Stereoselective total synthesis of antiplasmodial resorcylic acid lactone paecilomycin F

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This manuscript is dedicated to Dr. J. S. Yadav on occasion of his 65th birthday.

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Abstract
A facile and convergent approach for the total synthesis of 14-membered resorcylic acid lactone paecilomycin F is described. The synthesis emanates from the readily available inexpensive (+)-diethyl L-tartrate. Mitsunobu etherification, Stille coupling and ring-closing metathesis are key steps in the synthesis.

Keywords: Macrolactone, metathesis, resorcylic acid lactone, Swern oxidation

Introduction

The impressive biological properties i.e., antifungal,[1] antibiotic,[2] inhibition of ATPase activity of HSP90,[3] exhibited by the first resorcylic acid lactone (RAL) radicicol (Figure 1),[4] a 14-membered benzannulated macrolide, has attracted significant attention to the related RALs[5] (both synthetic and natural RALs) which have emerged over the last two decades. The resorcylic acid lactones with unique structural architecture are also found to exhibit potent biological activities ranging from antimalarial,[6] antiviral, antiparasitic,[7] antifungal,[8] cytotoxic,[9] estrogenic[10] to nematocidal[11] activities. Over the years, these molecules have emerged as common targets for total synthesis and have led medicinal chemists to design analog programmes leading to a number of clinical trials.[12-15] Chen *et al*. have recently isolated six new resorcylic acid lactones, namely paecilomycin A-F[16-18] (Figure 1) along with other known RALs from the mycelial solid culture of *Paecilomyces* fungus SC0924. Interestingly, when these compounds were subjected to screening for plasmodicidal activity, paecilomycin F was found to display antiplasmodial activity against *Plasmodium falciparum* line 3D7 with an IC_{50} value of 20.0 nM and moderate activity against *P. falciparum* line Dd2. Eventhough, the structures of these compounds were determined

by extensive NMR analysis and chemical correlations, our own investigation for the total synthesis of paecilomycin E and F lead to the structural reassignment[18,19] for these two molecules and was however later reconfirmed by total synthesis from Mohapatra *et al*[20] and also our group.[21] In continuation of our work on the total synthesis of lactonic natural products,[22-27] herein we present a facile and convergent strategy for the total synthesis of paecilomycin F.[28]

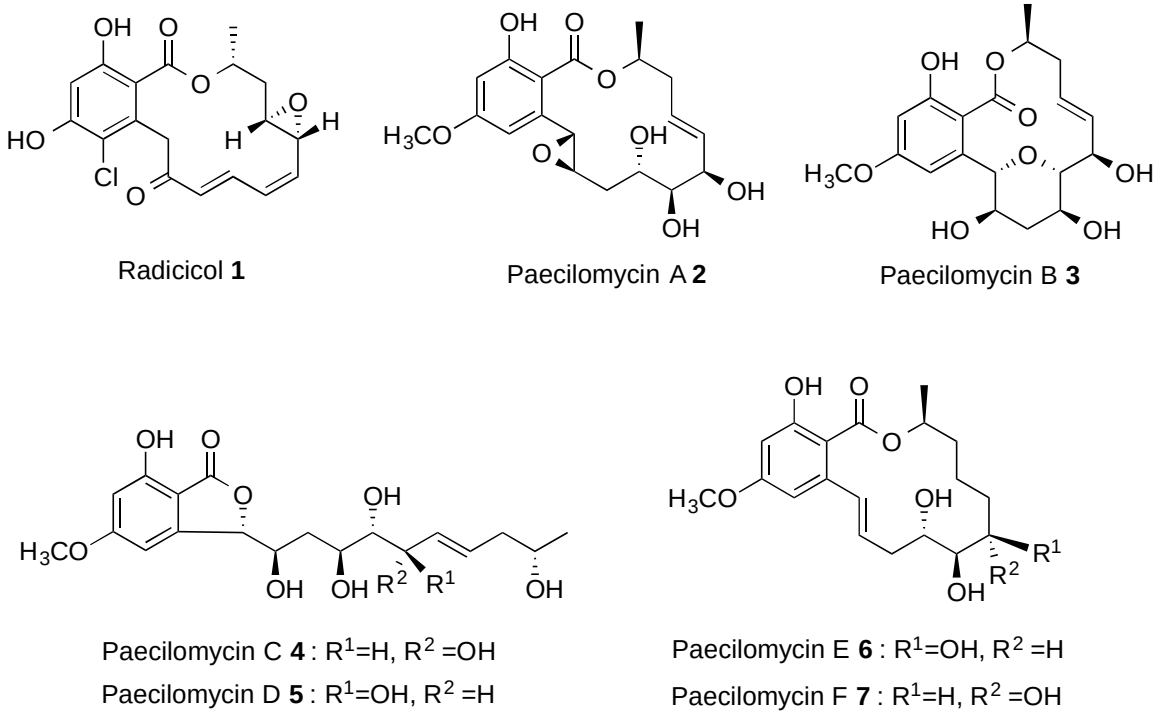
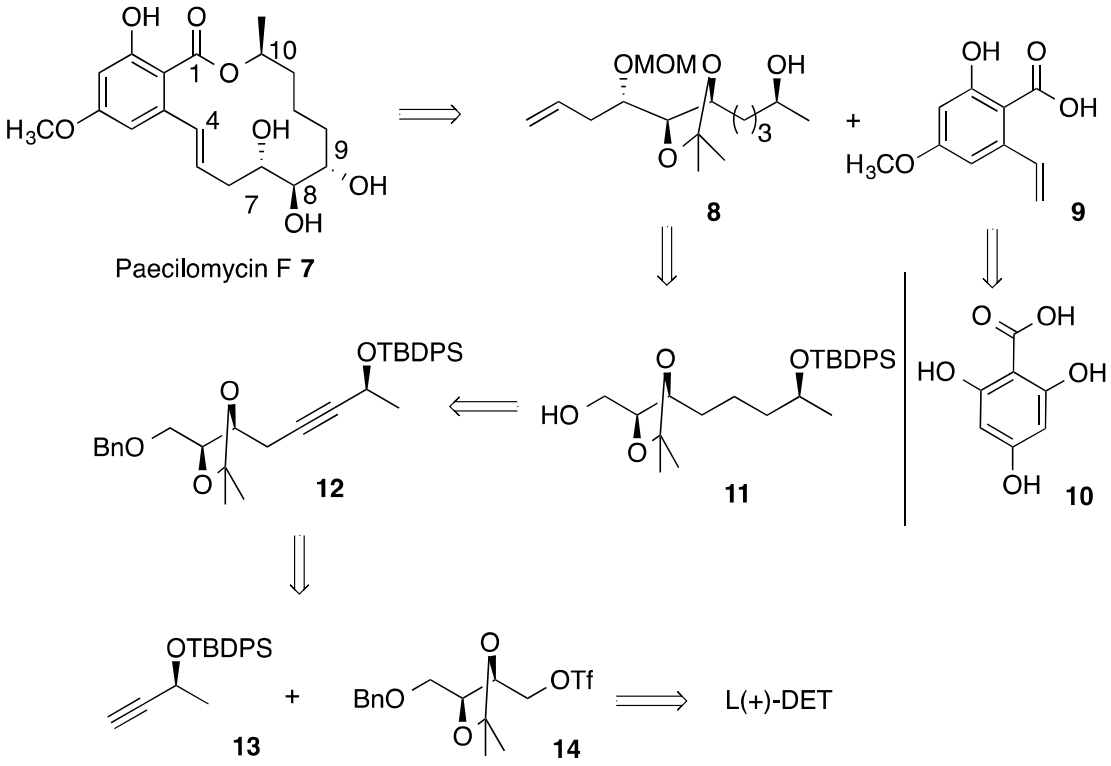


