D^{25}$ +4.1 (c 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 – 7.63 (m, 4H), 7.48 – 7.36 (m, 6H), 6.29 (t, *J* = 7.3 Hz, 1H), 5.27 (t, *J* = 6.8 Hz, 1H), 3.96 – 3.86 (m, 1H), 3.81 – 3.68 (m, 2H), 2.83 (dd, *J* = 15.1 Hz, 7.3 Hz, 1H), 2.77 (dd, *J* = 15.1 Hz, 7.3 Hz, 1H), 2.18 (t, *J* = 6.8 Hz, 2H), 1.73 (s, 3H), 1.72 – 1.66 (m, 2H), 1.08 (s, 9H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.3, 135.6, 134.0, 132.3, 129.6, 129.5, 127.6, 123.9, 89.3, 69.3, 60.9, 39.9, 36.1, 35.9, 26.9, 25.9, 23.6, 19.2, 18.1, –4.4, –4.7; **IR** (KBr, cm^{-1}) 2927, 2854, 1722, 1428, 1113, 821, 702; **HRMS** (ESI, m/z) calcd for $C_{32}H_{48}Br_2O_2Si_2$ $[M+Na]^+$: 703.1437, found: 703.1441.

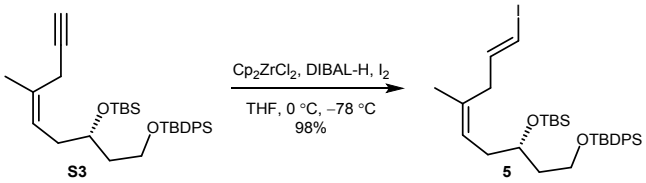
Synthesis of terminal alkyne S3



To a solution of dibromide **S2** (1.99 g, 2.92 mmol) in THF (40 mL) at –78 °C was added MeLi (11.68 mL, 1 M in THF, 11.68 mmol) dropwise. The reaction mixture was stirred at –78 °C for 30 min then stirred at 0 °C for 30 min before being quenched with water carefully. The reaction mixture was extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (PE/EtOAc = 200:1) afforded **S3** (1.47 g, 97% yield) as a colorless oil.

$[\alpha]_D^{25}$ +12.6 (c 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 4H), 7.44 – 7.33 (m, 6H), 5.24 (t, *J* = 6.8 Hz, 1H), 3.95 – 3.86 (m, 1H), 3.77 – 3.65 (m, 2H), 2.90 (dd, *J* = 17.3 Hz, 1.9 Hz, 1H), 2.84 (dd, *J* = 17.3 Hz, 1.9 Hz, 1H), 2.16 (t, *J* = 6.8 Hz, 2H), 1.91 (t, *J* = 2.6 Hz, 1H), 1.82 (s, 3H), 1.70 – 1.62 (m, 2H), 1.04 (s, 9H), 0.85 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.58, 135.57, 134.0, 131.3, 129.54, 129.51, 127.6, 123.3, 82.0, 69.2, 68.3, 60.9, 39.9, 36.0, 26.9, 25.9, 23.1, 21.4, 19.2, 18.0, –4.4, –4.7; **IR** (KBr, cm^{-1}) 3312, 3071, 2956, 2929, 2856, 1428, 1256, 1089, 836, 504; **HRMS** (ESI, m/z) calcd for $C_{32}H_{48}O_2Si_2$ $[M+Na]^+$: 543.3085, found: 543.3085.

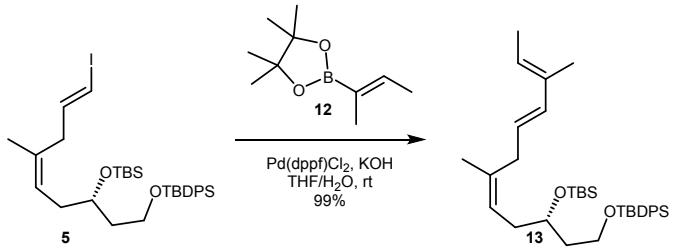
Synthesis of (*E*)-vinyl iodide 5



To a solution of Cp_2ZrCl_2 (6.24 g, 21.36 mmol) in THF (120 mL) at 0 °C was added DIBAL-H (21.36 mL, 1 M in hexane, 21.36 mmol). The resultant suspension was stirred at 0 °C for 30 min. To the suspension at 0 °C was added a solution of terminal alkyne **S3** (3.72 g, 7.12 mmol) in THF (25 mL). The reaction mixture was stirred at rt for 2 h and then cooled to −78 °C before the addition of iodine (7.23 g, 28.48 mmol) in THF (25 mL) dropwise. The reaction mixture was stirred at −78 °C for 30 min then warmed to rt, quenched with saturated Na_2SO_3 solution carefully, and extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (PE/EtOAc = 200:1) afforded **5** (4.53 g, 98% yield) as a colorless oil.

