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 RALs5 (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 estrogenic10 to nematocidal11 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-F16-18 (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 plasmodциdal activity, paecilomycin F was found to display antiplasmodial activity against Plasmodium falciparum line 3D7 with an IC50 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\textsuperscript{18,19} for these two molecules and was however later reconfirmed by total synthesis from Mohapatra \textit{et al.}\textsuperscript{20} and also our group.\textsuperscript{21} In continuation of our work on the total synthesis of lactonic natural products,\textsuperscript{22-27} herein we present a facile and convergent strategy for the total synthesis of paecilomycin F.\textsuperscript{28}

![Chemical structures](image)

**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, \textit{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 \(\text{15}\) followed by the diester reduction with lithium aluminium hydride to deliver 1,4-diol \(\text{16}\). The diol \(\text{16}\) was sequentially protected as the corresponding benzyl ether \(\text{17}\) by treatment with benzyl bromide and NaH and activated as the triflate \(\text{14}\). The alkyn \(\text{13}\) (obtained from the commercially available (S)-but-3-yn-2-ol after protection with TBDPSCl) was metalated with n-BuLi in presence of hexamethylphosphoramide (HMPA) and treated with triflate \(\text{14}\) to furnish the di-substituted alkyn \(\text{12}\).\(^{30}\) One pot benzyl deprotection and alkyn reduction was achieved smoothly with Pd/C under hydrogen atmosphere to provide the primary alcohol \(\text{11}\) in good yield (Scheme 2). The alcohol \(\text{11}\) 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\(_4\)Cl 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 \(\text{18}\). Thus, treatment of the major diastereomer \(\text{18}\) with TBAF resulted in the formation of \(\text{8}\), 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 protocol33 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 conditions34 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 coupling35 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 conditions36 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\textsuperscript{37} in \( \text{CH}_2\text{Cl}_2 \) 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\textsuperscript{16,18} of the natural product (See table 1).


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

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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 wafers. $^1$H 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, PTSA, LAH, BnBr, Tf$_2$O, (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 (4R,5R)-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$_2$SO$_4$. 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$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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.

**Diethyl (4S,5S)-2,2-dimethyl-1,3-dioxolane-4,5-diyldimethanol (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$_2$SO$_4$ (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$_2$SO$_4$, 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, 1736, 1251, 1165, 1108, 1053, 844 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 3.97-3.89 (m, 2H), 3.76-3.65 (m, 4H), 1.39 (s, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 109.2, 78.3, 62.0, 26.8. MS (ESI): $m/z$ 269 [M+Na]. HRMS (ESI): calcd for C$_{11}$H$_{18}$NaO$_6$ 269.1001, found 269.0992.

**Diethyl (4S,5S)-(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$_2$SO$_4$, 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$^{-1}$. $^{1}$H NMR (300 MHz, CDCl$_3$): $\delta$ 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, 1H), 2.18 (br s, 1H), 1.39 (s, 3H), 1.38 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 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). TBDPSCI (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$_2$Cl$_2$ (20 mL) at 0 °C and the resulting mixture was stirred for 15 h at room temperature. After 15 h, CH$_2$Cl$_2$ (10 mL) and H$_2$O (20 mL) were added. The layers were separated and the aqueous phase extracted with CH$_2$Cl$_2$ (3 × 20 mL). The combined organic phase was washed with brine (20 mL), dried over Na$_2$SO$_4$, 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, 1297, 1058, 975, 703 cm$^{-1}$. $^{1}$H NMR (300 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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-[(4S,5S)-5-((Benzzyloxy)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$_2$Cl$_2$ (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$_4$Cl (5 mL) with CH$_2$Cl$_2$ (40 mL). The organic layer was washed with brine (10 mL), dried over Na$_2$SO$_4$, 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$_4$Cl (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$_2$SO$_4$, 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); [α]$_{20}^D$ -59.0 (c 2.0, CHCl$_3$). IR (neat): 3540, 3069, 2932, 2859, 1457, 1429, 1373, 1246, 1215, 1108, 822, 738 cm$^{-1}$. $^1$H 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$_4$SiNa: m/z 565 [M+Na].