Figure 1. Structures of radicicol and paecilomycins A-F.

Results and Discussion

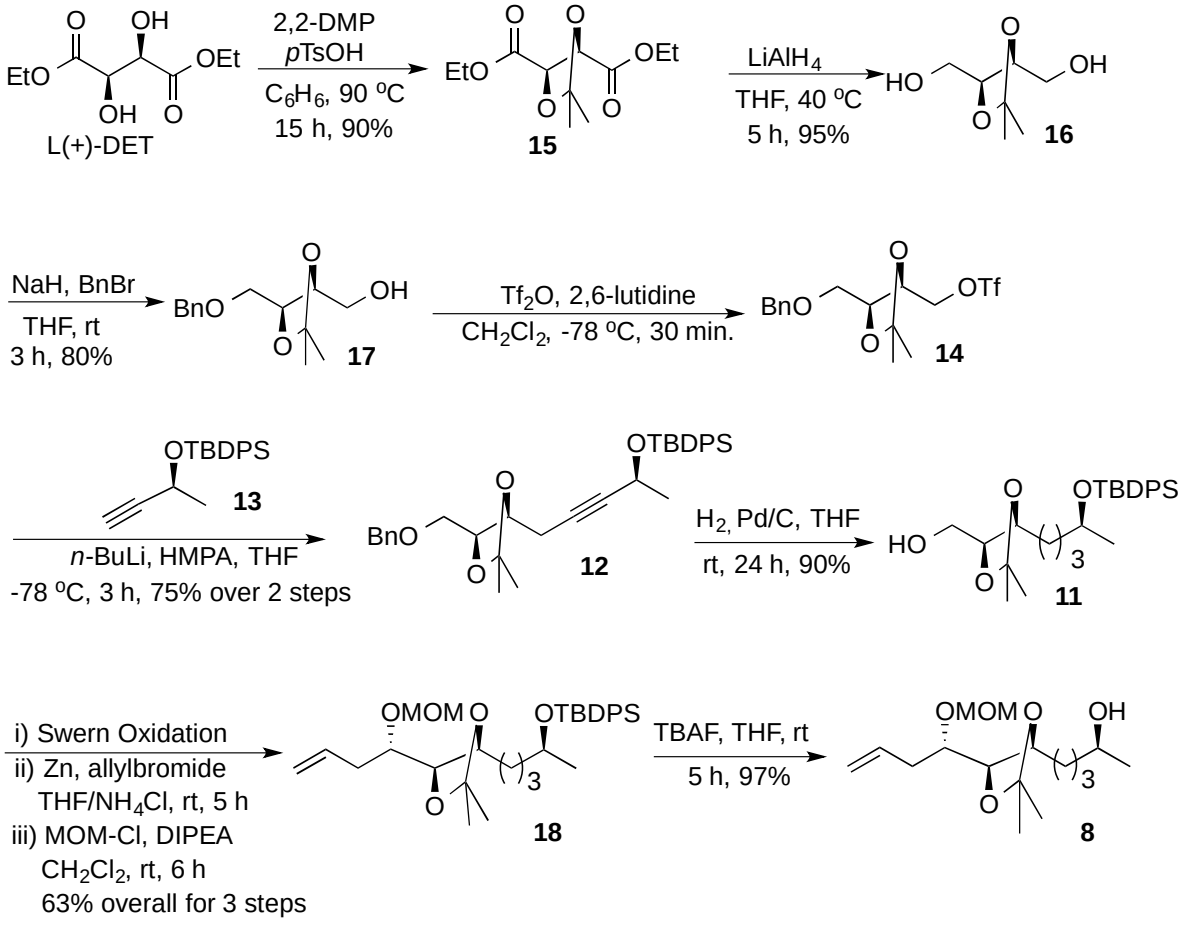
Our retrosynthesis is based on a convergent approach and involved two key intermediates, an aliphatic chiral chain **8** comprising a double bond and a secondary alcohol, and an aromatic acid (**9**). These two compounds can be coupled in an esterification followed by a ring closing metathesis to provide the precursor skeleton for the target molecule. The aromatic acid **9** can be synthesized from 2,4,6-trihydroxybenzoic acid in five known steps, and the aliphatic side chain **8** can be synthesized from the alcohol **11** by a four step sequence, *i.e.* oxidation, allylation, MOM protection of the resulting allyl alcohol, and deprotection of the TBDPS moiety (Scheme 1). The alcohol **11** can be synthesized from alkyne **12** in a one-pot reaction through hydrogenation, which in turn can be synthesized by a coupling reaction of terminal alkyne **13** with triflate **14**. The triflate is easily accessible from the commercially available (+)-diethyl L-tartrate (L(+)-DET).



