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Stereoselective synthesis of C12–C21 common fragment of thermolides 1–5

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ABSTRACT

A highly stereoselective synthesis of **C12–C21** common fragment of thermolides **1–5** has been described. The salient features of the synthesis are the utilization of desymmetrization protocol, Barton-McCombie reaction, Brown's asymmetric allylation and Wacker oxidation.

Introduction

Thermolides are PKS-NRPS hybrid metabolites, which were isolated in 2012 by Niu et al., from thermophilic fungus *Thermomyces thermophilus* YM 3–4 (1–6) collected from tengchong hotspring of Yunnan, China [1,2] (Fig. 1). Thermolides **1** and **2** exhibits potent inhibitory activity against a wide range of nematodes including economically destructive rootknot nematode (*Meloidogyne incognita*) and pine-wood nematode (*Bursaphelenchus xylophilus*) [3]. Compounds **3** and **4** also show a moderate nematicidal activity against above two nematodes.

From structural side, all natural products containing a common 13-membered lactam-bearing macrolactone. Thermolides **1–5** have a common C_9 polypropionate side chain with three methyl groups and three hydroxyls, in which two hydroxyls at C16 and C18 are *syn* to each other and third hydroxyl at C20 is *anti*-relationship with C16 and C18. These unusual structural features, twelve stereogenic centers, sensitive functionalities and nematicidal activities make thermolides **1–5** attractive for synthesis [1,2].

For the last two decades, our group has explored the potentiality of desymmetrization strategy for the synthesis of biologically active natural and designed molecules [4]. This strategy offers the generation of contiguous chiral centers from a single bicyclic precursor by using desymmetrization strategy.

Herein, we describe stereoselective synthesis of **C12–C21** common fragment of thermolides **1–5** by using desymmetrization protocol, Brown's asymmetric allylation and Wacker oxidation as key reactions.

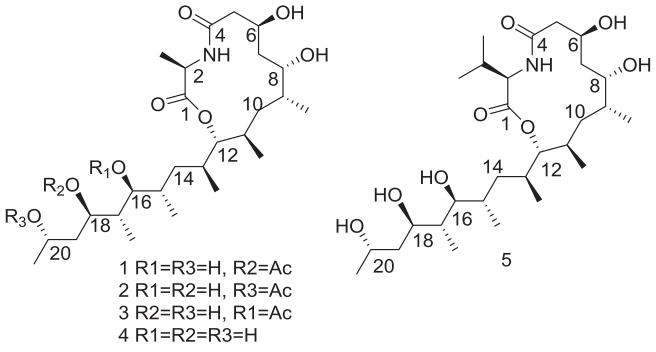

Fig. 1. Structures of thermolides **1–5**.

The retrosynthetic analysis of **C12–C21** fragment of thermolides **1–5** is outlined in Scheme 1. We envisioned that fragment **2** could be synthesized from Brown's allylated compound **3** by using Wacker oxidation and anti-reduction. The allyl compound **3** could be obtained from triol **4**, which in turn could be easily synthesized from known bicyclic olefine **5** [5].

Results and discussion

Our synthesis was commenced from reductive cleavage of bicyclic lactone **6**, which was synthesized by desymmetrization

