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First total synthesis of herbarumin III ☆

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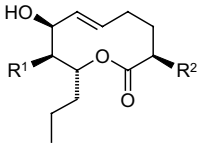
Abstract—An asymmetric 10-step total synthesis of herbarumin III in 24% overall yield is described using ring-closing metathesis as the key step.

The interesting biological activities of herbarumin I (**2**) and II (**3**) and the reinvestigation of the fermentation broth and mycelium of the fungus *Phoma herbarum* led to the isolation of a new phytotoxic nonenolide (7*R*,9*R*)-7-hydroxy-9-propyl-5-nonen-9-olide (herbarumin III, **1**), along with herbarumin I (**2**) and II (**3**).[1] The structure of **1** was elucidated by spectroscopic methods combined with molecular modeling. Compounds **1** to **3** interacted with bovine-brain calmodulin and inhibited the activation of the calmodulin-dependent enzyme camp phosphodiesterase.



1. $R^1 = R^2 = H$ (Herbarumin III)
2. $R^1 = OH$, $R^2 = H$ (Herbarumin I)
3. $R^1 = R^2 = OH$ (Herbarumin II)

In general, synthetic approaches to lactones have focused mainly on the use of fragmentation/ring expansion reactions and on lactonization strategies in order to build the lactone ring.[2] Ring-closing metathesis (RCM)[3] is a modern synthetic protocol to access various lactone rings. Total syntheses of herbarumin I (**2**)[4] and herbarumin II (**3**)[5] have been reported recently following RCM or Nozaki–Hiyama–Kishi reactions as the key steps. Our synthetic strategy for the total synthesis of herbarumin III (**1**) also hinges on ring-closing metathesis (RCM) for lactone ring formation with the required chiral aliphatic diol envisaged to arise from D-glucose.

We began our synthesis with D-glucose as the starting material which was converted to its diacetonide and corresponding xanthate derivative followed by deoxygenation under the Barton–McCombie protocol using *n*-Bu_3SnH and a catalytic amount of AIBN in toluene under reflux conditions to provide the 3-deoxyglucose derivative **4** in 58% yield over three steps.[6a,b] Regioselective monohydrolysis of the 5,6-*O*-isopropylidene moiety of **4** with 0.8% H_2SO_4 in MeOH at ambient temperature afforded the diol **5** in 84% yield. Introduction of the *n*-propyl group at the C-4 position was achieved in three steps via oxidative cleavage of diol **5** using silica gel supported[7] $NaIO_4$ and a two carbon homologation using ethyltriphenylphosphonium bromide and *n*-BuLi in anhydrous THF at −78 °C, followed by hydrogenation using 10% Pd/C to afford the *n*-propyl derivative **8** in 72% overall yield. Deprotection of the 1,2-*O*-isopropylidene group of compound **8** with 20% acetic acid in H_2O and a catalytic amount of H_2SO_4 afforded the lactol **9** in 93% yield, which after work up, was subjected to Wittig methylenation[8] with in situ generated methylenetriphenylphosphorane to afford the olefinic intermediate **10**. Selective protection of the allylic hydroxyl group as its PMB-ether and esterification of the other hydroxyl group with 5-hexenoic acid[9] under Yamaguchi et al. conditions[10] at room temperature afforded the desired ring-closing metathesis precursor **12** in 82% yield.

The ring-closing metathesis was then investigated using Grubbs' first and second generation catalysts. In our

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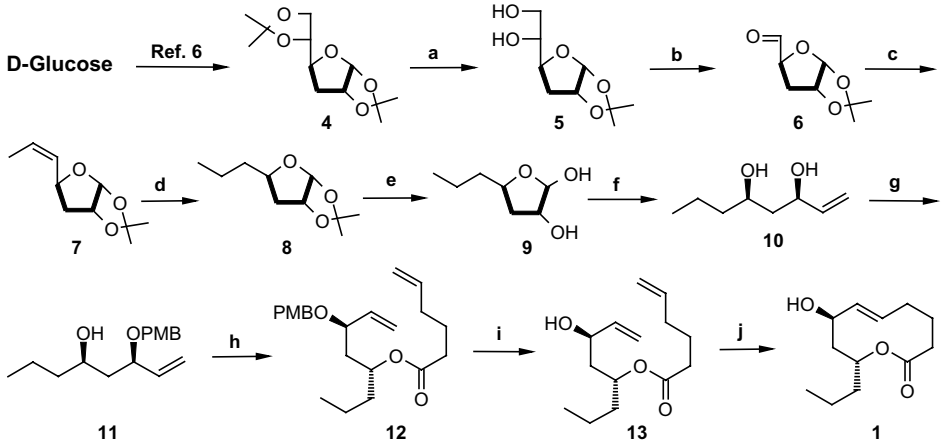

Scheme 1. Reagents, conditions and yields: (a) 0.8% H_2SO_4, MeOH, rt, 12 h, (84%); (b) silica gel supported $NaIO_4$, CH_2Cl_2, rt, 30 min (95%); (c) $Br^-P^+Ph_3CH_2CH_3$, *n*-BuLi, THF, −78 to 0 °C, 3 h (82%); (d) H_2, Pd/C, 1 bar, rt, 3 h (92%); (e) 20% AcOH in H_2O, concd H_2SO_4 (catalytic), reflux, 6 h (93%); (f) $I^-P^+Ph_3CH_3$, *n*-BuLi, THF, 0 °C to rt, 12 h (76%); (g) PMBCl, NaH, DMF, 0 °C, 1 h, (94%); (h) 5-hexenoic acid, 2,4,6-trichlorobenzoyl chloride, DMAP, THF, **11** in THF, 0 °C to rt, 4 h (82%); (i) DDQ, CH_2Cl_2/H_2O (18:1), rt, 30 min (94%); (j) (i) $RuCl_2(=CHPh)(PCy_3)_2$, CH_2Cl_2, reflux, 4 days, (36%) (52% starting material recovered), (ii) $RuCl_2(=CHPh)(PCy_3)(IEMS)$, CH_2Cl_2, reflux, 16 h, (78%).

hands, RCM of compound **12** led to the formation of the homodimer as the major product. With the use of precursor **13** for RCM, we could almost completely suppress the homodimerization. The reaction of **13** with the first generation Grubbs' catalyst in CH_2Cl_2 (high dilution) under reflux conditions gave the natural product **1** in 36% yield as the only product after 4 days with 52% recovery of the starting material, while the second generation catalyst provided the final compound **1** in 78% yield (Scheme 1). Spectral and analytical data obtained for **1** were consistent with those reported in the literature.[1]

In conclusion, we have completed the first total synthesis of the biologically active natural product herbarumin III (**1**) starting from D-glucose.

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