Scheme 1. Retrosynthesis of paecilomycin F.

The synthesis began with isopropylidene protection[29] of the readily available (+)-diethyl L-tartrate to get the corresponding acetonide product **15** followed by the diester reduction with lithium aluminium hydride to deliver 1,4-diol **16**. The diol **16** was sequentially protected as the corresponding benzyl ether **17** by treatment with benzyl bromide and NaH and activated as the triflate **14** by triflic anhydride in presence of 2,6-lutidine to set up the stage for coupling with the terminal acetylene **13**. The alkyne **13** (obtained from the commercially available (*S*)-but-3-yne-2-ol after protection with TBDPSCl) was metalated with n-BuLi in presence of hexamethylphosphoramide (HMPA) and treated with triflate **14** to furnish the di-substituted alkyne **12**.[30] One pot benzyl deprotection and alkyne reduction was achieved smoothly with Pd/C under hydrogen atmosphere to provide the primary alcohol **11** in good yield (Scheme 2). The alcohol **11** was oxidized under Swern conditions[31] to yield the aldehyde and then subjected to allylation with allyl bromide in presence of Zinc[32] and NH_4Cl and further treated with MOM-Cl to furnish the corresponding MOM ethers. The product obtained after allylation was a mixture of diastereomers, which were inseparable and were directly treated with MOM-Cl to get the corresponding MOM ethers (9:1) which were easily separable by column chromatography. Based on the earlier experience for the allylation reaction,[19,21] we proceeded further with the major diastereomer **18**. Thus, treatment of the major diastereomer **18** with TBAF resulted in the formation of **8**, the key side chain fragment with the required stereochemistry.

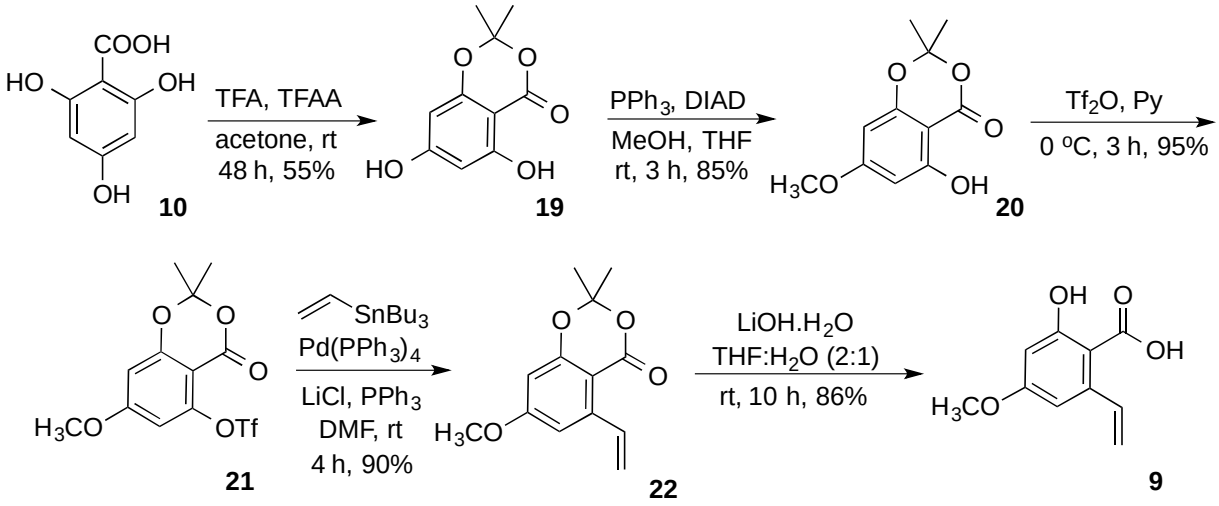
The other key fragment aromatic acid **9** was synthesized starting from 2,4,6-trihydroxybenzoic acid **10** (THBA) following known protocols as shown in Scheme 3. Thus, THBA **10** was treated with trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA) following Danishefsky's protocol[33] to get the acetonide protected product **19**. The regioselective methylation of **19** at *para*- position to carboxylic functionality was easily achieved with MeOH under Mitsunobu conditions[34] to yield **20** in 85% yield. The free hydroxyl group in **20** *ortho*- to carboxylic acid functionality was activated by converting it to the corresponding triflate **21** with triflic anhydride and later subjected to Stille coupling[35] with n-tributyl(vinyl tin) to furnish the vinylated aromatic ester **22** (Scheme 3). Ester hydrolysis of **22** with LiOH at room temperature provided the aromatic acid **9** in 86% yield, which can be used for coupling reaction towards the target synthesis.



