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Stereoselective total synthesis of (−)-pyrenophorol

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ABSTRACT

An efficient stereoselective total synthesis of (−)-pyrenophorol 1 is described. The key steps involved in this synthesis are hydrolytic kinetic resolution (HKR), MacMillan α-hydroxylation, Horner–Wadsworth–Emmons (HWE) reaction, and Mitsunobu cyclization.

The family of macrodiolide antibiotics consists of two classes of natural compounds displaying interesting biological properties.[1] The first class consists of 16-membered macrocycles with C_2 symmetry, such as pyrenophorol **1**, pyrenophorin **2**, tetrahydropyrenophorol **4**[2], and vermiculin **5**[3]. The macrolide dilactone pyrenophorol **1** was originally isolated from *Byssochlamys niveah*[4a] and *Stemphylium radicinum*.[4b] Subsequently, the diolide **1** was also isolated from the imperfect fungus *Alternaria alternata* and was named as helmidiol[5] which exhibits pronounced anthelmintic properties.[5,6] Pyrenophorol **1** was moderately active against the fungus *Microbotryum violaceum*.[2] (−)-Pyrenophorin **2**[7] is an anti-fungal antibiotic produced by the plant pathogenic fungi *Pyrenophora avenae* and *Stemphylium radicinum*, which is closely related structurally to (−)-pyrenophorol **1**. Colletallol **3** is a 14-membered macrodiolide which has been isolated from culture filtrates of the plant pathogen *Colletotrichum capcisi*.[8] The natural isomer of pyrenophorol was synthesized by Kibayashi and Machinaga[9] and by Zwanenburg and co-workers[10] by means of two successive esterifications. The (5*R*,8*S*,13*R*,16*S*)-isomer of pyrenophorol was also synthesized by Le Floc'h and Amigoni.[11]

The promising biological activity and the unique structure of this family of macrolactones make them attractive synthetic targets (Fig. 1).

In continuation of our interest on the total synthesis of biologically active natural products, we herein report the total synthesis of (−)-pyrenophorol **1** utilizing the Jacobsen's hydrolytic kinetic resolution and the MacMillan α-hydroxylation for the creation of two stereogenic centers. Finally, an intermolecular Mitsunobu cyclization strategy was used for the construction of 16-membered macrolide.

In our retrosynthetic analysis (Scheme 1), we envisaged that the construction of macrolide **1** could be achieved from the key intermediate γ-hydroxy-α,β-unsaturated ester **15**. This enoate intermediate could be synthesized from (*S*)-1,5-hexanediol **13** by using MacMillan α-hydroxylation and Horner–Wadsworth–Emmons (HWE) reaction. Compound **13** could in turn be obtained from 1,6-hexanediol by means of a Jacobsen's hydrolytic kinetic resolution process (Scheme 1).

Accordingly (Scheme 2), the selective protection of 1,6-hexanediol with benzyl bromide in the presence of NaH and TBAI gave monobenzyl ether **6**[12], which in turn was transformed into the iodo compound **7**. This was then treated with *t*-BuOK in THF to give the 5-hexen-1-ol **8** in good yield. The resulting olefin **8** was treated with *m*-chloroperoxybenzoic acid (MCPBA) to give the racemic oxirane **9**. Compound **9** was hydrolyzed employing (*R*,*R*)-Salen-Co(OAc) Jacobsen's catalyst[13] to give the chiral epoxide **10**. The epoxide **10** was reduced with lithium aluminum hydride to generate the secondary alcohol **11** (97% ee, by HPLC analysis) in good yield, which was protected as its *tert*-butyldimethylsilyl ether **12**. Removal of benzyl group with carbon-supported palladium afforded primary alcohol **13** in 92% yield. Oxidation of compound **13** under Swern oxidation conditions[14] gave the corresponding aldehyde **14**. Treatment of aldehyde **14** with D-proline and nitrosobenzene gave an intermediate α-oxyamino aldehyde with high levels of enantioselectivity[15,16] by means of α-oxidation. Olefination using Horner–Wadsworth–Emmons conditions followed by cleavage of the aminoxy bond gave the γ-hydroxy-α,β-unsaturated ester **15**[17]

