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Stereoselective total synthesis of paecilomycin E

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ABSTRACT

First total synthesis of recently isolated resorcylic acid lactone paecilomycin E has been accomplished. The key reactions include olefin metathesis, Mitsunobu reaction, Stille coupling and regioselective allylation.

Ever since the isolation and biological evaluation of radicicol, a β-resorcylic acid lactone, there has been an increased interest in other naturally occurring resorcylic acid lactones (RAL).[1] This has been mainly attributed to the potent biological properties such as antifungal,[2] antimalarial, antiviral, antiparasitic,[3] cytotoxic,[4] oestrogenic,[5] nematicidal,[6] protein tyrosine kinase and ATPase inhibition activities[7] being displayed by them. Recently, Chen et al.[8] have disclosed isolation of new resorcylic acid lactones from paecilomyces fungus SC0924 and named them paecilomycins A–F along with other known RALs (Fig. 1).

Of the new compounds, paecilomycin E was found to display antiplasmodial activity against *Plasmodium falciparum* line 3D7 with IC_{50} value of 20.0 nM and moderate activity against *P. falciparum* line Dd2. The structure and preliminary biological property of paecilomycin E has prompted us to take up its total synthesis along with its analogues for further biological property evaluation. In continuation to our programme on the total synthesis of newly isolated potent natural products,[9] we here-in describe a convergent approach for the total synthesis of paecilomycin E.

Our retrosynthetic analysis revealed two key fragments: an aliphatic side chain with free secondary hydroxyl moiety **9**, and an aromatic acid **10** which can be coupled via Mitsunobu esterification to give the intermediate **8** (Scheme 1). The intermediate **8** upon olefin metathesis reaction followed by MOM and acetonide deprotection provides the target molecule **5**. While the aromatic acid **10** can be synthesized from 2,4,6-trihydroxybenzoic acid **11** in six steps, the chiral aliphatic fragment **9** was obtained from **12** in four steps. The compound **12** could be obtained from **13** which in turn was obtained from alkyne **15** via an epoxide opening reaction. The compound **15** can be accessed from commercially available L-(+)-diethyl tartarate.

The aromatic acid was synthesized as depicted in Scheme 2 starting from 2,4,6-trihydroxybenzoic acid. Accordingly, the 2,4,6-trihydroxybenzoic acid was subjected to Danishefsky's modified protocol[10] for the conversion to the corresponding acetonide protected compound **12** using trifluoroacetic acid and trifluoroacetic

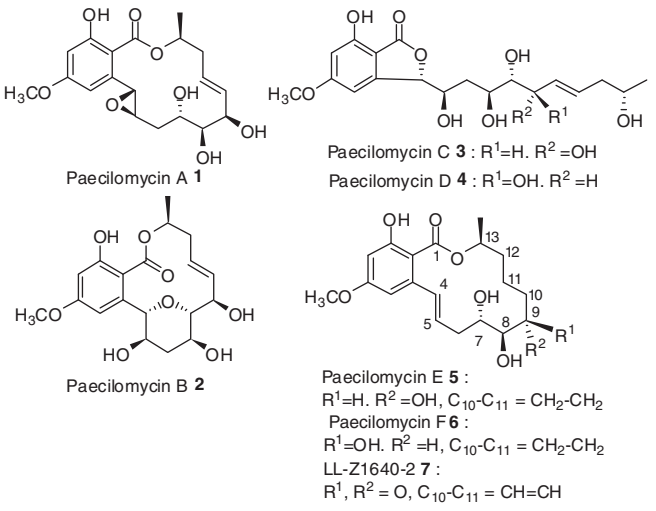

Figure 1. Structures of paecilomycins A–F **1**–**6**.

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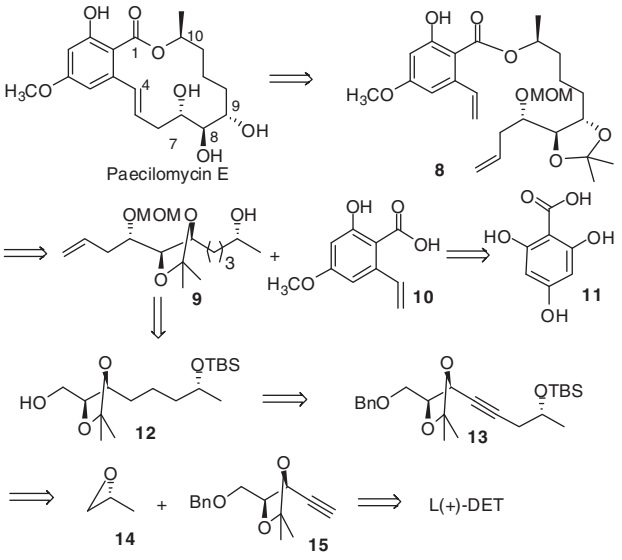
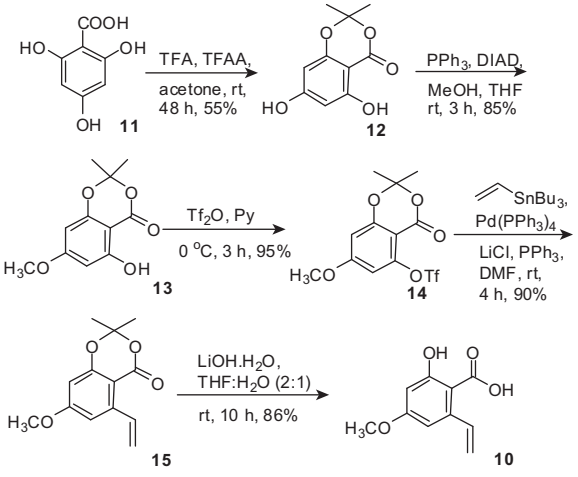