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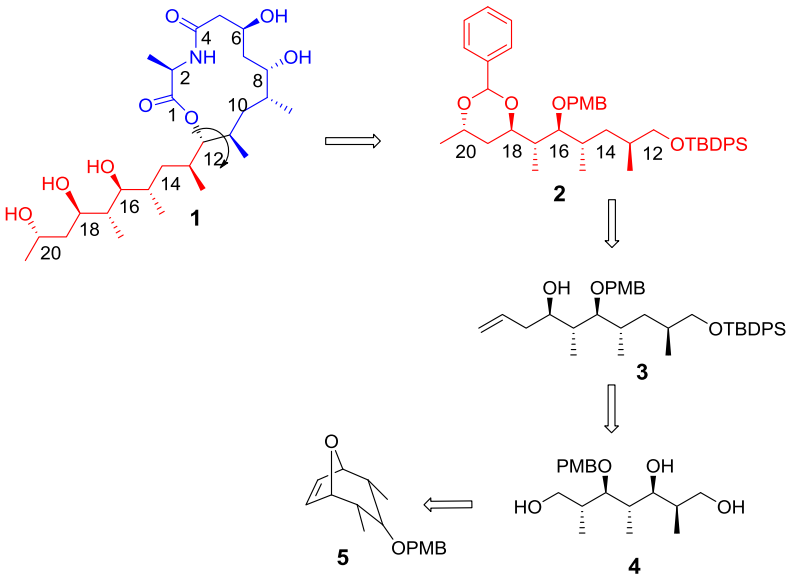
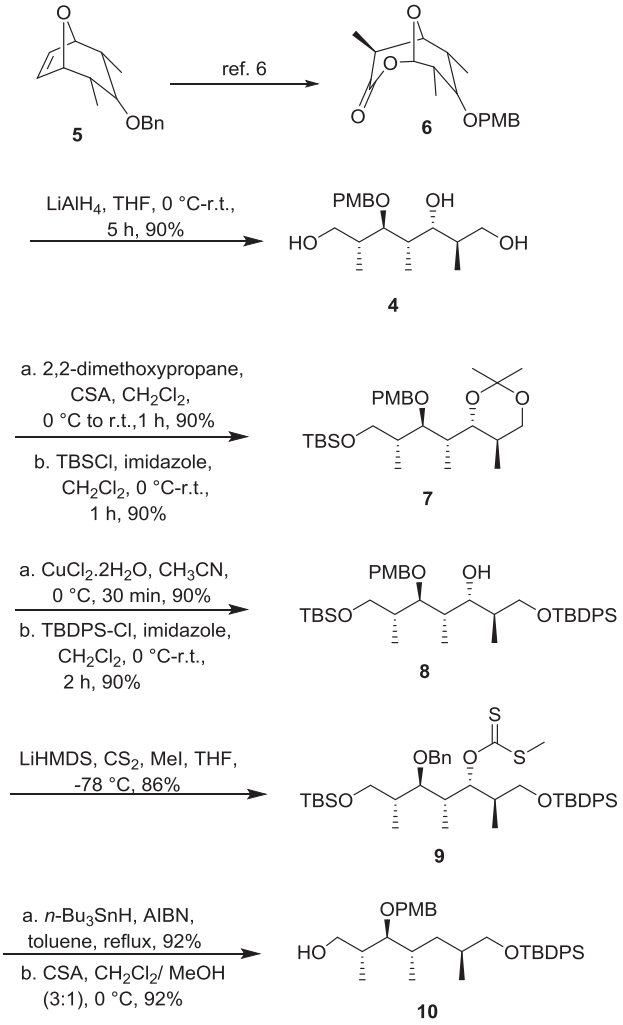


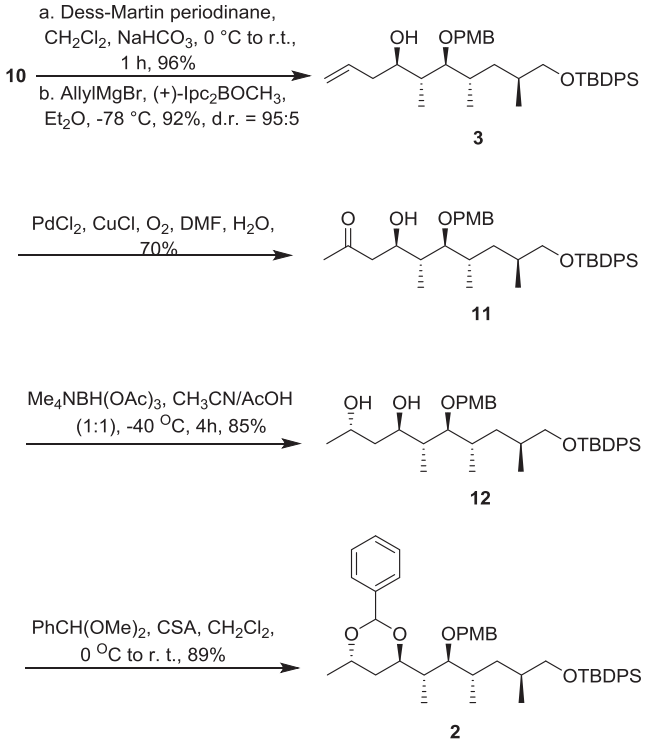
Scheme 1. Retrosynthetic analysis of thermolides.