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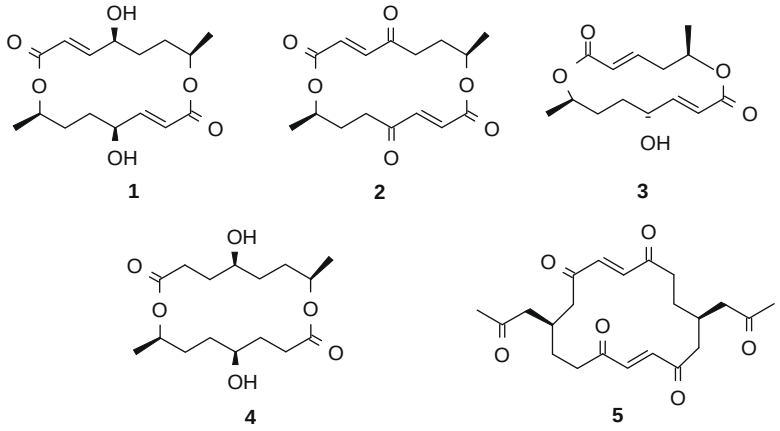
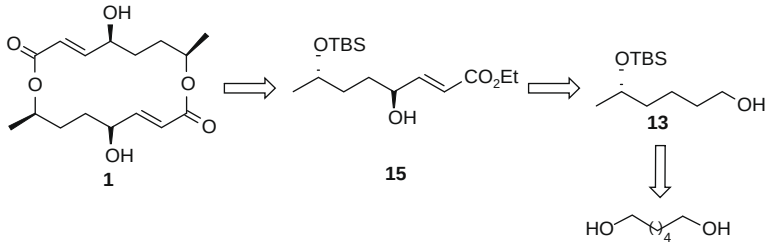
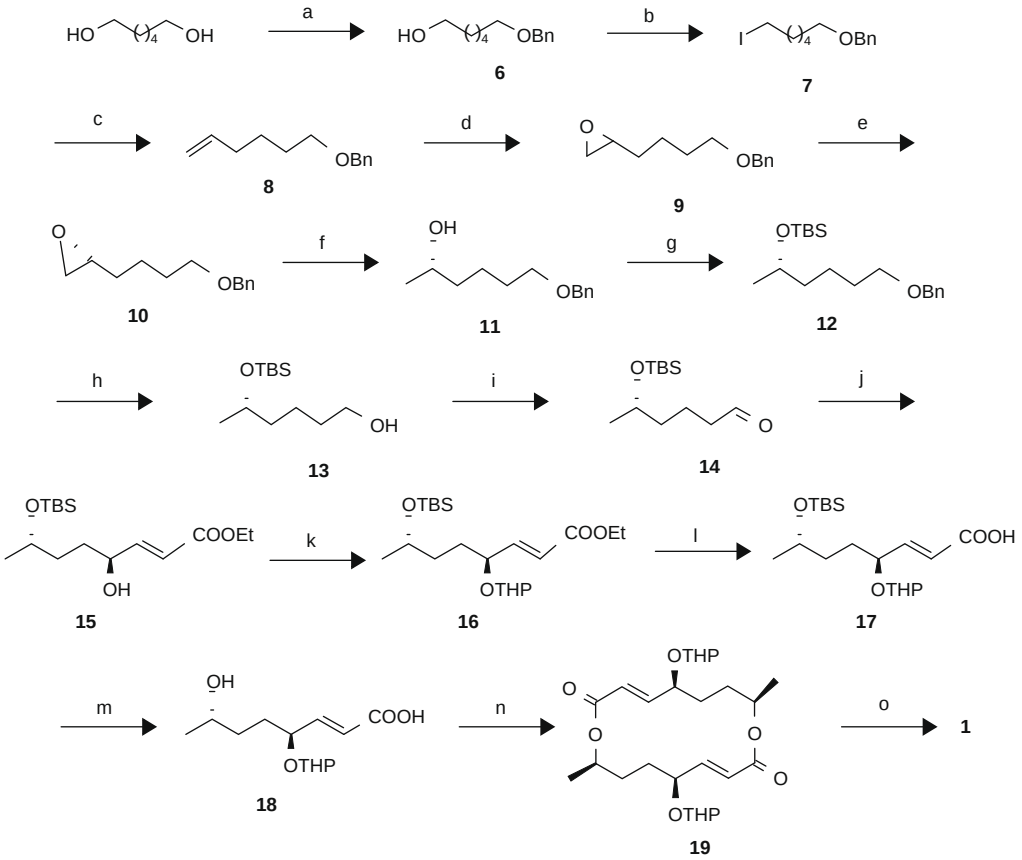


Figure 1. Pyrenophorol **1**, pyrenophorin **2**, colletallol **3**, tetrahydropyrenophorol **4**, and vermiculin 5



Scheme 1. Retrosynthetic analysis of (−)-pyrenophorol **1**.



