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Chemoenzymatic total synthesis of the phytotoxic lactone herbarumin III

Samik Nanda*

Biotechnology Research Center, Toyama Prefectural University, 5180 Kurokawa, Kosugi, Toyama 939-0398, Japan

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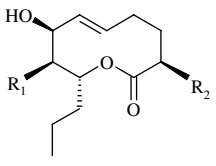
Abstract—Asymmetric total synthesis of phytotoxic nonenolide herbarumin III was accomplished by a chemoenzymatic approach. The main highlight of the synthesis was to fix the hydroxyl stereocenters (**C7** and **C9**) by lipase catalyzed irreversible transesterification.

Bioassay guided fractionation of a culture broth of the fungus *Phoma herbarum* Westend (Sphaeropsidaceae) led to a new nonenolide with the two previously isolated compounds named herbarumin I (**1**) and II (**2**).[1] According to the previous nomenclature,[2] this compound was named herbarumin III (**3**) and possessing the nonenolide core with one hydroxyl group (Fig. 1). Its structural features and conformational analysis were established perfectly.[1] Herbarumin III (**3**) showed relevant phytotoxic effects when tested against seedlings of A. hypochondriacus using the Petri dish bioassay.[3] The lactone ($IC_{50} = 2 \times 10^{-5}$ M) inhibited radicle growth with higher potency than 2,2-dichlorophenoxyacetic acid ($IC_{50} = 2 \times 10^{-4}$ M), used as positive control. Herbarumin III (**3**) also interacted with bovine brain calmodulin and has an inhibitory effect same as those of herbarumin I (**1**) and II (**2**). Thus, compounds **1**–**3** are calmodulin inhibitors and should have physiological effects of agrochemical and medicinal interest. Both herbarumin I and II were recently synthesized by a concise approach involving RCM or Nozaki–Hiyama–Kishi coupling reaction as the key step for the formation of the medium-sized ring.[4]



R_1 = OH, R_2 = H; Herbarumin I
R_1 = R_2 = OH; Herbarumin II
R_1 = R_2 = H; Herbarumin III

Figure 1.

The first total synthesis of herbarumin III was reported last year,[5] which also involves RCM as a key step. In this letter, I wish to report the asymmetric total synthesis of herbarumin III by a chemoenzymatic approach. The two stereocenters (C7 and C9) both were installed by lipase catalyzed irreversible transesterification, and in the final step macrolactonization, by applying Yamaguchi's protocol as well as lipase catalyzed irreversible acyl transfer method yielded herbarumin III.

The synthesis starts from the *trans* cinamaldehyde (**1a**–**c**), which on addition with propylmagnesium bromide yields the allylic alcohol **2a**–**c**. The allylic alcohol **2a**–**c** was subjected to lipase catalyzed irreversible transesterification with vinyl acetate and CAL-B (immobilized on macroporous acrylic resin) to afford (*R*)-acetate and the slow reacting enantiomer (*S*)-alcohol. The mixture of (*R*)-acetate and (*S*)-alcohol was converted to (*R*)-acetate by employing an elegant strategy reported by Kanerva and Vanttinen[6] involving Mitsunobu inversion, thus effectively converting a racemic alcohol to (*R*)-acetate (whereas in traditional enzymatic transesterification reaction maximum 50% possible yield was obtained). The absolute configuration of the product acetate in the enzyme catalyzed transesterification can be predicted by Kazlauskas empirical model[7] where the sizes of the two side chains determine which enantiomer will

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* Tel.: +81 766567500; fax: +81 766 56 7500x532; e-mail: snanda@sunny.ocn.ne.jp

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undergo fast reaction. The enantioselectivity (ee) was measured by chiral HPLC and it was observed that substrates **1b** and **1c** provide better ee than **1a** (Table 1; due to presence of bulky substituents in *para* position in **1b** and **1c**). The choice of benzyl and 4-methoxybenzyl was judiciously done to have an effective steric difference between the two side chains in the allylic alcohols. And from Table 1, it shows that substrate **1c** provides best enantioselectivity (98% ee for the acetate and 96% for the remaining alcohol which was inverted by using Mitsunobu protocol).

