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Chemoenzymatic total synthesis of paecilocin A and 3-butyl-7-hydroxyphthalide

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ABSTRACT

A highly enantioselective total synthesis of paecilocin A and 3-butyl-7-hydroxyphthalide is described. The key steps involved in this synthesis are enzymatic kinetic resolution and Alder–Rickert reaction.

The new polyketide, paecilocin A (**1**) was isolated along with the other three new polyketides **3**,**4**,**5** (Fig. 1) from the fungus *Paecilomyces variotii*, which was derived from the jellyfish *Nemopilema nomurai*.[1] Compounds **1**, **3** and **4** are found to exhibit a promising inhibitory activity against pathogenic bacteria including methicillin-resistant *Staphylococcus aureus* 3089 (MRSA) and multi-drug-resistant (MDR) *Vibrio parahaemolyticus* 7001. The structure of **1** is almost identical to 3-butyl-7-hydroxyphthalide **2** (Fig. 1), which was isolated previously from a culture broth of *Penicillium vulpinum*.[2] The relative configuration of 3-butyl-7-hydroxyphthalide **2** was determined in 2003 by Ohzeki and Mori.[3] To the best of our knowledge, there are no reports on the synthesis of paecilocin A (**1**). Furthermore, the lactones are known to show diverse biological activities such as hormones, pheromones and antibiotics, therefore we were interested to take up the synthesis of these natural products **1** and **2** in an elegant way using lipase mediated kinetic resolution of the propargyl alcohol (to create the stereocenter of the target molecule) and Alder–Rickert reaction (to construct the functionalized aromatic precursor) as the key steps.

The retrosynthetic analysis of target molecules **1** and **2** is depicted in Scheme 1. The synthesis of target molecules was proposed to be accomplished from the aromatic moieties **6a** and **6b** which in turn could be prepared via the Alder–Rickert reaction between 1,4-cyclohexadiene **8** and alkyne esters **7a** and **7b** respectively.

The key alkyne esters **7a** and **7b** were proposed to be obtained from readily accessible aldehydes **9a** and **9b** via the formation of chiral propargyl alcohols using a known literature procedure.[4a]

The synthesis of target molecules **1** and **2** began from the commercially available aldehydes **9a** and **9b** respectively. Accordingly, the propargyl alcohols **10a** and **10b** were easily prepared in 87% & 83% yield by the addition of monolithiumacetylide[4b] to aldehydes **9a** and **9b** respectively.

The enzymatic kinetic resolution of racemic propargylic alcohols **10a** and **10b** using Novozym-435[5,6] in the presence of vinyl

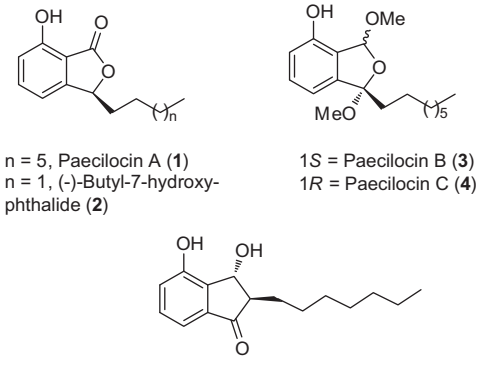

Figure 1. Naturally occurring paecilocins (**A**–**D**) and (−)-butyl-7-hydroxyphthalide (**2**).

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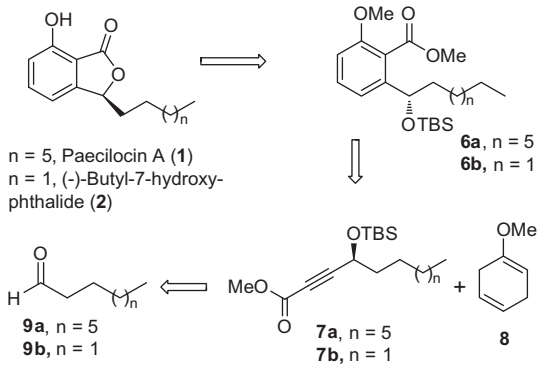
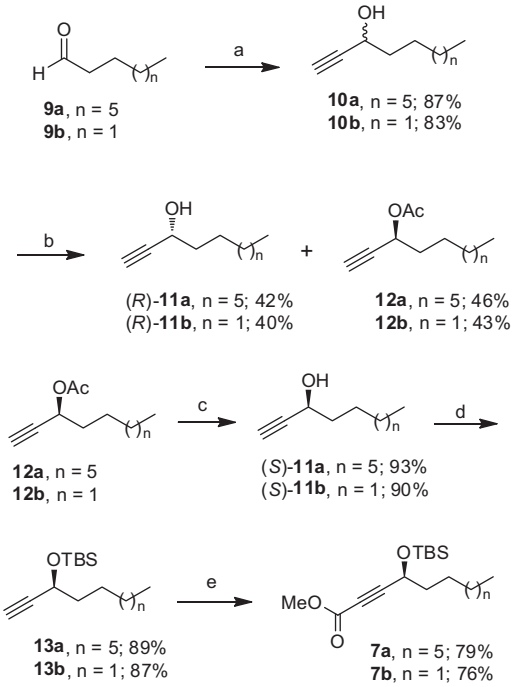