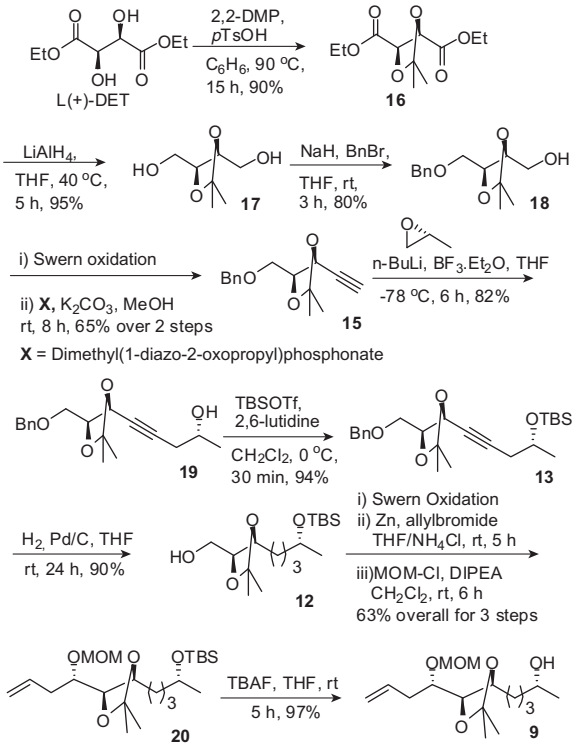
Scheme 1. Retrosynthesis for paecilomycin E.

anhydride. Regioselective methylation on 4-hydroxy group was achieved under Mitsunobu conditions[11] to get **13**. The free 2-hydroxy group (phenol) was converted to the corresponding triflate **14** with trifluoromethanesulfonic anhydride and was then subjected to Stille coupling[12] with vinyl tributyl tin to afford styrene **15**. Deprotection of isoproylidene moiety with $LiOH{\cdot}H_2O$ afforded the aromatic key fragment **10**.

The synthesis of other key fragment **9** commenced with the conversion of L-(+)-DET to its corresponding acetonide **16** with 2,2-dimethoxy propane in the presence of pTSA.[13] The compound **16** was treated with $LiAlH_4$ to get the diol **17**[14] which was mono protected as its corresponding benzyl ether **18** upon treatment with benzyl bromide in the presence of NaH. The free primary hydroxyl moiety was oxidised under Swern condition[15] to get the aldehyde and then subjected to Bestmann Ohira reaction[16] to yield the terminal acetylene **15**. The alkyne **15** was metallated with ^{n}BuLi and then treated with (*R*)-propylene oxide to afford the chiral homo-propargyl alcohol **19**.[17] The alkynol **19** was protected as the corresponding silyl ether **13** with TBDMSOTf in the presence of 2, 6-lutidine and was then subjected to one pot alkyne reduction and benzyl deprotection with Pd/C under hydrogen atmosphere to yield alcohol **12**. Oxidation of alcohol under Swern conditions



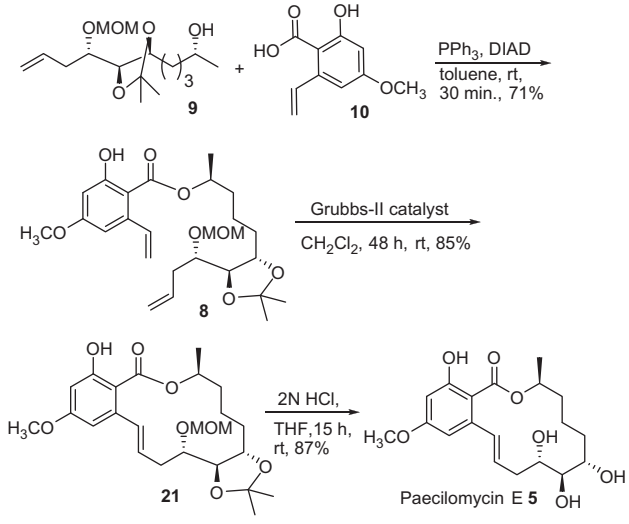
Scheme 2. Synthesis of key fragment **10**.