$[\alpha]_D^{25}$ +7.3 (c 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.67 (m, 4H), 7.46 – 7.39 (m, 6H), 6.43 (dt, *J* = 14.3, 6.9 Hz, 1H), 6.01 (d, *J* = 14.3 Hz, 1H), 5.28 (t, *J* = 6.7 Hz, 1H), 3.95 – 3.86 (m, 1H), 3.80 – 3.70 (m, 2H), 2.76 (dd, *J* = 14.9 Hz, 6.9 Hz, 1H), 2.70 (dd, *J* = 14.9 Hz, 6.9 Hz, 1H), 2.15 (t, *J* = 6.7 Hz, 2H), 1.71 (s, 3H), 1.70 – 1.65 (m, 2H), 1.09 (s, 9H), 0.89 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.3, 135.6, 133.9, 132.5, 129.6, 129.5, 127.6, 123.6, 75.4, 69.3, 60.8, 39.9, 38.6, 36.0, 26.9, 25.9, 23.5, 19.2, 18.1, –4.4, –4.7; **IR** (KBr, cm^{-1}) 2954, 2928, 2856, 1682, 1428, 1255, 836, 504; **HRMS** (ESI, m/z) calcd for $C_{32}H_{49}IO_2Si_2$ $[M+Na]^+$: 671.2208, found: 671.2206.

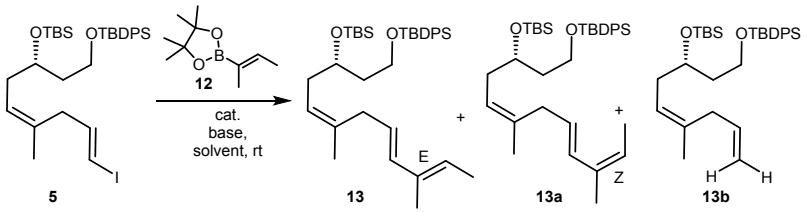
Synthesis of (*Z*,*E*,*E*)-skipped triene 13 via Suzuki cross coupling



To a solution of (*E*)-vinyl iodide **5** (4.53 g, 6.98 mmol) in THF (40 mL) at rt was added $Pd(dppf)Cl_2$ (0.26 g, 0.35 mmol), degassed with argon for 5 min. To the mixture were added vinyl borate **12**[3] (1.85 g, 9.07 mmol) and KOH (13.96 mL, 2 M, 27.92 mmol) aqueous. The reaction mixture was stirred at rt for 12 h then diluted with water, extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (PE/EtOAc = 200:1) afforded **13** (4.01 g, 99% yield) as a colorless oil.

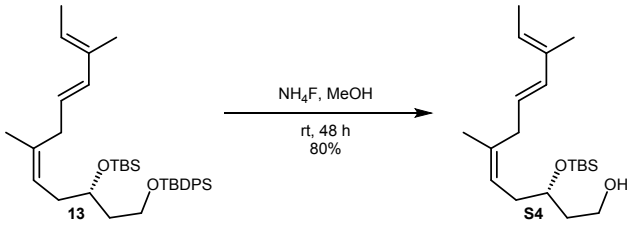
$[\alpha]_D^{25}$ +4.3 (c 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.66 (m, 4H), 7.46 – 7.35 (m, 6H), 6.07 (d, *J* = 15.4 Hz, 1H), 5.50 – 5.40 (m, 2H), 5.22 (t, *J* = 7.0 Hz, 1H), 3.95 – 3.86 (m, 1H), 3.80 – 3.69 (m, 2H), 2.81 (dd, *J* = 14.7 Hz, 6.9 Hz, 1H), 2.76 (dd, *J* = 14.7 Hz, 6.9 Hz, 1H), 2.26 – 2.12 (m, 2H), 1.75 – 1.64 (m, 11H), 1.07 (s, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.58, 135.56, 135.2, 134.4, 134.0, 129.51, 129.49, 127.6, 124.7, 124.1, 121.9, 69.6, 61.0, 39.9, 36.1, 35.5, 26.9, 25.9, 23.6, 19.2, 18.1, 13.7, 12.1, –4.4, –4.7; **IR** (KBr, cm^{-1}) 2956, 2929, 1721, 1472, 1257, 836, 702, 505; **HRMS** (ESI, m/z) calcd for $C_{36}H_{56}O_2Si_2$ $[M+Na]^+$: 599.3711, found: 599.3728.