Scheme 2. Reagents and conditions: (a) NaH, TBAI, BnBr, DMF, 0 °C–rt, 6 h, 82%; (b) I_2, imidazole, TPP, THF, 0 °C–rt, 1 h, 98%; (c) *t*-BuOK, THF, 0 °C–rt, 3 h, 90%; (d) MCPBA, CH_2Cl_2, 2 h, rt, 84%; (e) (*R*,*R*)-Salen-Co-(OAc)(0.45 mol %), H_2O, rt, 12 h, 45%; (f) LAH, THF, 0 °C–rt, 30 min, 95%; (g) TBDMSCl, imidazole, CH_2Cl_2, 0 °C–rt, 1 h, 96%; (h) 10% Pd/C, H_2, EtOAc, rt, 10 h, 92%; (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h, 80%; (j) nitrosobenzene (1.0 equiv), D-proline (0.4 equiv), DMSO, 20 °C, 25 min, then triethylphosphonoacetate, DBU, LiCl, 0 °C, 15 min, then MeOH, NH_4Cl, $Cu(OAc)_2$, 24 h, 55% (one pot); (k) 2,3-dihydropyran, CSA, CH_2C1_2, rt, 1 h, 86%; (l) 20% aq NaOH, MeOH, rt, 30 min, 85%; (m) Bu_4NF, THF, 80 °C, 2 h, 90%; (n) Ph_3P, DEAD, toluene–THF (10:1), −25 °C, 10 h; 58%; (o) TsOH–H_2O, MeOH, rt, 30 min, 98%.

(95% ee, by HPLC analysis). After protecting the secondary alcohol of enoate as the tetrahydropyranyl ether, the ester was hydrolyzed under basic aqueous conditions and then desilylated to give the hydroxy carboxylic acid **18**. Finally, compound **18** was subjected to the Mitsunobu cyclization by Gerlach's procedure[18] for the macrolactonization to take place with complete inversion of chirality at C-4 to furnish **19**[19] in 58% yield. Removal of THP group (TsOH, MeOH) gave the target macrolide **1** in 98% yield as a white solid, mp 136–137 °C; $[\alpha]_D^{25}$ −3.2 (*c* 0.25, acetone) {lit.[4a] mp 135 °C; $[\alpha]_D^{20}$ −3.0 (*c* 1.0, acetone)}, the analytical and spectral data of the compound **1** were in good agreement with the literature. [20]

In summary, we have developed an efficient route for the synthesis of pyrenophorol starting from readily available 1,6-hexanediol. The synthetic strategy is based on the facile tandem MacMillan α-hydroxylation and HWE reaction for the construction of key intermediate, that is, γ-hydroxy-α,β-unsaturated ester in a single step, which allows the preparation of target molecule in a short and efficient route.

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20. *Spectral data for compound* **15**: Pale yellow oily liquid, $[\alpha]_D^{25}$ +11.6 (c 1.5, $CHCl_3$), IR (KBr): ν_{max} 3442, 2927, 2855, 1721, 1656, 1465, 1255, 1043, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.89 (dd, *J* = 15.8 Hz, 1H), 6.02 (dd, *J* = 15.8 Hz, 1H), 4.28–4.20 (m, 1H), 4.18 (q, *J* = 14.3, 6.8 Hz, 2H), 3.94–3.87 (m, 1H), 1.74–1.52 (m, 4H), 1.30 (t, *J* = 6.8 Hz, 3H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.3, 150.2, 120.0, 71.0, 68.4, 60.1, 35.3, 32.2, 25.9, 23.1, 18.1, 14.3, −4.3, −4.6; ESI-MS: *m/z*: 317 $(M+H)^+$; HRMS (ESI) calcd for $C_{16}H_{32}O_4NaSi$: 339.1967, found: 339.1974. *Compound* **1**: white solid mp 136–138 °C; $[\alpha]_D^{25}$ −3.2. (c 0.25, acetone) IR (KBr): ν_{max} 3382, 2924, 2854, 1713, 1647, 1274, 1173, 1119 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.83 (dd, *J* = 15.6 Hz, 2H), 5.89 (dd, *J* = 15.6 Hz, 2H), 5.10–5.01 (m, 2H), 4.24–4.16 (m, 2H), 2.69–2.48 (m, 2H), 2.01–1.53 (m, 8H), 1.20 (dd, *J* = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.0, 149.3, 122.0, 70.3, 69.7, 30.4, 28.8, 18.2; ESI-MS: *m/z*: 330 $(M+NH_4)$, 335 $(M+Na)^+$.