HETEROCYCLES, Vol. 97, No. 2, 2018, pp. 702 - 707. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 14th February, 2018, Accepted, 7th March, 2018, Published online, 9th March, 2018
DOI: 10.3987/COM-18-S(T)54

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

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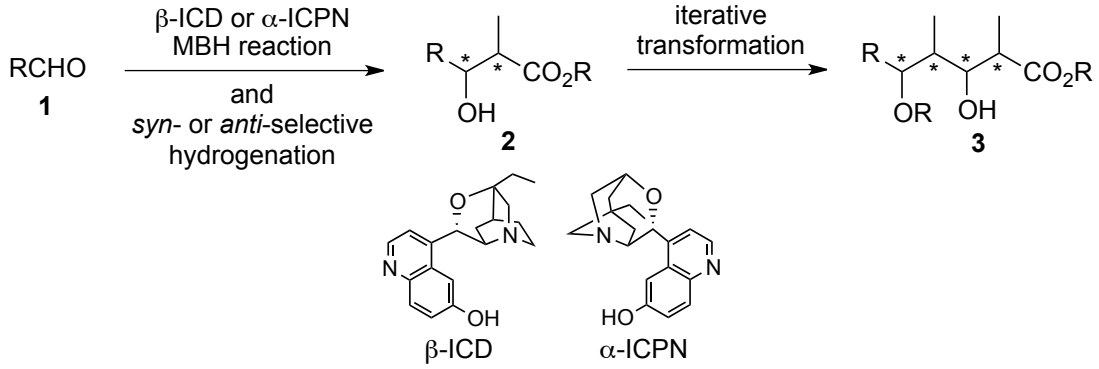
Abstract – The C10-C21 fragment of nematocidal thermolides, macrocyclic PKS-NRPS hybrid metabolites isolated from a thermophilic fungus, was prepared in a highly stereoselective manner. The stereocontrol was accomplished by taking advantage of a cinchona alkaloid-catalyzed Morita-Baylis-Hillman reaction 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 reaction[1] 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

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).[4,5] 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 comparable 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 yet to be reported. We herein report the highly enantio- and diastereoselective synthesis of the C10-C21 fragment.

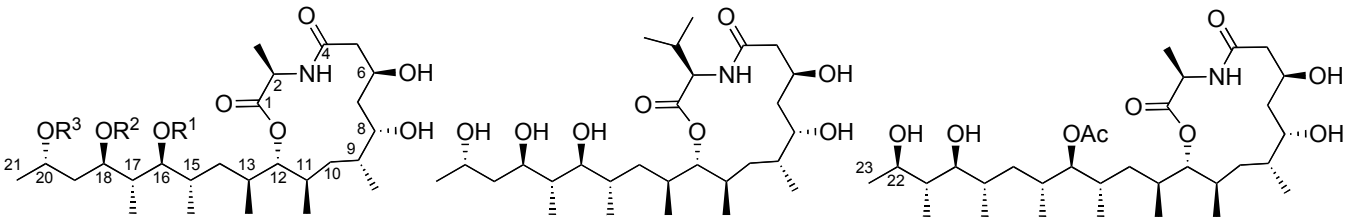
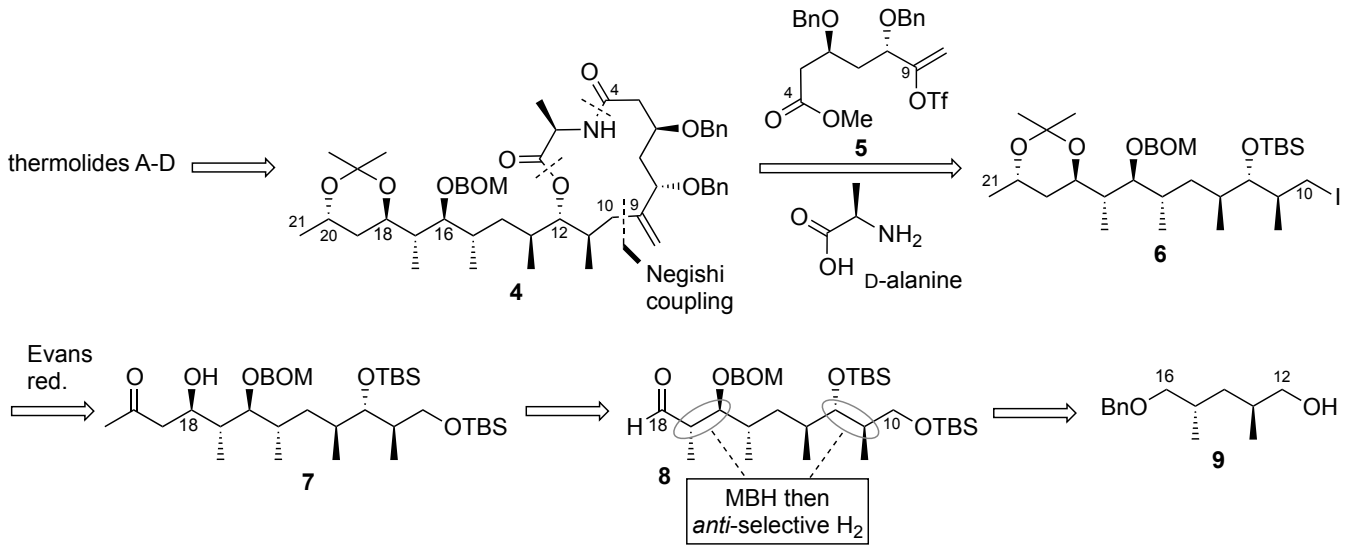