Table S2. Optimization of Suzuki Cross-Coupling



Entry	Catalyst (5 mol%)	Solvent	Base	Yield (%) (**13**/**13a**/**13b**)
1	$Pd(PPh_3)_4$	THF	Cs_2CO_3	(only **13b**)
2	$Pd(PPh_3)_4$	THF/H_2O 4:1	Cs_2CO_3	35 (2.2:0:1)
3	$Pd(PPh_3)_4$	THF/ H_2O 4:1	KOH	94 (4:1:0)
4	$Pd(PPh_3)_4$	THF/ H_2O 4:1	NaOH	87 (5:1:0)
5	$Pd(PPh_3)_4$	THF/ H_2O 4:1	LiOH	86 (3.8:1:0.7)
6	$Pd(PPh_3)_4$	THF/ H_2O 4:1	Ag_2O	40 (2.9:0:1)
7	$Pd(PPh_3)_4$	THF	KOH (solid)	47 (3.3:0:1)
8	$Pd(PPh_3)_4$	THF	KOH (sat. aq)	89 (8.4:0:1)
9	$Pd(dppf)Cl_2$	THF	KOH (2 M, aq)	99 (only **13**)

Synthesis of primary alcohol S4

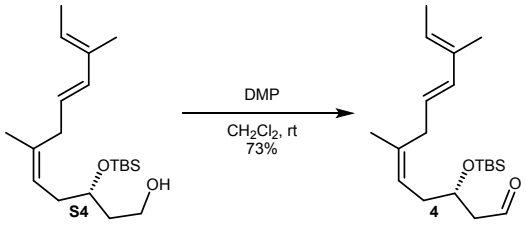


To a solution of (*Z*,*E*,*E*)-skipped triene **13** (1.43 g, 2.48 mmol) in MeOH (30 mL) at rt was added NH_4F (0.92 g, 24.8 mmol). The reaction mixture was stirred at rt for 48 h. Then the solvent was removed *in vacuo.* To the residue was added water, extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (PE/EtOAc = 40:1) afforded **S4** (0.67 g, 80% yield) as a colorless oil.

$[\alpha]_D^{25}$ +6.3 (c 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.05 (d, *J* = 15.5 Hz, 1H), 5.49 – 5.38 (m, 2H), 5.16 (t, *J* = 7.2 Hz, 1H), 3.96 – 3.87 (m, 1H), 3.86 – 3.76 (m, 1H), 3.76 – 3.65 (m, 1H), 2.81 (dd, *J* = 15.4 Hz, 6.8 Hz, 1H), 2.77 (dd, *J* = 15.4 Hz, 6.8 Hz, 1H), 2.46 (brs, 1H), 2.35 – 2.17 (m, 2H), 1.84 – 1.77 (m, 1H), 1.72 – 1.67 (m, 9H), 1.66 – 1.59 (m, 1H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.9, 135.6, 134.3, 124.9, 123.8, 121.2, 72.1, 60.3, 37.7, 35.5, 35.4, 25.8, 23.6, 17.9, 13.6, 12.0, –4.4, –4.9; **IR** (KBr, cm^{-1}) 3418, 2929, 2856, 1721, 1258, 1087, 837, 776;

MS (ESI, m/z) calcd for $C_{20}H_{38}O_2Si$ $[M+H]^+$: 339.3, found: 339.2.