Acetate group in **1c** was deprotected and benzyl protection was achieved by using benzylimidate to yield **3c**.[8] Ozonolysis of **3c** and reduction of the generated aldehyde functionality with $NaBH_4$ produced alcohol **4**. Compound **4** was converted to sulfone derivative **5** by a two-step method, first making the iodo compound and then treating it with paratoluenesulfenic acid sodium salt yielded **5** (Scheme 1).

The sulfone **5** was then condensed with (*E*)-7-(4-methoxybenzyloxy)hept-2-enal[9] in presence of LDA at −78 °C to yield compound **6** in 78% yield.[10] The paratoluene sulfone group was removed by treating compound **6** with amalgamated aluminum (Al/Hg) by Trost protocol[11] to furnish compound **7**. Compound **7** was subjected to second enzymatic kinetic transesterification with VAC in DIPE. In this case, the side chain bearing the parmethoxybenzyl group acts as a large substituent compared to the other one. Thus, the fast-reacting enantiomer can be predicted according to Kazlauskas rule. The previous strategy of Mitsunobu inversion was applied in tandem to yield the acetate **8** with required stereochemistry in 88% overall yield from **7**. The enantioselectivity (diastereoselection) was determined by chiral HPLC and it was observed that overall good de (90%) was obtained. After fixing the two stereocenters (C7 and C9), the remaining task was to construct the lactone ring in an efficient manner. Acetate group deprotection and formation of TBDPS ether were achieved to afford **10**. Removal of 4-methoxybenzyl group with DDQ[12] furnished alcohol **11**. The alcohol **11** was converted to acid **12** by a two-step procedure, first Swern oxidation followed by oxidation with $NaClO_2/NaH_2PO_4$ using Pinnick's protocol.[13] Finally, removal of benzyl group with Li–NH_3 (l) afforded hydroxyacid, the desired lactone precursor **13** in good yield.

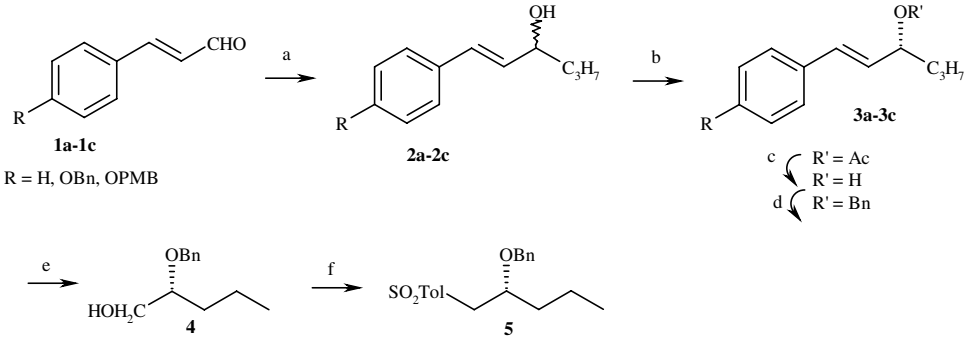
The formation of medium-sized ring lactone was reported by Lobell and Schneider[14] by lipase catalyzed irreversible intramolecular acyl transfer method. When the hydroxyacid **13** itself was subjected to lactonization (lipase) in TBME, no product lactone was detected from the reaction mixture. It was established by Lobell et al. that the hydroxyacid itself was a poor substrate and yields no lactone. Following a similar method reported by them, it is possible to obtain the required nonenolide from the corresponding carboxy vinylester of **13**. The vinylester of **13** was prepared successfully by employing Pd catalyzed transesterification with vinyl acetate. The vinylester when employed with lipase catalyzed intramolecular acyl transfer reaction, moderate yield of required nonenolide was observed with some other oligomeric product. Immobilized lipase from *Pseudomonas* sp. provides best yield, where as TBME is the solvent choice. The yield of products is summarized in Table 2. To the best of our knowledge, this is the first report of lipase catalyzed macrolactonization approach for total synthesis of a natural product precursor. The major drawback associated with lipase catalyzed intramolecular acyl transfer reaction leading to medium-sized lactone is mainly the formation of oligomeric rings, which cause less yield for the required lactone precursor of herbarumin III. So finally lactonization was achieved by applying Yamaguchi's protocol.[15] The hydroxyacid **13** when treated with 2,4,6-trichlorobenzoylchloride in refluxing benzene, the required lactone **14** was obtained in overall