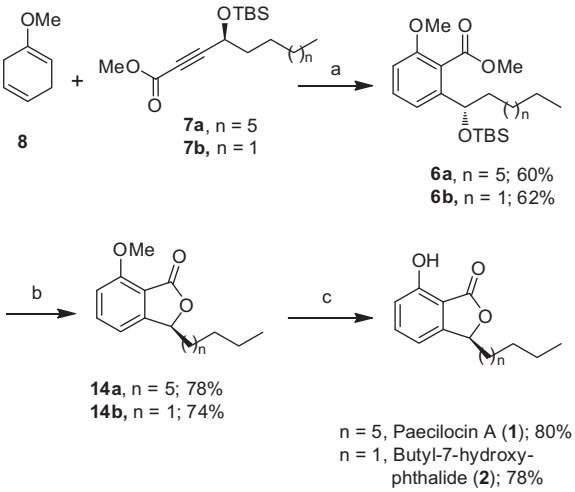
Scheme 1. Retrosynthetic analysis of paecilocin A (**1**) and (−)-butyl-7-hydroxyphthalide (**2**).

acetate in *tert*-butyl methyl ether afforded the (*S*)-acetates **12a** and **12b** (97% & 95 ee) in 46% and 43% yields, respectively. Deacetylation of **12a** and **12b** was achieved by treatment with NaOMe to furnish **11a** and **11b** in 93% and 90% yields, respectively. Protection of secondary alcohols **11a** and **11b** with TBSCl in the presence of imidazole and a cat. DMAP in CH_2Cl_2 gave the TBS ethers **13a** and **13b** in 89% and 87% yields respectively. Treatment of alkynes **13a** and **13b** with *n*-BuLi followed by addition of methyl chloroformate gave the acetylenic esters **7a** and **7b** in 79% and 76% yields respectively (Scheme 2).[7]

With acetylenic esters **7a** and **7b** and 1-methoxycyclohexa-1,4-diene[8] **8** in hand, we attempted the critical Alder–Rickert reaction to construct the functionalized aromatic moiety of the target molecules. Accordingly, the Alder–Rickert reaction was performed in a sealed tube at 180 °C with a catalytic amount of *N*,*N*-dimethylaniline to produce the aromatic cores **6a** and **6b** in 60% & 62% yields respectively.[9] Deprotection of TBS groups from compounds **6a** and **6b** with TBAF in anhydrous THF gave the phthalates **14a** and **14b** in 78% and 74% yields respectively.[10] Demethylation of methoxyl groups from **14a** and **14b** using boron trichloride in dichloromethane at −78 °C afforded the target molecule **1** in 80% yield. The optical rotation and spectral data of the synthetic compound **1**[11] are in agreement with the data reported for the natural product (Scheme 3).[1]



Scheme 2. Reagents and conditions: (a) Lithium acetylide–ethylenediamine complex, DMSO, rt; (b) Novozym-435, vinyl acetate, MTBE, rt; (c) NaOMe, MeOH, 0 °C, 1 h; (d) TBSCl, DMAP, imidazole, CH_2Cl_2, 0 °C to rt, 3 h; (e) $ClCO_2Me$, *n*-BuLi, THF, −78 °C, 1 h.



Scheme 3. Reagents and conditions: (a) *N*,*N*-dimethylaniline (cat.), sealed tube, 180 °C, 48 h; (b) TBAF, THF, 0 °C to rt, 3 h; (c) BCl_3, CH_2Cl_2, −78 °C to rt.

Similarly, (−)-butyl-7-hydroxyphthalide (**2**) was synthesized from the commercially available pentanal **9b** following the above sequence of reactions. The analytical data of the (−)-butyl-7-hydroxyphthalide **2**[11] were indistinguishable with the data reported in the literature.[2,3]

In summary, we have successfully demonstrated the enantioselective total synthesis of paecilocin A and (−)-butyl-7-hydroxyphthalide using lipase mediated kinetic resolution of propargyl alcohol and Alder–Rickert reaction.

Acknowledgments

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11. *Spectral data for selected compounds:*

Paecilocin A (1): $[\alpha]_D^{25}$ −9.4 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.01–7.67 (br s, 1H), 7.54 (t, 1H, *J* = 7.9 Hz), 6.92 (d, 1H, *J* = 7.9 Hz), 6.90 (d, 1H, *J* = 7.9 Hz), 5.49 (dd, 1H, *J* = 7.7, 4.1 Hz), 2.09–1.94 (m, 1H), 1.86–1.70 (m, 1H), 1.58–1.41 (m, 1H), 1.40–1.16 (m, 11H), 0.88 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.1, 156.4, 150.3, 136.7, 115.2, 113.0, 111.1, 82.9, 34.5, 31.7, 29.6, 29.2, 29.1, 24.7, 22.5, 14.0; IR (KBr): ν_{max} 3430, 2923, 2853, 1742, 1462, 1191, 1079, 967 cm^{-1}; ESI-MS: *m*/*z* 263 [M+H].