Synthesis of skipped trienaldehyde 4

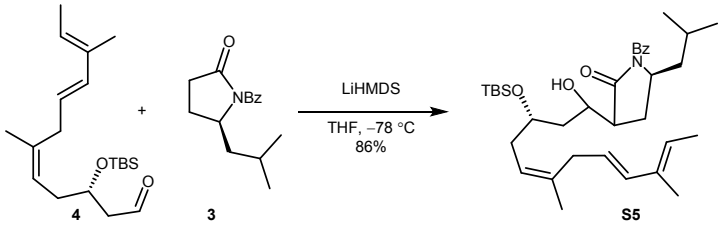


To a solution of primary alcohol **S4** (107 mg, 0.315 mmol) in CH_2Cl_2 (10 mL) at rt was added DMP (200 mg, 0.472 mmol). The reaction mixture was stirred at rt for 30 min then quenched with saturated Na_2SO_3 solution and saturated $NaHCO_3$ solution, extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (PE/EtOAc = 80:1) afforded **4** (77 mg, 73% yield) as a colorless oil.

$[\alpha]_D^{25}$ +14.0 (c 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.78 (t, *J* = 2.5 Hz, 1H), 6.05 (d, *J* = 15.4 Hz, 1H), 5.49 – 5.37 (m, 2H), 5.18 (t, *J* = 7.3 Hz, 1H), 4.25 – 4.13 (m, 1H), 2.83 – 2.72 (m, 2H), 2.50 (dd, *J* = 5.9, 2.5 Hz, 2H), 2.37 – 2.17 (m, 2H), 1.72 – 1.67 (m, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.2, 136.8, 135.8, 134.2, 125.0, 123.6, 120.5, 68.5, 50.6, 36.3, 35.4, 25.7, 23.7, 18.0, 13.7, 12.1, –4.4, –4.9; **IR** (KBr, cm^{-1}) 3354, 2928, 2856, 2719, 1727, 1471, 1257, 1092, 776; **HRMS** (ESI, m/z) calcd for $C_{20}H_{36}O_2Si$ $[M+Na]^+$: 359.2377, found: 359.2376.

2.2 Total synthesis of periconiasin A

Synthesis of *β*-hydroxy lactam S5

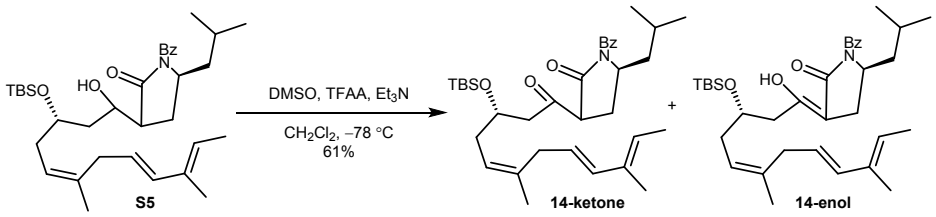


To a solution of lactam **3**[4] (151 mg, 0.615 mmol) in THF (10 mL) at −78 °C was added LiHMDS (0.67 mL, 1 M in THF, 0.671 mmol). The reaction mixture was stirred at −78 °C for 1 h before the addition of trienaldehyde **4** (188 mg, 0.559 mmol) in THF (2 mL). The reaction mixture was stirred at −78 °C for 2 h then quenched with saturated NH_4Cl solution, extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash

chromatography (PE/EtOAc = 40:1) afforded **S5** (280 mg, 86% yield) as a colorless oil.

Data for one of the diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.51 (m, 3H), 7.45 – 7.39 (m, 2H), 6.05 (d, *J* = 15.5 Hz, 1H), 5.51 – 5.39 (m, 2H), 5.17 (t, *J* = 7.2 Hz, 1H), 4.63 – 4.54 (m, 1H), 4.17 (s, 1H), 4.04 – 3.92 (m, 2H), 2.85 – 2.71 (m, 3H), 2.34 – 2.25 (m, 1H), 2.23 – 2.14 (m, 1H), 1.96 (dd, *J* = 10.0, 4.9 Hz, 2H), 1.76 – 1.64 (m, 12H), 1.50 – 1.38 (m, 2H), 1.00 (d, *J* = 5.5 Hz, 3H), 0.98 (d, *J* = 5.5 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.2, 170.1, 135.7, 135.6, 134.8, 134.3, 132.0, 128.5, 127.9, 124.8, 123.9, 121.3, 69.0, 68.96, 53.9, 47.3, 43.0, 40.8, 36.2, 35.4, 27.0, 25.9, 25.5, 23.6, 23.4, 21.7, 18.0, 13.7, 12.1, –4.4, –4.9; **HRMS** (ESI, m/z) calcd for $C_{35}H_{55}NO_4Si$ $[M+Na]^+$: 604.3793, found: 604.3793.

