SYNTHETIC STUDY OF THERMOLIDES: STEREOSELECTIVE CONSTRUCTION OF THE C10-C21 FRAGMENT

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Abstract – The C10-C21 fragment of nematocidal thermolides, macrocyclic PKS-NRPS hybrid metabolites isolated from a thermophilic fungus, was prepared in a highly stereoselective manner. The stereocontrol was accomplished by taking advantage of a cinchona alkaloid-catalyzed Morita-Baylis-Hillman reaction followed by diastereoselective hydrogenation and a cinchona alkaloid-catalyzed asymmetric β-lactone formation.

Recently, we have developed an enantio- and diastereoselective method for the synthesis of a β-methyl-γ-hydroxy ester 2 from an aldehyde 1 in catalyst-controlled manner, which involves a cinchona alkaloid-catalyzed asymmetric Morita-Baylis-Hillman reaction¹ and subsequent syn- or anti-selective hydrogenation. The iterative use of this transformation allowed us to construct all possible stereoisomers of a polypropionate stereotetrad 3 having four contiguous stereogenic centers (Scheme 1).² In addition, we have achieved asymmetric syntheses of tirandamycin family of antibiotics utilizing this methodology.³ To further demonstrate the synthetic utility, we became interested in the synthesis of the thermolides.

![Scheme 1. Polypropionate synthesis based on asymmetric MBH reactions](image)

Dedicated with respect to Dr. Kiyoshi Tomioka on the occasion of his 70th birthday
In 2012, Zhag and Niu et al. reported the isolation of thermolides A-F from the culture broths of a thermophilic fungus *Talaromyces thermophilus* (Figure 1). These compounds belong to macrocyclic PKS-NRPS hybrid metabolites and possess characteristic mixed polyketide/amino acid structures containing a 13-membered lactam bearing macrolactone. Interestingly, thermolides A and B exhibited potent inhibitory activities against three notorious nematodes (LC$_{50}$ = 0.5-1 µg/mL), which are to those of avermectins (LC$_{50}$ = 0.5-0.8 µg/mL). The intriguing biological activities and molecular architectures make the thermolides good targets for synthesis; however, even the synthetic studies have to be reported. We herein report the highly enantio- and diastereoselective synthesis of the C10-C21 fragment.

**Figure 1.** Thermolides A-F

![Thermolides A-F](image)

Retrosynthetically, we envisioned 4 as a common precursor of thermolides A-D, from which site selective acetylation of C16, C18, or C20 hydroxy group and stereoselective hydrogenation of C9 methylene would be possible (Scheme 2). To access 4 we envisioned a convergent approach through Negishi coupling of C10-C21 fragment 6 with C4-C9 fragment 5, amidation, and macrolactonization.

**Scheme 2.** Retrosynthetic analysis of thermolides
The synthesis of 6, the topic of this report, would be realized from 8 through stereoselective formation of β-hydroxy ketone 7 and Evans’ anti-selective reduction. The aldehyde 8 could, in turn, be stereoselectively accessed from known chiral building block 9 by taking advantage of our methodology shown in Scheme 1.

The synthesis of C10-C21 fragment 6 began with α-isocupreine (α-ICPN)-catalyzed MBH reaction of aldehyde 10, prepared by Swern oxidation of enantiomerically pure alcohol 9 with 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) (Scheme 3). The reaction was conducted using 0.3 equiv of α-ICPN and 4 equiv of HFIPA in DMF at –55 °C and MBH adduct 11 was obtained in 61% yield together with the corresponding C12-epimer (6%). It is important to note that when the MBH reaction was undertaken employing β-isocupreidine (β-ICD) in place of α-ICPN under the same conditions, the C12-epimer was obtained as a single diastereomer in 61% yield. Upon methanolysis and hydrogenation under the conditions using 0.04 equiv of rhodium catalyst A, compound 11 afforded 12 in excellent anti-selectivity. The absolute configuration of the C12 position was determined to be S by the modified Mosher’s method. The 11,12-anti stereochemistry was confirmed by the NOESY spectrum of acetonide 14 derived from 12 by LiAlH4 reduction followed by acetonidation.