of the bicyclic olefine **5**. Compound **6** was treated with $LiAlH_4$ in dry THF to afford the triol **4** in 90% yield [6] (Scheme 2).



Scheme 2. Synthesis of alcohol compound **10**.

The 1,3-diol group of compound **4** was protected as an acetonide [6] using 2,2-dimethoxypropane (2,2-DMP) and catalytic amount of CSA in CH_2Cl_2 and the free primary hydroxyl group of acetonide was protected as its TBS ether to furnish **7**. The TBS ether **7** was treated with $CuCl_2{\cdot}2H_2O$ in acetonitrile followed by the selective silylation of the primary hydroxy group as its TBDPS ether **8** was achieved in 90% yield under the classical conditions (TBDPSCl, imidazole in CH_2Cl_2). The free secondary hydroxyl group of **8** was converted into the corresponding xanthate ester **9** using LiHMDS, CS_2 and methyl iodide at −78 °C with 86% yield [6a,7]. Later the compound **9** was deoxygenated under Barton-McCombie conditions using tri-*n*-butyltin hydride and catalytic amount of



Scheme 3. Synthesis of C12–C21 fragment **2**.

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AIBN as radical initiator, followed by selective deprotection of TBS group by using CSA in CH_2Cl_2/MeOH (3:1) to afford compound **10** in 92% yield (Scheme 2).

The compound **10** was oxidized to aldehyde using Dess-Martin periodinane in CH_2Cl_2, which on subsequent asymmetric allylboration using Brown's conditions [8] to afford the homoallylic alcohol **3** with desired (*R*)-configuration in a diastereomeric ratio of 95:5. This asymmetric reaction fixed the chiral center at C-18 of the target molecule (Scheme 3). The allyl compound **3** was subjected to Wacker oxidation [8a,9] by using oxygen, $PdCl_2$ and CuCl in DMF and water to afford methyl ketone **11** in 70% yield. The methyl ketone **11** was converted into *anti* diol **12** by the treatment with tetramethylammonium triacetoxyborohydride [10] in CH_3CN: AcOH (1:1) at −40 °C in an 85% yield (96:4 dr). The 1,3-anti diol was protected as its benzylidene acetal [11] with benzaldehyde dimethyl acetal in the presence of a catalytic amount of CSA to afford compound **2** in 89% yield (Scheme 3). The synthesis of C12–C21 fragment of thermolides **1**–**5** involved 13 steps starting from *exo*-methylated bicyclic lactone **6** with a 20.1% overall yield. Further efforts towards the completion of the total synthesis of thermolides 1–5 are currently underway.

Conclusion

In conclusion, a concise and highly stereoselective approach for **C12–C21** fragment of thermolides **1**–**5** were achieved by employing desymmetrization strategy, Barton-McCombie reaction, Brown's asymmetric allylation, Wacker oxidation and *anti*-reduction as key steps. The synthesis involved 13 steps starting from bicylic lactone **6** with a 20.1% overall yield. Further work towards the total synthesis of thermolides **1**–**5** is ongoing.

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