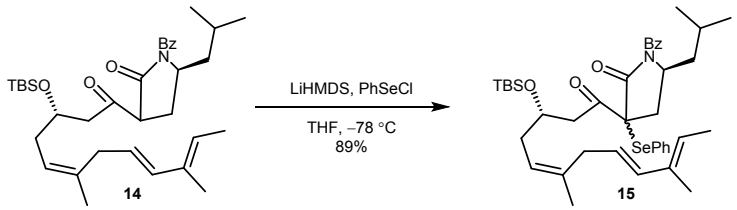
Synthesis of *β*-keto lactam 14



To a solution of TFAA (0.03 mL, 0.233 mmol) in CH_2Cl_2 (2 mL) at −78 °C was added a solution of DMSO (0.03 mL, 0.389 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at −78 °C for 20 min before the addition of *β*-hydroxy lactam **S5** (49.2 mg, 0.078 mmol) in CH_2Cl_2 (2 mL). Then the mixture was stirred at −78 °C for 40 min before the addition of Et_3N (0.11 mL, 0.778 mmol). The resultant mixture was stirred −78 °C for 20 min then warmed to rt, quenched with water, extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (PE/EtOAc = 60:1) afforded **14** (30.1 mg, 61% yield, ketone/enol = 1:1) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.64 (s, 0.07H), 11.58 (s, 0.49H), 7.63 – 7.50 (m, 3H), 7.45 – 5.35 (m, 2H), 6.12 – 5.98 (m, 1H), 5.51 – 5.35 (m, 2H), 5.25 – 5.09 (m, 1H), 4.58 – 4.37 (m, 1H), 4.26 – 4.06 (m, 1H), 3.93 (t, *J* = 8.4 Hz, 0.24H), 3.78 – 3.70 (m, 0.20H), 3.04 – 2.89 (m, 1H), 2.87 – 2.59 (m, 3H), 2.44 – 2.21 (m, 4H), 1.94 – 1.75 (m, 2H), 1.74 – 1.66 (m, 9H), 1.45 – 1.34 (m, 1H), 1.05 – 0.94 (m, 6H), 0.89 – 0.82 (m, 9H), 0.09 – –0.02 (m, 6H); **HRMS** (ESI, m/z) calcd for $C_{35}H_{53}NO_4Si$ $[M+Na]^+$: 602.3636, found: 602.3635.

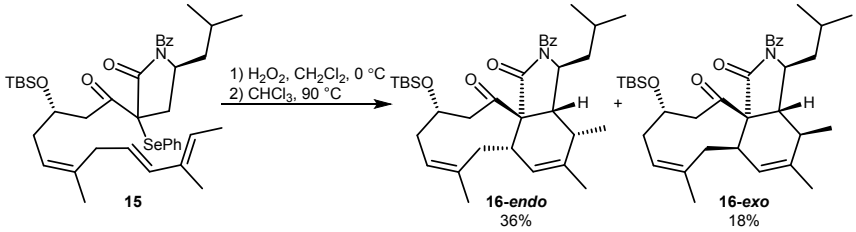
Synthesis of 15



To a solution of *β*-keto lactam **14** (52.0 mg, 0.0897 mmol) in THF (3 mL) at −78 °C was added LiHMDS (0.10 mL, 1 M in THF, 0.103 mmol). The reaction mixture was stirred at −78 °C for 1 h before the addition of PhSeCl (21.4 mg, 0.112 mmol) in THF (2 mL). The resultant mixture was stirred −78 °C for 1 h then warmed to rt, quenched with saturated NH_4Cl solution, extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (PE/EtOAc = 80:1) afforded **15** (58.9 mg, 89% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.30 (m, 10H), 56.10 – 6.00 (m, 1H), 5.51 – 5.34 (m, 2H), 5.23 (t, *J* = 7.1 Hz, 0.7H), 5.10 (t, *J* = 7.1 Hz, 0.3H), 4.35 – 4.14 (m, 2H), 3.41 – 3.13 (m, 2H), 3.07 – 2.69 (m, 3H), 2.36 – 2.24 (m, 2H), 2.19 – 2.08 (m, 1H), 1.94 – 1.75 (m, 2H), 1.71 – 1.62 (m, 9H), 1.46 – 1.32 (m, 1H), 0.88 (m,15H), 0.09 – 0.03 (m, 6H); **HRMS** (ESI, m/z) calcd for $C_{41}H_{57}NO_4SeSi$ $[M+Na]^+$: 758.3114, found: 758.3115.