(4S,5S)-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$_2$SO$_4$, 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); [α]$_{20}^D$ -17.50 (c 1.2, CHCl$_3$). IR (neat): 3463, 2932, 2859, 1428, 1374, 1242, 1218, 1049, 703 cm$^{-1}$. $^1$H 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, 2H), 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$_4$SiNa 479.2593, found 479.2612

tert-Butyl-[(S)-1-[(4S,5S)-5-[(S)-1-(methoxymethyloxy)but-3-en-1-yl]-2,2-dimethyl-1,3-dioxolan-4-yl]propan-2-yl]oxydiphenylsilane (18). To a solution of oxalyl chloride (0.11 mL, 1.14 mmol) in CH$_2$Cl$_2$ (5 mL) was added a solution of DMSO (0.19 mL, 2.63 mmol) in CH$_2$Cl$_2$ (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$_2$Cl$_2$ (3 mL) was added dropwise over 5 min. After the solution had stirred for an additional 30 min, Et$_3$N (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$_2$O, extracted with CH$_2$Cl$_2$ (2 × 10 mL). The organic layers were washed with brine (10 mL), dried over Na$_2$SO$_4$, 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$_4$Cl (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 °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%). \( Rf \) 0.8 (hexane/EtOAc 9:1); \[ \alpha \] \(_{D}^{20} \) -18.63 (c 0.8, CHCl\(_3\)). IR (neat): 3453, 2932, 1635, 1399, 1217, 1107, 1037, 760 cm\(^{-1}\). \( ^1\text{H NMR} \) (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). \( ^{13}\text{C NMR} \) (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, 53.5, 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\(_5\)SiNa 563.3163, found 563.3148.

\((S)-1\)\-[(4(S),5S)-5\-\{(4(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 °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\(_2\)O (10 mL) and brine (10 mL), dried over Na\(_2\)SO\(_4\), 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%). \( Rf \) 0.2 (hexane/EtOAc 8:2); \[ \alpha \] \(_{D}^{20} \) +7.5 (c 0.8, CHCl\(_3\)). IR (neat): 3448, 3168, 2921, 2851, 1647, 1609, 1573, 1385, 1257, 1209, 1159, 1036, 916, 770 cm\(^{-1}\). \( ^1\text{H NMR} \) (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), 4.60 (q, J 6.8 Hz, 2H), 4.27 (q, J 6.8 Hz, 2H), 4.07 (q, J 6.8 Hz, 2H), 3.97 (q, J 6.8 Hz, 2H), 3.90 (q, J 6.8 Hz, 2H), 3.84-3.65 (m, 2H), 3.38 (s, 3H), 2.60-2.57 (m, 2H), 1.70-1.48 (m, 6H), 1.37 (s, 3H), 1.19 (d, J 6 Hz, 3H). 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),5S)-4\-\{(4(S)-1\-(Methoxymethyloxy)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 °C, allowed to stir about 12 h till the complete disappearance of the starting materials (TLC). After 12 h, EtOAc (10 mL) and H\(_2\)O (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\(_2\)SO\(_4\), 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%). \( Rf \) 0.4 (hexane/EtOAc 8:2); \[ \alpha \] \(_{D}^{20} \) +7.5 (c 0.8, CHCl\(_3\)). IR (neat): 3448, 3168, 2921, 2851, 1647, 1609, 1573, 1385, 1257, 1209, 1159, 1036, 916, 770 cm\(^{-1}\). \( ^1\text{H NMR} \) (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), 4.60 (q, J 6.8 Hz, 2H), 4.27 (q, J 6.8 Hz, 2H), 4.07 (q, J 6.8 Hz, 2H), 3.97 (q, J 6.8 Hz, 2H), 3.90 (q, J 6.8 Hz, 2H), 3.84-3.65 (m, 2H), 3.38 (s, 3H), 2.60-2.57 (m, 2H), 1.70-1.48 (m, 6H), 1.37 (s, 3H), 1.19 (d, J 6 Hz, 3H). MS (ESI): \( m/z \) 325 [M+Na]. HRMS (ESI): calcd for C\(_{16}\)H\(_{30}\)NaO\(_5\) 325.1990, found 325.1999.
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\(_3\)): 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.

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

A solution of compound 23 (50 mg, 0.104 mmol) in CH\(_2\)Cl\(_2\) (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\(_2\)Cl\(_2\) 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°C; [\(\alpha\)]\(_{20}\)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\(_3\)):
\[
\delta 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\(_3\)):
\[
\delta 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\(_2\)O (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\(_2\)SO\(_4\), 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°C; [\(\alpha\)]\(_{20}\)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\(_3\)):
\[
\delta 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\(_3\)):
\[
\delta 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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