Figure 1. Thermolides A-F

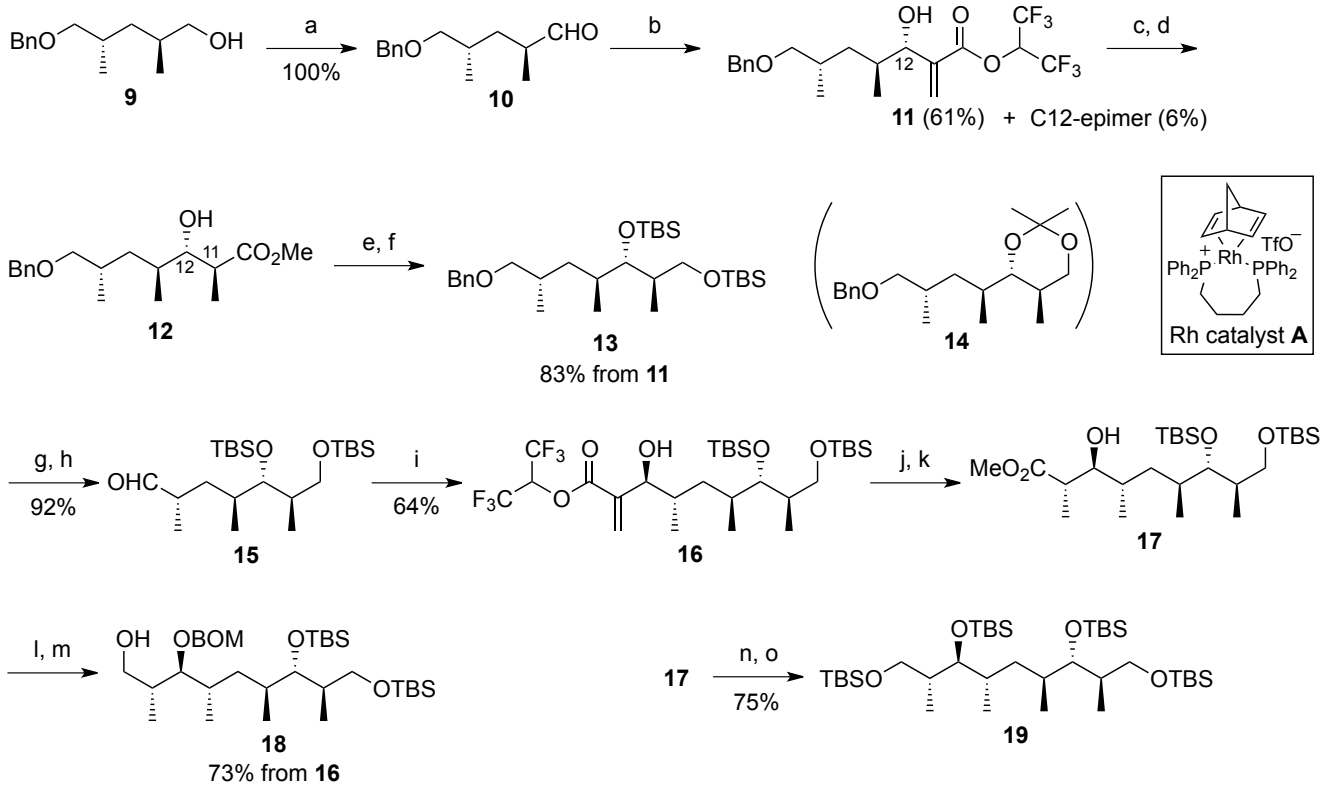
Retrosynthetically, we envisioned **4** as a common precursor of thermolides A-D, from which site selective acetylation of C16, C18, or C20 hydroxy group and stereoselective hydrogenation of C9 methylene would be possible (Scheme 2). To access **4** we envisioned a convergent approach through Negishi coupling[6,7] 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.[8] The aldehyde **8** could, in turn, be stereoselectively accessed from known chiral building block **9**[9] by taking advantage of our methodology shown in Scheme 1.