Synthesis of 9/6/5 tricyclic lactam 16 via intramolecular Diels−Alder reaction



To a solution of **15** (52.0 mg, 0.0897 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added H_2O_2/H_2O (0.23 mL, 30% H_2O_2/H_2O (v/v) = 1:2). The reaction mixture was stirred at 0 °C for 45 min then quenched with cooled saturated $NaHCO_3$ solution, extracted with cooled $CHCl_3$. The combined organic layer was dried over $MgSO_4$, filtered through a pad of celite. The filtrate include crude product was used in next step.

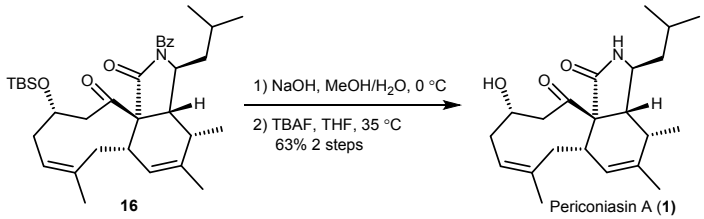
$CHCl_3$ (20 mL) was added to the crude product (from previous step) in $CHCl_3$. The mixture was heated to 90 °C in a sealed tube under argon and stirred for 6 h, then cooled to rt and concentrated *in vacuo.* Purification of the residue by flash chromatography

(PE/EtOAc = 50:1) afforded **16-*endo*** (10.5 mg, 36% yield over 2 steps) as a colorless oil, **16-*exo*** (5.3 mg, 18% yield over 2 steps) as a colorless oil.

16-*endo*: $[\alpha]_D^{25}$ −34.8 (c 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 – 7.50 (m, 3H), 7.46 – 7.40 (m, 2H), 5.51 (s, 1H), 5.18 (dd, *J* = 9.7, 7.1 Hz 1H), 4.27 (dd, *J* = 9.7, 3.6 Hz, 1H), 4.12 – 4.02 (m, 1H), 3.94 – 3.78 (m, 1H), 3.50 (brs, 1H), 2.72 – 2.50 (m, 4H), 2.42 – 2.30 (m, 1H), 2.10 – 2.01 (m, 1H), 1.78 (s, 3H), 1.76 – 1.64 (m, 3H), 1.62 (s, 3H), 1.60 – 1.57 (m, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 0.98 (d, *J* = 6.3 Hz, 3H), 0.90 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 208.9, 175.2, 169.8, 139.9, 137.4, 134.7, 132.0, 129.3, 128.4, 128.0, 122.5, 70.5, 70.2, 54.0, 51.3, 48.4, 46.0, 45.6, 38.6, 34.7, 31.6, 25.8, 24.7, 23.5, 23.4, 21.6, 19.1, 18.0, 13.5, –4.8, –4.9; **IR** (KBr, cm^{-1}) 2957, 2927, 2855, 1731, 1698, 1462, 1287, 1069, 836; **HRMS** (ESI, m/z) calcd for $C_{35}H_{51}NO_4Si$ $[M+Na]^+$: 600.3480, found: 600.3475.

16-*exo*: $[\alpha]_D^{25}$ −43.6 (c 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 (t, *J* = 7.1 Hz, 1H), 7.45 – 7.34 (m, 4H), 5.67 (d, *J* = 6.7 Hz, 1H), 5.22 (t, *J* = 8.12 Hz, 1H), 4.48 – 4.37 (m, 1H), 4.05 (d, *J* = 9.5 Hz, 1H), 3.33 (dd, *J* = 16.9, 10.7 Hz, 1H), 3.19 – 3.10 (m, 2H), 2.30 – 2.15 (m, 3H), 2.15 – 1.98 (m, 3H), 1.94 – 1.85 (m, 1H), 1.80 (s, 3H), 1.76 (s, 3H), 1.64 – 1.48 (m, 2H), 1.17 (d, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 206.3, 173.1, 170.3, 139.5, 138.6, 134.8, 132.0, 128.2, 128.0, 125.7, 118.9, 69.0, 67.9, 64.2, 44.4, 42.5, 41.1, 40.4, 40.2, 36.0, 32.5, 25.8, 25.2, 23.9, 23.8, 22.6, 21.7, 21.5, 18.0, –4.8; **IR** (KBr, cm^{-1}) 2956, 2928, 2855, 1734, 1701, 1472, 1287, 1070, 838; **HRMS** (ESI, m/z) calcd for $C_{35}H_{51}NO_4Si$ $[M+Na]^+$: 600.3480, found: 600.3480.