Scheme 3. Synthesis of aliphatic side chain **9**.

followed by zinc mediated allylation,[18] and in situ protection with MOMCl afforded corresponding MOM ether **20**[19] along with its diastereomer **20a** in 9:1 ratio. Deprotection of silyl ether in **20** with TBAF yielded the aliphatic key fragment **9** in quantitative yield (Scheme 3).

With the two intermediates in hand, the stage was set for completion of total synthesis. Accordingly, the two fragments **9** and **10** were subjected to esterification reaction employing Mitsunobu conditions to get an ester **8**. Exposure of ester **8** with two free terminal olefins to Grubbs II generation catalyst at room temperature provided the *trans* olefin **21** exclusively.[20] The compound **21** upon treatment



Scheme 4. Synthesis of paecilomycin E.

with 2 N HCl underwent one pot MOM and acetonide deprotection to yield the target molecule paecilomycin E (Scheme 4).

When the spectral and analytical data of our synthetic compound were compared with that of isolated product,[8a] it was found that the structure was identical to the reported paecilomycine E, and surprisingly, the analytical data[21] was matching with the data given to paecilomycin F. As the configuration at C8 and C9 stereocentres were derived from L-(+)-diethyl tartarate, the configuration at these centres are unequivocally established by our synthesis.

In conclusion, the first total synthesis of paecilomycin E has been achieved. The strategy can be also utilised for generation of other analogues by either varying the chiral epoxide or esterification reaction. Also by varying the allylation conditions, the other diastereomers can be made accessible. Further studies toward the total synthesis of other paecilomycins and their analogues are being currently investigated.

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Supplementary data

Supplementary data (experimental procedures and analytical data for all the new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.137.

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21. *Spectroscopic data for selected products* **9**. $[\alpha]_D^{20} = -20.25$ (*c* 0.8, $CHCl_3$); IR (neat): 3433, 3077, 2931, 1641, 1458, 1374, 1248, 1214, 1152, 1101, 1038, 917, 879 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.91–5.77 (m, 1H), 5.14–5.06 (m, 2H), 4.65(q, *J* = 6.7 Hz, 2H), 3.94–3.88 (m, 1H), 3.84–3.76 (m, 1H), 3.71–3.62 (m, 2H), 3.36 (s, 3H), 2.39–2.34 (m, 2H), 1.62–1.42 (m, 6H), 1.36 (s, 3H), 1.35 (s, 3H), 1.12 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.2, 117.5, 108.4, 96.1, 81.4, 78.4, 77.1, 67.7, 55.7, 39.0, 35.5, 34.1, 27.3, 27.0, 23.3, 22.4; MS (ESI): *m*/*z* = 325 [M+Na]; HRMS (ESI): calcd for $C_{16}H_{30}O_5Na$, 325.1990, found 325.1999. **8**. $[\alpha]_D^{20} = +8.5$ (*c* 0.6, $CHCl_3$); IR (neat): 3448, 3168, 2921, 2851, 1647, 1609, 1573, 1385, 1257, 1209, 1159, 1036, 916, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 11.73 (s, 1H), 7.25 (dd, *J* = 17.3, 11.3 Hz, 1H), 6.42 (d, *J* = 2.2 Hz, 1H), 6.36 (d, *J* = 2.2 Hz, 1H), 5.90–5.76 (m, 1H), 5.37 (dd, *J* = 17.3, 2.2 Hz,1H), 5.22–5.13 (m, 2H), 5.08–5.05 (m, 1H), 4.63 (q, *J* = 6.7 Hz, 2H), 3.91–3.84 (m, 1H), 3.82 (s, 3H), 3.70–3.58 (m, 2H), 3.34–3.33 (m, 1H), 3.31 (s, 3H), 2,44–2.28 (m, 2H), 1.85–1.43 (m, 6H), 1.37 (d, *J* = 6.7 Hz, 3H), 1.35 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 164.9, 163.8, 143.6, 138.5, 134.1 (2C), 117.5, 115.2, 108.4, 108.1, 100.0, 96.0, 81.4, 78.4, 77.1, 72.5, 55.7, 55.3, 35.7, 35.6, 34.1, 27.3, 26.5, 21.9, 19.9; MS (ESI): *m*/*z* = 501 [M+Na]; HRMS (ESI): calcd for $C_{26}H_{38}O_8Na$ 501.2464, found 501.2452. **21**. mp 119 °C; $[\alpha]_D^{20} = -131.49$ (*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}; ^1H 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 $C_{24}H_{34}O_8Na$ 473.2151, found 473.2151. Paecilomycine E **5**. mp 168 °C; $[\alpha]_D^{20} = -93.83$ (*c* 0.12, MeOH); IR (KBr): 3448, 2926, 1616, 1595, 1508, 1367, 1264, 1153, 1087, 1012, 964, 778, 691 cm^{-1}; ^1H 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 $C_{19}H_{26}O_7Na$ 389.1576, found 389.1591.