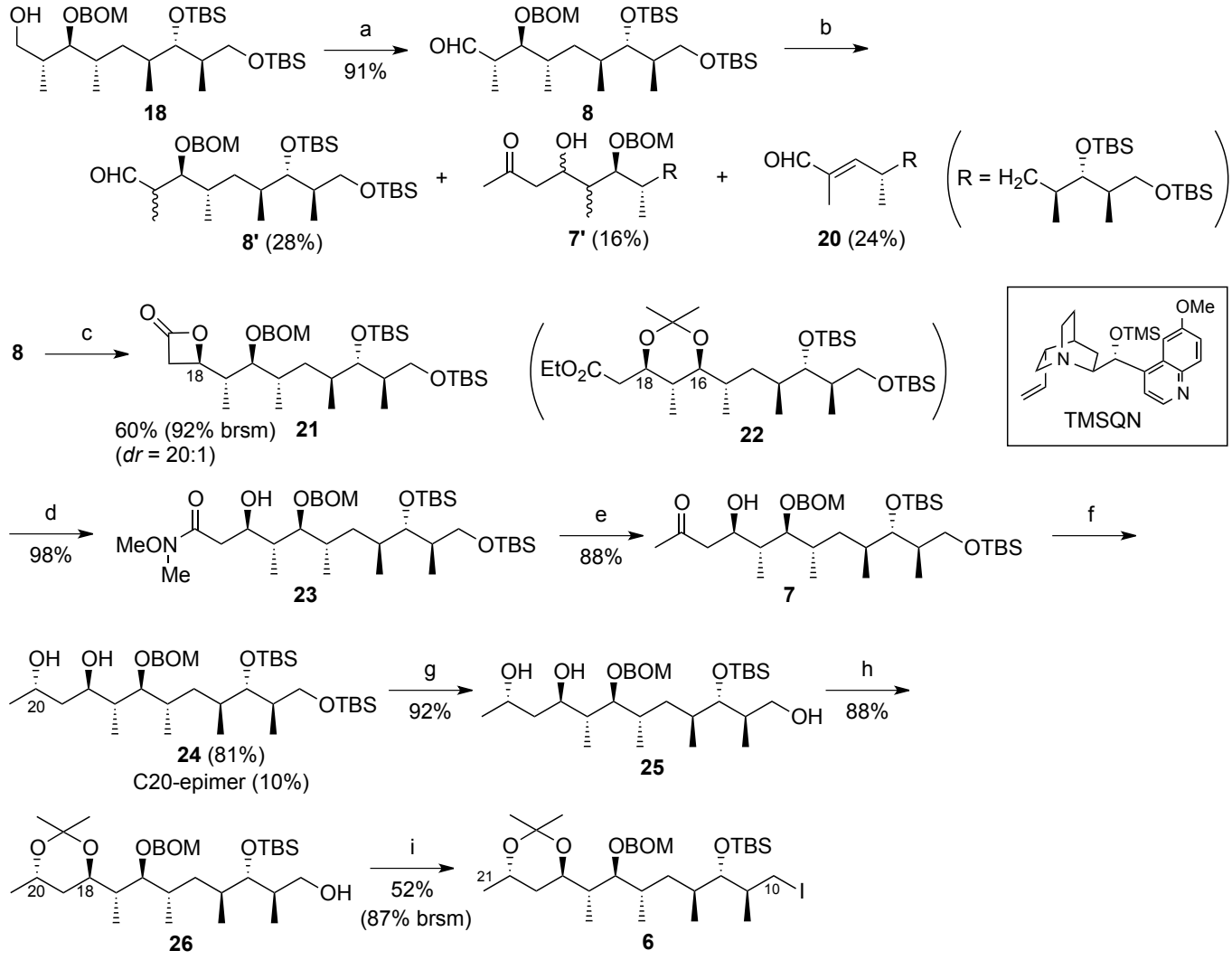
The synthesis of C10-C21 fragment **6** began with α-isocupreine (α-ICPN)-catalyzed MBH reaction of aldehyde **10**, prepared by Swern oxidation of enantiomerically pure alcohol **9**,[9] with 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) (Scheme 3). The reaction was conducted using 0.3 equiv of α-ICPN 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%).[10] 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**,[11] 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.[12] The 11,12-*anti* stereochemistry was confirmed by the NOESY spectrum of acetonide **14** derived from **12** by $LiAlH_4$ reduction followed by acetonidation.