Synthesis of periconiasin A (1)



To a solution of lactam **16** (113 mg, 0.196 mmol) in MeOH (15 mL) at 0 °C was added NaOH (0.59 mL, 1 M, 0.588 mmol) aqueous. The reaction mixture was stirred at 0 °C for 1.5 h then diluted with water, extracted with Et_2O. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was used in the next step without further purification.

To a solution of the crude product (from previous step) in THF (15 mL) at rt was added

TBAF (0.78 mL, 1 M in THF, 0.784 mmol). The reaction mixture was heated to 35 °C for 4 h, then quenched with water, extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (PE/EtOAc = 1:1) afforded periconiasin A (**1**) (44.1 mg, 63% yield over 2 steps) as a colorless gum.

Periconiasin A (1): $[\alpha]_D^{20}$ −20.3 (c 0.1, MeOH), reported optical rotation[5] for natural **1**: $[\alpha]_D^{20}$ −21.7 (c 0.12, MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.62 (s, 1H), 5.57 (s, 1H), 5.15 (dd, *J* = 9.5, 7.1 Hz, 1H), 3.88 (brs, 1H), 3.79 – 3.59 (m, 1H), 3.17 (d, *J* = 9.5 Hz, 1H) 3.05 – 2.84 (m, 1H), 2.63 – 2.47 (m, 1H), 2.47 – 2.35 (m, 2H), 2.18 – 2.10 (m, 1H), 1.97 – 1.84 (m, 1H), 1.80 (d, *J* = 14.2 Hz, 1H), 1.73 (s, 3H), 1.67 (s, 3H), 1.65 – 1.56 (m, 1H), 1.27 – 1.22 (m, 2H), 1.18 (d, *J* = 7.2 Hz, 3H), 1.10 – 1.02 (m, 1H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 214.4, 175.7, 140.1, 138.9, 129.8, 120.5, 70.5, 67.8, 52.3, 50.9, 48.3, 42.5, 36.1, 35.4, 31.8, 29.6, 24.8, 23.8, 23.5, 21.3, 19.6, 13.2; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.17 (s, 1H), 5.40 (s, 1H), 5.08 (dd, *J* = 10.4, 6.8 Hz, 1H), 4.81 (d, *J* = 4.0 Hz, 1H), 4.14 – 4.04 (m, 1H), 3.80 – 3.70 (m, 1H), 3.31 – 3.26 (m, 1H), 3.02 (brs, 1H), 2.69 (dd, *J* = 12.4, 10.4 Hz, 1H), 2.44 – 2.31 (m, 3H), 2.14 – 2.07 (m, 1H), 2.00 (dd, *J* = 12.4, 6.8 Hz, 1H), 1.70 (s, 3H), 1.63 – 1.55 (m, 2H), 1.54 (s, 3H), 1.11 (d, *J* = 7.2 Hz, 3H), 1.06 – 0.98 (m, 2H), 0.83 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 212.2, 175.7, 138.7, 136.6, 128.9, 122.7, 69.3, 65.9, 55.3, 49.6, 48.8, 46.7, 43.6, 37.3, 34.8, 30.9, 24.0, 23.6, 23.5, 21.7, 19.4, 12.9; **IR** (KBr, cm^{-1}) 3206, 2960, 2924, 2855, 1689, 1462, 1384, 1294, 1260, 1164, 1048, 897, 799, 659; **HRMS** (ESI, m/z) calcd for $C_{22}H_{33}NO_3$ $[M+Na]^+$: 382.2353, found: 382.2352.

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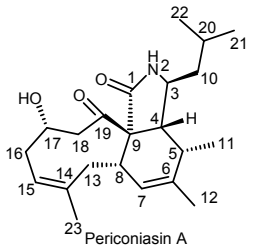
5 D. Zhang, H. Ge, D. Xie, R. Chen, J.-h. Zou, X. Tao and J. Dai, *Org. Lett.*, 2013, **15**, 1674.