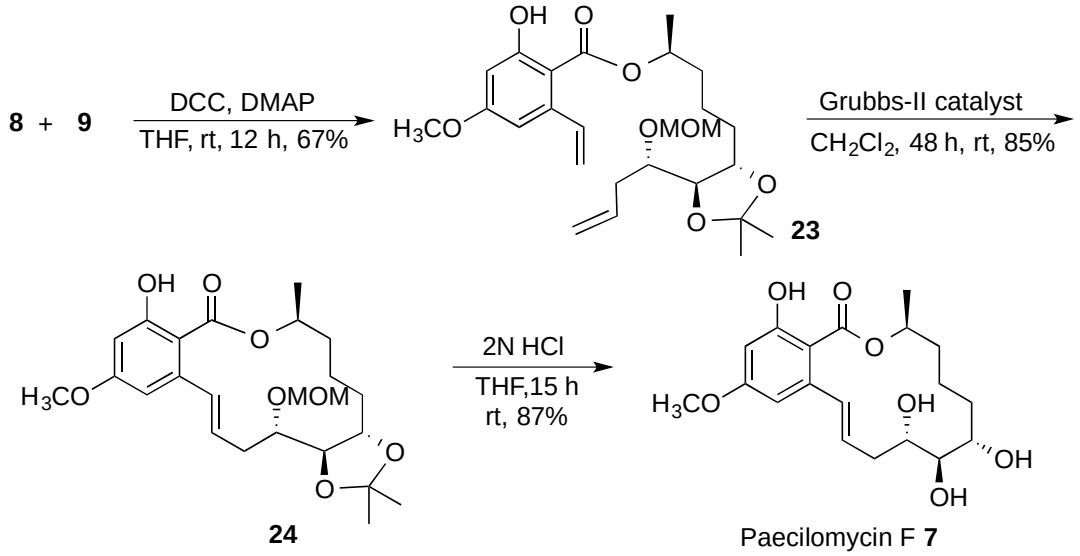
Scheme 2. Synthesis of aliphatic chiral key intermediate **8**.

With the two key intermediates **8** and **9** in hand, the stage was set to proceed further for coupling to get the macrocyclic core skeleton. This was performed under Steglich esterification conditions[36] to furnish the ester **23** in 67% yield. Although, our initial attempts at ring-closing

metathesis of **23** with Grubbs first generation catalyst did not succeed and ended up with the recovery of starting material, the reaction was successful with Grubbs second generation catalyst[37] in CH_2Cl_2 at room temperature to provide the desired core structure **24** exclusively in 85% yield (Scheme 4). The geometry of the product was characterized based on the coupling constant value of 14.9 Hz for the olefinic protons. The compound **24** when exposed to 2N HCl for 15 h underwent complete deprotection of MOM and acetonide functionalities furnishing the target molecule paecilomycin F. The spectroscopic data of the synthesized product was in full agreement with the reported data[16,18] of the natural product (See table 1).



Scheme 3. Synthesis of aromatic acid **9.**



Scheme 4. Conclusion of synthesis of paecilomycin F **7**.

Table 1. Comparative ^{1}H and ^{13}C NMR data of natural and synthetic paecilomycin F

Position	Isolated paecilomycin F		Synthetic paecilomycin F	
	^{1}H NMR ($CDCl_3$, 400 MHz)	^{13}C NMR ($CDCl_3$, 100 MHz)	^{1}H NMR ($CDCl_3$, 500 MHz)	^{13}C NMR ($CDCl_3$, 75 MHz)
1		103.3		103.3
2	12.26 br s (phenolic-OH)	164.0	12.22 s (phenolic-OH)	164.0
3	6.38 s	100.2	6.38 s	100.2
4		165.9		165.9
5	6.38 s	109.0	6.38 s	109.0
6		142.9		142.9
7		171.4		171.4
1’	7.11 dd (15.4, 1.7)	127.3	7.12 d (14.8)	127.3
2’	5.68 ddd (15.4, 11.2, 3.3)	134.1	5.64-5.70 m	134.1
3’	2.47 dt (14.4, 11.2), 2.67 m	38.7	2.44-2.52 m 2.66-2.69 m,	38.7
4’	4.12-4.18 m	76.1	4.13-4.19 m	76.1
5’	3.52 br s	68.9	3.52 s	68.8
6’	4.12-4.18 m	66.9	4.13-4.19 m	66.9
7’	1.90 m, 1.33 m	30.9	1.78-1.96 m, 1.28-1.34 m	30.9
8’	1.44 m, 1.28 m	20.9	1.41-1.64 m, 1.28-1.34 m	20.9
9’	1.81 m, 1.61 m	35.2	1.78-1.96 m, 1.41-1.64 m	35.2
10’	4.94 m	73.7	4.90-5.00 m	73.7
11’	1.39 d (6.1)	21.2	1.38 d (5.9)	21.2
4-OMe	3.79 s	55.4	3.79 s	55.4

Conclusions

We have achieved a total synthesis of paecilomycin F from the readily available (+)-diethyl L-tartrate. Ring closing metathesis and standard DCC, DMAP coupling (Steglich esterification) have been once again pivotal for constructing the macrocycle core. The synthesis involved 12 steps with an overall yield of 14 %. Synthesis of other paecilomycins are currently being investigated in our laboratory.

Experimental Section

General. Column chromatography was performed using silica gel 60-120 mesh. All the solvents were dried and distilled prior to use. IR spectra were recorded on a Perkin-Elmer Infrared spectrophotometer as neat or in $CHCl_3$ as a thin film or as KBr wrafers. ^1H and ^{13}C NMR were recorded on a Bruker Avance 300 MHz instrument using TMS as internal standard. Mass spectra were recorded on Micromass VG 7070H mass spectrometer for EI, VG Autospec mass spectrometer for FABMS and micromass Quatro LC triple quadrupole mass spectrometer for ESI analysis. The optical rotations were recorded on a MCP 200 modular circular polarimeter. L(+)-DET, *P*TSA, LAH, BnBr, Tf_2O, (*S*)-but-3-yn-2-ol, HMPA, and vinylstannane were purchased from Sigma-Aldrich. 2,6-Lutidine, allyl bromide, TFA, TFAA, TPP, DIAD were purchased from Spectrochem, and all these reagents were directly utilized for the reactions.