Scheme 3. Reagents and conditions: (a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, –78 °C to rt; (b) α-ICPN (0.3 equiv), HFIPA (4 equiv), DMF, –55 °C; (c) MeOH, $NaHCO_3$; (d) Rh catalyst **A** (0.04 equiv), H_2, CH_2Cl_2; (e) $LiAlH_4$, Et_2O, 0 °C; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (g) H_2, Pd/C, AcOEt; (h) DMPI, $NaHCO_3$, CH_2Cl_2; (i) α-ICPN (0.3 equiv), HFIPA (4 equiv), DMF, –55 °C; (j) MeOH, $NaHCO_3$; (k) Rh catalyst **A** (0.04 equiv), H_2, CH_2Cl_2; (l) BOMCl, $^iPr_2NEt$, CH_2Cl_2, reflux; (m) $LiAlH_4$, Et_2O, 0 °C; (n) $LiAlH_4$, Et_2O, 0 °C; (o) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C.

The crude **12** obtained from **11** was then subjected to $LiAlH_4$ reduction followed by silylation to give **13** in 83% yield over 4 steps. Successive debenzylation 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,[11] protection as a benzyloxymethyl (BOM) ether, and $LiAlH_4$ reduction in 73% overall yield. The stereochemistry of **17** was confirmed by its conversion to C2 symmetrical tetra-TBS ether **19** by $LiAlH_4$ reduction followed by silylation.

To obtain β-hydroxy ketone **7**, we first examined L-proline-catalyzed cross aldol reaction[13] 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-$CHCl_3$ (1:1) at room temperature.



Scheme 4. Reagents and conditions: (a) DMPI, $NaHCO_3$,CH_2Cl_2; (b) L-proline (0.3 equiv), DMSO-CH_2Cl_2 (1:1), 8 days; (c) TMSQN (0.2 equiv), $LiClO_4$ (4 equiv), AcCl, $^iPr_2NEt$, CH_2Cl_2, –78 °C; (d) NHMe(OMe)·HCl, Et_2AlCl, CH_2Cl_2, 0 °C; (e) MeLi, Et_2O, 0 °C; (f) $NMe_4BH(OAc)_3$, AcOH, MeCN, –20 °C; (g) CSA, MeOH, 0 °C; (h) $Me_2C(OMe)_2$, PPTS, acetone, then PPTS, EtOH; (i) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C to rt.

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.[14] When aldehyde **8** was reacted with acetyl chloride using 0.2 equiv of TMSQN and 4 equiv of $LiClO_4$ at –78 °C according to Nelson's protocol,[14] the reaction was proceeded with excellent diastereoselectivity (*dr* = 20:1) and β-lactone **21** was obtained in 60% yield (92% brsm).[15] The stereochemistry of the C18 position was determined by applying Rychnovsky's method[16] 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.[17] β-Hydroxy ketone **7**, thus obtained, was subjected to Evans' *anti*-selective reduction[8] 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.[16] 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.

ACKNOWLEDGEMENTS

This work was supported by the Grant-in-Aid for Scientific Research (B) (16H05074) from JSPS and the Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysis" (No. 2304) (26105747) from MEXT. H.Y. thanks a JSPS Research Fellowship for Young Scientists.

SUPPORTING INFORMATION

^{1}H and ^{13}C NMR spectra for all new compounds are available.

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