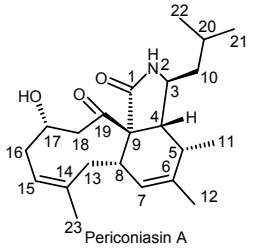
Table S3. [1]H NMR (DMSO-d_6) spectroscopic data comparison of natural and synthetic periconiasin A.



Periconiasin A

Position	Natural δ [1]H [ppm, mult, *J* (Hz)] 400 MHz	Synthetic δ [1]H [ppm, mult, *J* (Hz)] 400 MHz	Err (Natural–Synthetic) Δ δ (ppm)
1			
2	8.19 (s, 1H)	8.17 (s, 1H)	0.02
3	3.02 (brs, 1H)	3.02 (brs, 1H)	0
4	2.11 (dd, *J* = 5.6, 1.6 Hz, 1H)	2.11 (m, 1H)	0
5	2.39 (overlapped, 1H)	2.39 (overlapped, 1H)	0
6			
7	5.40 (s, 1H)	5.40 (s, 1H)	0
8	2.41 (overlapped, 1H)	2.41 (overlapped, 1H)	0
9			
10	1.02 (m, 2H)	1.02 (m, 2H)	0
11	1.11 (d, *J* = 7.2 Hz, 3H)	1.11 (d, *J* = 7.2 Hz, 3H)	0
12	1.70 (s, 3H)	1.70 (s, 3H)	0.1
13	4.08 (m, 1H) 1.58 (m, 1H)	4.08 (m, 1H) 1.58 (m, 1H)	0 0
14			
15	5.08 (dd, *J* = 10.4, 6.8 Hz, 1H)	5.08 (dd, *J* = 10.4, 6.8 Hz, 1H)	0
16	2.69 (dd, *J* = 12.4, 10.4 Hz, 1H) 1.99 (dd, *J* = 12.4, 6.8 Hz, 1H)	2.69 (dd, *J* = 12.4, 10.4 Hz, 1H) 2.00 (dd, *J* = 12.4, 6.8 Hz, 1H)	0 -0.01
17	3.75 (m, 1H)	3.75 (m, 1H)	0
18	3.30 (m, 1H) 2.35 (overlapped, 1H)	3.30 (m, 1H) 2.35 (overlapped, 1H)	0 0
19			
20	1.60 (m, 1H)	1.60 (m, 1H)	0
21	0.83 (d, *J* = 6.4 Hz, 3H)	0.83 (d, *J* = 6.4 Hz, 3H)	0
22	0.83 (d, *J* = 6.4 Hz, 3H)	0.83 (d, *J* = 6.4 Hz, 3H)	0
23	1.54 (s, 3H)	1.54 (s, 3H)	0
─OH	4.82 (d, *J* = 4.0 Hz, 1H)	4.81 (d, *J* = 4.0 Hz, 1H)	0.01

Table S4. ^{13}C NMR (DMSO-d_6) spectroscopic data comparison of natural and synthetic periconiasin A.



Position	Natural δ ^{13}C [ppm, mult, *J* (Hz)] 100 MHz	Synthetic δ ^{13}C [ppm, mult, *J* (Hz)] 100 MHz	Err (Natural–Synthetic) Δ δ (ppm)
1	**175.7**	**175.7**	**0**
2			
3	**49.5**	**49.6**	**-0.1**
4	**55.3**	**55.3**	**0**
5	**34.8**	**34.8**	**0**
6	**138.7**	**138.7**	**0**
7	**128.9**	**128.9**	**0**
8	**43.6**	**43.6**	**0**
9	**65.9**	**65.9**	**0**
10	**48.8**	**48.8**	**0**
11	**12.9**	**12.9**	**0**
12	**19.4**	**19.4**	**0**
13	**30.8**	**30.9**	**-0.1**
14	**136.6**	**136.6**	**0**
15	**122.7**	**122.7**	**0**
16	**37.3**	**37.3**	**0**
17	**69.3**	**69.3**	**0**
18	**46.7**	**46.7**	**0**
19	**212.2**	**212.2**	**0**
20	**23.9**	**24.0**	**-0.1**
21	**21.6**	**21.7**	**-0.1**
22	**23.5**	**23.5**	**0**
23	**23.6**	**23.6**	**0**