Diethyl (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (**15**). A solution of (+)-diethyl L-tartrate (20.0 g, 97.08 mmol) and *p*-toluenesulfonic acid (184 mg, 0.97 mmol) in benzene (50 mL) and 2,2-dimethoxypropane (17.8 mL, 145.63 mmol) was heated under reflux for 15 h. The mixture was allowed to cool to ambient temperature. The reaction mixture was washed with aq. saturated sodium bicarbonate solution (50 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (hexane/EtOAc 8:2) to give product **15** as a colorless liquid (21.5 g, 90%). R_f 0.7 (hexane/EtOAc 7:3). $[\alpha]^{20}_D$ +42.9 (*c* 1.0, MeOH); Lit.[38] $[\alpha]^{20}_D$ +41.2 (*c* 1.0, MeOH). IR (neat): 2990, 2942, 1758, 1450, 1375, 1255, 1211, 1111, 1026, 856 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.66-4.62 (m, 2H), 4.20 (q, *J* 7.5 Hz, 4H), 1.42 (s, 6H), 1.27 (t, *J* 7.5 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 113.0, 76.7, 61.4, 26.4, 14.0. MS (ESI): *m*/*z* 269 [M+Na]. HRMS (ESI): calcd for $C_{11}H_{18}NaO_6$ 269.1001, found 269.0992.

(4*S*,5*S*)-(2,2-Dimethyl-1,3-dioxolane-4,5-diyl)dimethanol (**16**). A solution of compound **15** (10.0 g, 40.65 mmol) in THF (50 mL) was slowly added to a suspension of $LiAlH_4$ (3.08 g, 81.30 mmol) in THF (50 mL) at 0 °C over a period of 30 min. The resulting mixture was heated at 40 °C for 5 h to complete the reduction. The reaction was carefully quenched with saturated aqueous Na_2SO_4 (10 mL) at 0 °C and the resulting suspension was stirred for 3 h before it was filtered through a pad of silica gel. The filtrate was dried over Na_2SO_4, the solvent was evaporated and the residue purified by column chromatography (hexane/EtOAc 1:1) to give diol **16** as a colorless liquid (6.25 g, 95%). R_f 0.3 (hexane/EtOAc 6:4); $[\alpha]^{20}_D$ +11.2 (*c* 1.0, MeOH); Lit.[37] $[\alpha]^{20}_D$ +10.8 (*c* 0.5, MeOH). IR (neat): 3401, 2988, 2935, 2881, 1376, 1251, 1218, 1165, 1108, 1053, 844 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.97-3.89 (m, 2 H), 3.76-3.65 (m, 4H), 1.39 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 109.2, 78.3, 62.0, 26.8. MS (ESI): *m*/*z* 185 [M+Na]. HRMS (ESI): calcd for $C_7H_{14}NaO_4$ 185.0789, found 185.0786.

(4*S*,5*S*)-[5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methanol (**17**). A solution of diol **16** (5.0 g, 30.86 mmol) in THF (30 mL) was slowly added over a period of 30 min to a suspension of NaH (1.35 g, 30.86 mmol) in THF (30 mL) at 0 °C and the resulting mixture was

stirred at ambient temperature for 1 h until the evolution of gas had ceased and then cooled to 0 °C. To this mixture was added a solution of benzyl bromide (3.6 mL, 30.86 mmol) in THF (30 mL) dropwise over 30 min and the resulting mixture was stirred for 3 h. The reaction mixture was poured into crushed ice (300 mL) and extracted with EtOAc (120 mL). The organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (hexane/EtOAc 8:2) on silica gel to afford compound **17** as a pale yellow coloured liquid (6.27 g, 80% yield). R_f 0.6 (hexane/EtOAc 6:4); $[\alpha]^{20}_D$ +8.3 (*c* 1.0, $CHCl_3$), Lit.[38] $[\alpha]^{23}_D$ +8.2 (*c* 1.0, $CHCl_3$). IR (neat): 3466, 2988, 2932, 2872, 1453, 1375, 1250, 1216, 1167, 1085, 847, 741, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.34-7.24 (m, 5H), 4.56 (s, 2H), 4.02-3.96 (m, 1H), 3.92-3.86 (m, 1H), 3.74-3.63 (m, 3H), 3.54-3.48 (m, 1 H), 2.18 (br s, 1H), 1.39 (s, 3 H), 1.38 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ 137.4, 128.3 (2C), 127.6, 127.5 (2C), 109.2, 79.4, 76.3, 73.4, 70.2, 62.2, 26.8, 26.7. MS (ESI): *m*/*z* 275 [M+Na]. HRMS (ESI): calcd for $C_{14}H_{20}NaO_4$ 275.1259, found 275.1249.