Table 1. Enzymatic transesterification of **1a–c**

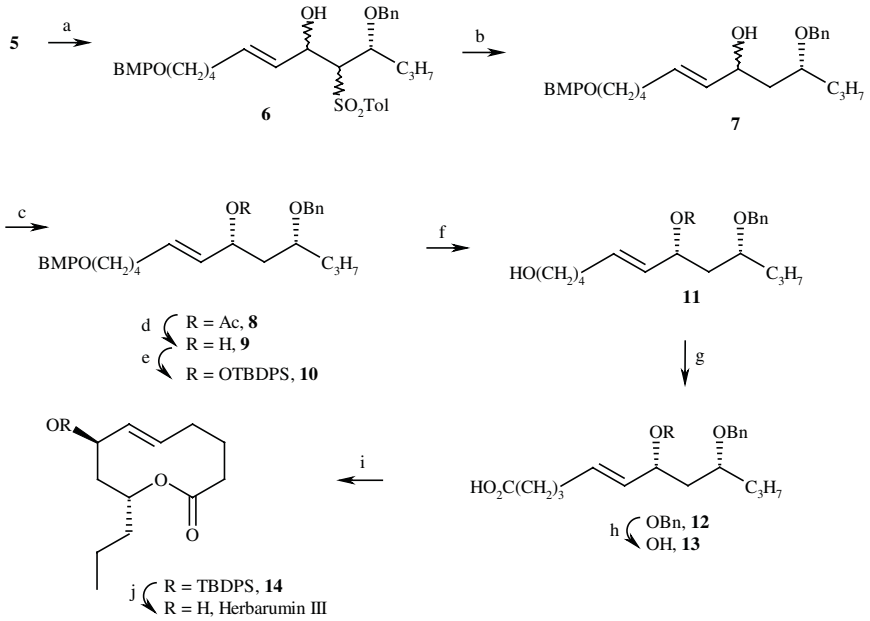
Substrate	Lipase	ee-Acetate (%)	ee-Alcohol (%)	E[16]
1a	CAL-B	90	88	55
1b	CAL-B	97	94	213
1c	CAL-B	98	96	412

Table 2. Enzyme catalyzed irreversible acyl transfer for nonenolide formation

Substrate	Lipase	Solvent	Yield (%)
Vinyl ester of **13**	PSL	TBME	31
Vinyl ester of **13**	CAL-B	TBME	11
Vinyl ester of **13**	PSL	TBME/hexane (8:2)	28



Scheme 1. Reagents and conditions: (a) ^{n}PrMgBr, ether, rt; (b) (i) VAC, CAL-B, DIPE; (ii) TPP, DIAD, AcOH, THF; (c) K_2CO_3, MeOH; (d) $BnO(C{=}NH)CCl_3$, CSA; (e) O_3, DCM, Me_2S; $NaBH_4$/MeOH, 82%; (f) (i) I_2, TPP, Im, 88%; (ii) $TolSO_2Na$, DMF, 65%.



Scheme 2. Reagent and conditions: (a) LDA, −78 °C, *E*-7-(4-methoxybenzyloxy)hept-2-enal, 78%; (b) Al/Hg, THF, 60%; (c) (i) CAL-B, VAC, DIPE; (ii) TPP, DIAD, AcOH, 90% de; (d) K_2CO_3/MeOH; (e) TBDPS-Cl, imidazole, DMF, 86%; (f) DDQ, 82%; (g) (i) DMSO, $(COCL)_2$, Et_3N, 88%; (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, 80%; (h) Li–NH_3 (1), 3-hexyne; (i) (i) vinyl acetate, $Pd(OAc)_2$, lipase, TBME, 31%; (ii) Et_3N, DMAP, pH, 80 °C, 83%.

good yield (Scheme 2). Finally, TBDPS group was removed by TBAF treatment to yield herbarumin III (**3**). The NMR (^1H and ^{13}C) spectra of synthesized and natural herbarumin III are in perfect agreement, its optical rotation value was little low {$[\alpha]_D$ +16.7 (*c* 1.0, EtOH); Literature value $[\alpha]_D$ +22.0 (*c* 1.0, EtOH)} compared with the natural product, and that may be due to the fact that the second enzymatic transesterification method (to fix the C7) was not completely enantioselective (de, 90%).

In summary, an efficient asymmetric total synthesis of herbarumin III is described for the first time by a chemoenzymatic approach.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2005.03.139.

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