Scheme 3. Reagents and conditions: (a) (COCl)2, DMSO, NEt3, CH2Cl2, –78 °C to rt; (b) -ICPN (0.3 equiv), HFIPA (4 equiv), DMF, –55 °C; (c) MeOH, NaHCO3; (d) Rh catalyst A (0.04 equiv), H2, CH2Cl2; (e) LiAlH4, Et2O, 0 °C; (f) TBSOTf, 2,6-lutidine, CH2Cl2, 0 °C; (g) H2, Pd/C, AcOEt; (h) DMPI, NaHCO3, CH2Cl2; (i) -ICPN (0.3 equiv), HFIPA (4 equiv), DMF, –55 °C; (j) MeOH, NaHCO3; (k) Rh catalyst A (0.04 equiv), H2, CH2Cl2; (l) BOMCl, iPr2NEt, CH2Cl2, reflux; (m) LiAlH4, Et2O, 0 °C; (n) LiAlH4, Et2O, 0 °C; (o) TBSOTf, 2,6-lutidine, CH2Cl2, 0 °C.
The crude 12 obtained from 11 was then subjected to LiAlH₄ reduction followed by silylation to give 13 in 83% yield over 4 steps. Successive debenzylolation and Dess-Martin oxidation converted 13 to 15 in 92% yield. The aldehyde 15 was again subjected to α-ICPN-catalyzed MBH reaction with HFIPA under the same conditions as those employed for the conversion of 10 to 11 and MBH adduct 16 was obtained as a single diastereomer in 64% yield. Compound 16 was then converted to 18 via 17 by a four step-sequence involving methanolysis, rhodium-catalyzed anti-selective hydrogenation, protection as a benzyloxymethyl (BOM) ether, and LiAlH₄ reduction in 73% overall yield. The stereochemistry of 17 was confirmed by its conversion to C2 symmetrical tetra-TBS ether 19 by LiAlH₄ reduction followed by silylation.

To obtain β-hydroxy ketone 7, we first examined L-proline-catalyzed cross aldol reaction of aldehyde 8 with acetone (Scheme 4). Thus, alcohol 18 was oxidized to 8 in 91% yield, which was reacted with acetone in the presence of L-proline (0.3 equiv) in DMSO-CHCl₃ (1:1) at room temperature.

![Scheme 4](image-url)
However, the reaction was very sluggish to give a complex mixture including diastereoisomeric β-hydroxy ketone 7’ (16%), α,β-unsaturated aldehyde 20 (24%), and epimerized starting aldehyde 8’ (28%). With this failure, we then investigated an alternative approach via a cinchona alkaloid-catalyzed cyclocondensation reaction. When aldehyde 8 was reacted with acetyl chloride using 0.2 equiv of TMSQN and 4 equiv of LiClO₄ at –78 °C according to Nelson’s protocol, the reaction was proceeded with excellent diastereoselectivity (dr = 20:1) and β-lactone 21 was obtained in 60% yield (92% brsm). The stereochemistry of the C18 position was determined by applying Rychnovsky’s method to acetonide 22 derived from 21 by sequential ethanolysis, hydrogenolytic removal of the BOM group, and acetonidation. Compound 21 was then converted to the desired β-hydroxy ketone 7 via Weinreb amide 23 in 86% yield. β-Hydroxy ketone 7, thus obtained, was subjected to Evans’ anti-selective reduction to give diol 24 and its C20-epimer in 81% and 10% yields, respectively. After selective desilylation of the primary TBS ether of 24, the resulting triol 25 was converted to acetonide 26 by acetonidation followed by cleavage of the resulting mixed acetal of the primary alchol. The stereochemistry of the C20 position of 26 was clearly determined by Rychnovsky’s method. Finally, iodination of 26 allowed us to obtain the objective C10-C21 fragment 6 in 52% yield.

In conclusion, we have developed a highly enantio- and diastereoselective approach to the C10-C21 fragment 6 via a cinchona alkaloid-catalyzed asymmetric MBH reaction followed by a rhodium-catalyzed anti-selective hydrogenation and a cinchona alkaloid-catalyzed cyclocondensation reaction. The synthesis of thermolides along the retrosynthetic analysis shown in Scheme 2 is under progress in our laboratory.

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SUPPORTING INFORMATION
1H and 13C NMR spectra for all new compounds are available.

REFERENCES AND NOTES


10. In this report, the carbon numbers correspond to those of thermolides.


15. When quinidine TMS ether (TMSQD) was used in place of TMSQN, the C18-epimer of 21 was produced in 51% yield (94% brsm) and again in excellent diastereoselectivity (dr = 20:1).