(*S*)-(But-3-yn-2-yloxy)(*t*-butyl)diphenylsilane (**13**). TBDPSCl (4.4 mL, 17.14 mmol) was slowly added to a solution of (*S*)-but-3-yn-2-ol (1.0 g, 14.28 mmol) and imidazole (3.75 mL, 35.7 mmol) in CH_2Cl_2 (20 mL) at 0 °C and the resulting mixture was stirred for 15 h at room temperature. After 15 h, CH_2Cl_2 (10 mL) and H_2O (20 mL) were added. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4, concentrated under reduced pressure, and purified by silica gel column chromatography (hexane/EtOAc 98:2) to afford **13** (3.87 g, 94%) as a colorless oil. R_f 0.8 (hexane/EtOAc 95:5); $[\alpha]^{20}_D$ -61.20 (*c* 2.0, $CHCl_3$). IR (neat): 3302, 2958, 2934, 2859, 1428, 1107, 1058, 975, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.77-7.73 (m, 2H), 7.70-7.66 (m, 2H), 7.46-7.34 (m, 6H), 4.45 (qt, *J* 6.5, 2.1 Hz, 1H), 2.34 (d, *J* 2.1 Hz, 1H), 1.39 (d, *J* 6.5 Hz, 3H), 1.08 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9 (2C), 135.7 (2C), 133.6, 133.4, 129.7, 129.6, 127.6 (2C), 127.5 (2C), 127.4, 86.0, 71.5, 59.7, 26.8 (3C), 25.1, 19.1. MS (APCI): *m*/*z* 309 $[M+H]^+$. Anal. calcd for $C_{20}H_{24}OSi$: C 77.87, H 7.84; found: C 77.55, H 7.68 %.

[[(*S*)-5-[(4*S*,5*S*)-5-((Benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl]pent-3-yn-2-yl]oxy](*t*-butyl)diphenylsilane (**12**). To a solution of compound **17** (700 mg, 2.78 mmol) in CH_2Cl_2 (20 mL) was added a solution of trifluoromethanesulfonic anhydride (0.5 mL, 3.05 mmol) at -78 °C over 5 min, and the resulting solution was stirred for 30 min. To the reaction mixture was added saturated NH_4Cl (5 mL) with CH_2Cl_2 (40 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give the crude product (0.9 g) as pale yellow oil. The product was passed through short pad of silica gel column chromatography (hexane/EtOAc 9:1) to afford crude **14** (1.01 g, 95%) as a colorless oil. R_f 0.8 (hexane/EtOAc 7:3). A solution of n-BuLi (1.46 mL of a 1.6 M solution in hexane, 2.34 mmol) was added dropwise to a solution of compound **13** (0.818 g, 2.6 mmol) in THF (15 mL) over 5 min at 0 °C. Once addition was complete, the reaction mixture was warmed to rt for 1 h, then recooled to -78 °C. HMPA (1.6 mL, 9.36 mmol) was added *via* syringe, and the resultant

solution was stirred for 10 min. A solution of compound **14** (0.6 g, 1.56 mmol) in THF (10 mL) was added dropwise over 5 min. The mixture was stirred at rt for 6 h, then quenched with saturated aqueous NH_4Cl (10 mL). The layers were separated, and aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc 9:1) to afford **12** (0.760 g, 75%) as a colorless oil. R_f 0.4 (hexane/EtOAc 9:1); $[\alpha]^{20}_D$ -59.0 (*c* 2.0, $CHCl_3$). IR (neat): 3540, 3069, 2932, 2859, 1457, 1429, 1373, 1246, 1215, 1108, 822, 738 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.74-7.66 (m, 4H), 7.43-7.26 (m, 11H), 4.59-4.52 (m, 2H), 4.41-4.40 (m, 1H), 3.97-3.94 (m, 1H), 3.82-3.78 (m, 1H), 3.69-3.51 (m, 2H), 2.49-2.40 (m, 2H), 1.40 (s, 3H), 1.39 (s, 3H), 1.33 (d, *J* 6.3 Hz, 3H), 1.06 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 135.9 (2C), 135.7 (2C), 134.8, 133.8, 133.7, 129.6, 129.5, 128.3 (2C), 127.6 (2C), 127.5 (2C), 127.4 (2C), 109.2, 84.9, 79.6, 79.1, 75.6, 73.5, 70.6, 59.9, 27.1, 27.0, 26.8 (3C), 25.3, 23.0, 19.1. MS (ESI) for $C_{34}H_{42}O_4SiNa$: *m/z* 565 [M+Na].

(4*S*,5*S*)-5-[[2-[(*tert*-Butyldiphenylsilyl)oxy]propyl]-2,2-dimethyl-1,3-dioxolan-4-yl]methanol (**11**). The compound **12** (0.55 g, 1.2 mmol) was dissolved in THF (20 mL) and commercial Pd/C (55 mg, 10% w/w) was added. The resulting suspension was stirred under an atmosphere of H_2 for 15 h until complete conversion of the substrate occurred. The suspension was filtered through celite which was rinsed with EtOAc (150 mL). The combined filtrates were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc 8:2) to afford **11** as a colorless liquid (414 mg, 90%). R_f 0.3 (hexane/EtOAc 8:2); $[\alpha]^{20}_D$ -17.50 (*c* 1.2, $CHCl_3$). IR (neat): 3463, 2932, 2859, 1428, 1374, 1242, 1218, 1107, 1049, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.69-7.66 (m, 4H), 7.44-7.33 (m, 6H), 3.88-3.63 (m, 3H), 3.69-3.63 (m, 1H), 3.58-3.50 (m, 1H), 1.53-1.32 (m, 12H), 1.07 (s, 3H), 1.05 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.8 (4C), 134.8, 134.5, 129.4, 129.3, 127.4 (2C), 127.3 (2C), 108.5, 81.4, 76.8, 69.3, 62.0, 39.3, 33.0, 27.3 (2C), 27.0 (3C), 23.1, 21.5, 19.2. MS (ESI): *m/z* 479 [M+Na]. HRMS (ESI): calcd for $C_{27}H_{40}O_4SiNa$ 479.2593, found 479.2612