(−)-Butyl-7-hydroxyphthalide (2): $[\alpha]_D^{25}$ −49.7 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 8.01–7.67 (br s, 1H), 7.54 (t, 1H, *J* = 7.9 Hz), 6.92 (d, 1H, *J* = 7.9 Hz), 6.90 (d, 1H, *J* = 7.9 Hz), 5.49 (dd, 1H, *J* = 7.7, 4.1 Hz), 2.09–1.94 (m, 1H), 1.86–1.70 (m, 1H), 1.58–1.41 (m, 1H), 1.40–1.16 (m, 11H), 0.88 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.1, 156.4, 150.3, 136.7, 115.2, 113.0, 111.1, 82.9, 34.2, 26.7, 22.3, 13.8; IR (KBr): ν_{max} 3427, 2924, 2854, 1742, 1627, 1462, 1375, 1193, 1078, 769 cm^{-1}; ESI-MS: *m*/*z* 215 [M+H].

(*S*)-Methyl 2-(1-((*tert*-butyldimethylsilyl) oxy)nonyl)-6-methoxybenzoate (6a):

$[\alpha]_D^{20}$ +12.3 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32 (dd, 1H, *J* = 8.1, 7.9 Hz), 7.13 (d, 1H, *J* = 7.9 Hz), 6.78 (d, 1H, *J* = 8.1 Hz), 4.60 (dd, 1H, *J* = 6.2, 6.0 Hz), 3.90 (s, 3H), 3.82 (s, 3H), 1.65–1.54 (m, 2H), 1.32–1.17 (m, 12H), 0.93–0.81 (m, 12H), 0.01 (s, 3H), −0.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.4, 155.5, 144.9, 132.4, 130.2, 118.6, 109.0, 71.9, 55.8, 52.0, 40.5, 31.8, 29.4, 29.3, 29.2, 25.8, 22.6, 18.1, 14.0, −4.8, −5.2; IR (KBr): ν_{max} 2929, 2856, 1735, 1586, 1468, 1435, 1265, 1108, 1069, 835, 776 cm^{-1}; ESI-MS: *m*/*z* 445 [M+Na].

(*S*)-Methyl 2-(1-((*tert*-butyldimethylsilyl) oxy)pentyl)-6-methoxybenzoate (6b):

$[\alpha]_D^{31}$ +10.0 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32 (t, 1H, *J* = 7.9 Hz), 7.13 (d, 1H, *J* = 7.6 Hz), 6.78 (d, 1H, *J* = 8.2 Hz), 4.60 (t, 1H, *J* = 6.1 Hz), 3.89 (s, 3H), 3.82 (s, 3H), 1.65–1.54 (m, 2H), 1.32–1.17 (m, 4H), 0.93–0.81 (m, 12H), 0.01 (s, 3H), −0.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.4, 155.5, 144.9, 132.4, 130.2, 118.6, 109.0, 71.9, 55.8, 52.0, 40.5, 31.8, 29.4, 29.3, 29.2, 25.8, 22.6, 18.1, 14.0, −4.8, −5.2; IR (KBr): ν_{max} 2954, 2931, 2857, 1734, 1586, 1468, 1435, 1376, 1265, 1110, 1066, 938, 837, 776 cm^{-1}; ESI-MS: *m*/*z* 367 [M+H].

(*S*)-Undec-1-yn-3-ol (11a): $[\alpha]_D^{31}$ +12.6 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 4.40–4.34 (m, 1H), 2.46 (d, 1H, *J* = 2.1 Hz), 1.93–1.86 (br s, 1H), 1.76–1.67 (m, 2H), 1.52–1.41 (m, 2H), 1.39–1.21(m, 10H), 0.88 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 85.0, 72.7, 62.2, 37.6, 31.8, 29.4, 24.9, 22.6, 14.0; IR (KBr): ν_{max} 3311, 2925, 2855, 1462, 1028, 653, 627 cm^{-1}; EI-MS: *m*/*z* 191 [M+Na].

(*S*)-Hept-1-yn-3-ol (11b): $[\alpha]_D^{31}$ −20.0 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 4.07 (dd, 1H, *J* = 11.2, 4.7 Hz), 2.32 (d, 1H, *J* = 1.6 Hz), 1.67–1.63 (br s, 1H), 1.53–1.19 (m, 6H), 0.92 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 73.7, 72.0, 64.9, 42.7, 27.0, 22.6, 14.0; IR (KBr): ν_{max} 3448, 2957, 2928, 2865, 1713, 1650, 1461, 1377, 1122, 767 cm^{-1}; EI-MS: *m*/*z* 113 [M+H].