***tert*-Butyl-[[(*S*)-1-[(4*S*,5*S*)-5-[(*S*)-1-(methoxymethyloxy)but-3-en-1-yl]-2,2-dimethyl-1,3-dioxolan-4-yl]propan-2-yl]oxy]diphenylsilane** (**18**). To a solution of oxalyl chloride (0.11 mL, 1.14 mmol) in CH_2Cl_2 (5 mL) was added a solution of DMSO (0.19 mL, 2.63 mmol) in CH_2Cl_2 (2 mL) at -78 °C, and the resulting solution was stirred for 10 min at the same temperature. A solution of the alcohol **11** (0.3 g, 0.657 mmol) in CH_2Cl_2 (3 mL) was added dropwise over 5 min. After the solution had stirred for an additional 30 min, Et_3N (0.548 mL, 3.942 mmol) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was poured into H_2O, extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give the crude aldehyde (2.3 g) as pale yellow oil. To a pre-cooled (10 °C) and well-stirred mixture of crude aldehyde (0.3 g, 0.657 mmol) in THF (5 mL), zinc dust (0.172 g, 2.64 mmol) and allyl bromide (0.112 mL, 1.32 mmol) in THF (5 mL) was added a saturated aqueous solution of NH_4Cl (0.1 mL) in

portions over a period of 10 min. The reaction started vigorously soon after the addition of the first portion of the salt solution. The mixture was stirred for 5 h till the complete disappearance of the aldehyde (TLC). The reaction was quenched with MOM-Cl (0.084 mL, 1.058 mmol) at 0 ^{o}C and the resulting mixture was stirred for 6 h at room temperature. The mixture was filtered and washed with EtOAc (50 mL). Solvent removal under reduced pressure and column chromatography of the residue (hexane/EtOAc 98:2) afforded **18** as a colorless liquid (0.205 g, 63%). R_f 0.8 (hexane/EtOAc 9:1); $[\alpha]^{20}_{D}$ -18.63 (*c* 0.8, $CHCl_3$). IR (neat): 3453, 2932, 1635, 1399, 1217, 1107, 1037, 760 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69-7.67 (m, 4H), 7.41-7.33 (m, 6H), 5.94-5.80 (m, 1H), 5.16-5.08 (m, 2H), 4.68 (s, 2H), 3.94-3.82 (m, 2H), 3.74-3.65 (m, 2H), 3.37 (s, 3H), 2.39-2.36 (m. 2H), 1.60-1.43 (m, 6H), 1.36 (s, 6H), 1.07 (s, 3H), 1.04 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.8 (4C), 134.8, 134.5, 134.4, 129.4, 129.3, 127.4 (2C), 127.3 (2C), 117.5, 108.5, 96.2, 81.5, 78.4, 77.1, 69.4, 55.8, 39.3, 35.6, 34.4, 27.4, 27.0, 26.9 (3C), 23.0, 21.7, 19.2. MS (ESI): *m*/*z* 563 [M+Na]. HRMS (ESI): calcd for $C_{32}H_{48}O_5SiNa$ 563.3163, found 563.3148.

(*S*)-1-[(4*S*,5*S*)-5-[(*S*)-1-(Methoxymethyloxy)but-3-en-1-yl]-2,2-dimethyl-1,3-dioxolan-4-yl]-propan-2-ol (**8**). To a solution of **18** (0.2 g, 0.37 mmol) in THF (5 mL) at 0 ^{o}C, was added TBAF (1 M solution in THF, 0.74 mL, 0.74 mmol). After stirring for 5 h at room temperature, the mixture was diluted with EtOAc, washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc 8:2) to give **8** as colorless liquid (0.108 g, 97%). R_f 0.2 (hexane/EtOAc 8:2); $[\alpha]^{20}_{D}$ -1.17 (*c* 0.6, $CHCl_3$). IR (neat): 3447, 2927, 2855, 1737, 1461, 1377, 1216, 1103, 1038, 761 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.91-5.83 (m, 1H), 5.15-5.08 (m, 2H), 4.69 (q, *J* 6.6 Hz, 2H), 4.0-3.94 (m, 1H), 3.84-3.78 (m, 1H), 3.74-3.70 (m, 2H), 3.38 (s, 3H), 2.40-2.38 (m, 2H), 1.70-1.48 (m, 6H), 1.38 (s, 3H), 1.37 (s, 3H), 1.19 (d, *J* 6.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.2, 117.5, 108.5, 96.2, 81.5, 78.5, 77.2, 67.9, 55.8, 39.1, 35.6, 34.2, 27.4, 27.0, 23.4, 22.3. MS (ESI): *m*/*z* 325 [M+Na]. HRMS (ESI): calcd for $C_{16}H_{30}NaO_5$ 325.1990, found 325.1999.

(*S*)-5-{(4*S*,5*S*)-4-[(*S*)-1-(Methoxymethoxy)but-3-en-1-yl]-2,2-dimethyl-1,3-dioxolan-4-yl}pentan-2-yl 2-hydroxy-4-methoxy-6-vinylbenzoate (**23**). To the solution of compound **8** (50 mg, 0.165 mmol), acid **9**[19,21] (32 mg, 0.165 mmol) and DMAP (22 mg, 0.182 mmol) in THF (5 mL) was added DCC (37 mg, 0.182 mmol) at 0 ^{o}C, allowed to stir about 12 h till the complete disappearance of the starting materials (TLC). After 12 h, EtOAc (10 mL) and H_2O (10 mL) were added. The layers were separated and the aqueous phase extracted with EtOAc (2 × 10 mL). The combined organic portions were washed with brine solution (10 mL), dried over Na_2SO_4, concentrated under reduced pressure, the residue was purified by silica gel column chromatography (hexane/EtOAc 95:5) to give **23** as colorless syrup (52 mg, 67%). R_f 0.4 (hexane/EtOAc 8:2); $[\alpha]^{20}_{D}$ +7.5 (*c* 0.8, $CHCl_3$). IR (neat): 3448, 3168, 2921, 2851, 1647, 1609, 1573, 1385, 1257, 1209, 1159, 1036, 916, 770 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.80 (s, 1H), 7.27 (dd, *J* 17.2, 10.8 Hz, 1H), 6.47 (d, *J* 2.6 Hz, 1H), 6.40 (d, *J* 2.6 Hz, 1H), 5.92-5.78 (m, 1H), 5.40 (dd, *J* 17.1, 1.6 Hz, 1H), 5.22-5.14 (m, 2H), 5.10-5.06 (m, 1H), 4.67 (q, *J* 6.8 Hz, 2H),

3.96-3.90 (m, 1H), 3.81 (s, 3H), 3.74-3.66 (m, 2H), 3.39-3.35 (m, 1H), 3.33 (s, 3H), 2.39-2.35 (m, 2H), 1.78-1.48 (m, 6H), 1.37 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 164.9, 163.9, 143.7, 138.6, 134.2 (2C), 117.6, 115.3, 108.6, 108.2, 100.2, 96.1, 81.5, 78.5, 77.2, 72.6, 55.8, 55.3, 35.7, 35.6, 34.1, 27.3, 27.0, 22.0, 19.9. MS (ESI): *m*/*z* 501 [M+Na]. HRMS (ESI): calcd for $C_{26}H_{38}NaO_8$ 501.2464, found 501.2452.

(3a*S*,7*S*,17*S*,17a*S*,*E*)-10-Hydroxy-12-methoxy-17-(methoxymethyloxy)-2,2,7-trimethyl-3a,-4,5,6,7,16,17,17a-octahydro-9*H*-benzo[*c*][1,3]dioxolo[4,5-*i*][1]oxacyclotetradecin-9-one (24).[19]

A solution of compound **23** (50 mg, 0.104 mmol) in CH_2Cl_2 (75 mL) was treated with 5 mol% of Grubbs second generation catalyst and allowed to stir for 48 h. The reaction mixture was filtered through a pad of SiO_2, washed with CH_2Cl_2 and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc 9:1) gave **24** as a white solid (40 mg, 85%). R_f 0.3 (hexane/EtOAc 8:2); mp 119 ^oC; $[\alpha]^{20}_D$ -131.49 (*c* 1.16, $CHCl_3$). IR (KBr): 2982, 2933, 1647, 1608, 1574, 1445, 1376, 1357, 1319, 1257, 1211, 1159, 1103, 1034, 967, 864, 757 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.92 (s, 1H), 7.15 (dd, *J* 15.8, 2.2 Hz, 1H), 6.40 (s, 2H), 5.80-5.70 (m, 1H), 5.17-5.06 (m, 1H), 4.79 (q, *J* 6.7 Hz, 2H), 4.30-4.26 (m, 1H), 4.16-4.08 (m, 1H), 3.87 (dd, *J* 8.3, 1.5 Hz, 1H), 3.82 (s, 3H), 3.42 (s, 3H), 2.78-2.69 (m, 1H), 2.39-2.26 (m, 1H), 1.84-1.53 (m, 6H), 1.42 (d, *J* 6.0 Hz, 3H), 1.38 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 165.2, 163.8, 142.6, 133.9, 128.4, 123.5, 108.6, 100.2, 96.9, 78.9, 74.9, 74.1, 73.2, 55.5, 55.3, 36.5, 35.5, 32.5, 27.2, 26.8, 20.1, 18.9. MS (ESI): *m*/*z* 473 [M+Na]. HRMS (ESI): calcd for $C_{24}H_{34}NaO_8$ 473.2151, found 473.2151.

Paecilomycin F (7). A solution of compound **24** (40 mg, 0.067 mmol) in THF (5 mL) was treated with 2N HCl (5 mL) and allowed to stir for 15 h, then EtOAc (5 mL) and H_2O (5 mL) were added. The layers were separated and the aqueous phase was extracted with EtOAc (2x 5 mL). The combined organic portion was washed with saturated sodium bicarbonate solution (10 mL) followed by brine solution (10 mL), dried over Na_2SO_4, and then concentrated under reduced pressure, the residue was purified by silica gel column chromatography (hexane/EtOAc 4:6) to give paecilomycin F **7** as white solid (21 mg, 87%). R_f 0.4 (EtOAc 100%); mp 166-168 ^oC; $[\alpha]^{20}_D$ -93.83 (*c* 0.12, MeOH). (Lit.[13] $[\alpha]^{20}_D$ -96.4 (*c* 0.28, MeOH), (Lit.[21] $[\alpha]^{20}_D$ -94.0 (*c* 0.28, MeOH) ; IR (KBr): 3448, 2926, 1616, 1595, 1508, 1367, 1264, 1153, 1087, 1012, 964, 778, 691 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.22 (s, 1H), 7.12 (d, *J* 14.8 Hz, 1H), 6.38 (s, 2H), 5.70-5.64 (m, 1H), 5.00-4.90 (m, 1H), 4.19-4.13 (m, 2H), 3.79 (s, 3H), 3.52 (s, 1H), 2.69-2.66 (m, 1H), 2.52-2.44 (m, 1H), 1.96-1.78 (m, 2H), 1.64-1.41 (m, 2H), 1.38 (d, *J* 5.9 Hz, 3H), 1.34-1.28 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 165.9, 164.0, 142.9, 134.1, 127.3, 109.0, 103.3, 100.2, 76.1, 73.7, 68.8, 66.9, 55.4, 38.7, 35.2, 30.9, 21.2, 20.9. MS (ESI): *m*/*z* 389 [M+Na]. HRMS (ESI): calcd for $C_{19}H_{26}NaO_7$ 389.1576, found 389.1591.

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