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A total synthesis of (±)-1-desoxyhypnophilin: using ring closing metathesis for the construction of cyclic enones

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Abstract

The paper describes the first total synthesis of (±)-1-desoxyhypnophilin, a linear triquinane isolated from the East African mushroom *Lentinus crinitus* which displays promising antimicrobial activity. The key strategic feature is a new cyclopentannulation method for appending cycloalkenones onto ketones involving sequential use of a ring closing metathesis reaction with a tertiary allylic alcohol and a PCC induced oxidative rearrangement. © 2000 Elsevier Science Ltd. All rights reserved.

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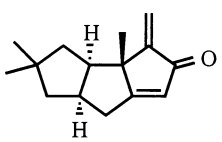
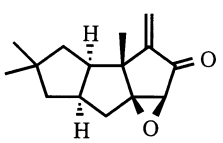
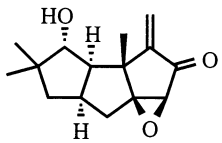
Identified in 1994 as a constituent of the East African mushroom *Lentinus crinitus*, 1-desoxyhypnophilin **2** has been shown to exhibit promising antimicrobial activity.[1] Closely related to hypnophilin **3** and coriolin **4**, these naturally occurring oxygenated triquinanes are presumed to be derived in Nature from a common precursor, diene **1**.[1–3] While numerous syntheses of hypnophilin and coriolin have been reported, many utilising ingenious cyclopentannulation strategies,[4] diene **1** and 1-desoxyhypnophilin **2** have yet to succumb to total synthesis.



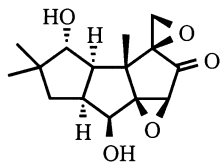
1



1-Desoxyhypnophilin **2**



Hypnophilin **3**



Coriolin **4**

The route we envisioned for the synthesis of 1-desoxyhypnophilin involved a four-step annulation strategy for the synthesis of cyclic enones (Scheme 1). Thus, allylation of bicyclic

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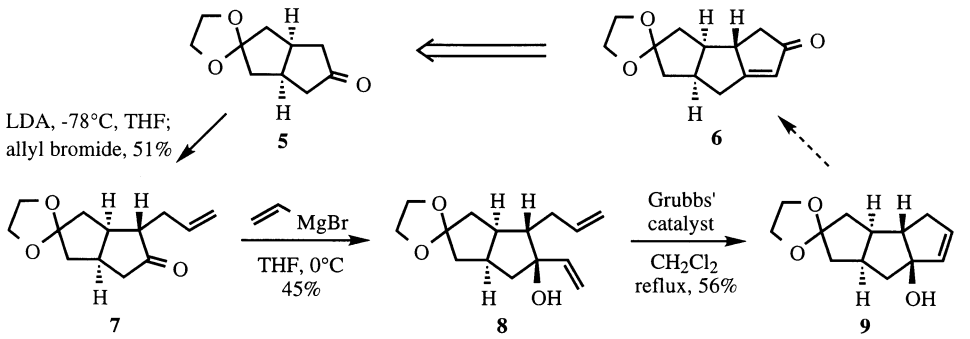
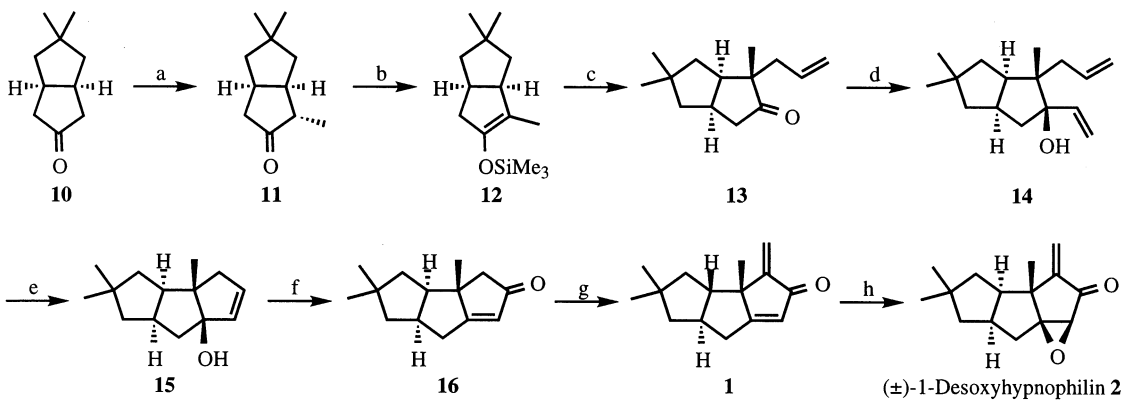
ketone **5** was followed by treatment of the resulting enone **7** with vinylmagnesium chloride/cerium(III) chloride complex to give diene **8**. A ring closing metathesis using Grubbs' catalyst then gave **9**.[5] Though exposure of **9** to PCC failed to provide tricyclic enone **6**,[6] we were sufficiently encouraged to embark on the target synthesis using the known ketone **10** as a convenient starting point.[7]



Scheme 1.

Firstly the ketone **10** was enolised and methylated to give **11**, which in turn was enolised and allylated to provide **13**.[8] A cerium(III) chloride promoted addition of vinylmagnesium chloride to the ketone then provided diene **14** which underwent ring closure to **15** when exposed to Grubbs' catalyst.[8] Oxidation with pyridinium chlorochromate to enone **16** and methyleneation according to the procedure of Greene then gave diene **1**.[9] Finally, selective epoxidation with hydrogen peroxide provided (±)-1-desoxyhypnophilin **2** (Scheme 2): our synthetic sample exhibiting spectral characteristics identical to those reported previously.[1]



Scheme 2. *Reagents and conditions*: (a) LDA, THF–HMPA, −90°C, 2 h then MeI, −90°C, 6 h, 84%; (b) Et_3N, DMF, TMSCl, Δ, 24 h, 74%; (c) MeLi, THF–HMPA, −78°C, 15 min then allyl bromide, −78°C, 3 h, 90%; (d) vinylMgBr, $CeCl_3$, THF, 0°C, 15 h, 70%; (e) $(PCy_3)_2Cl_2Ru{=}CHPh$, CH_2Cl_2, reflux, 3 h, 88%; (f) PCC, 4 Å MS, CH_2Cl_2, rt, 18 h, 60%; (g) HCO_2Me, LiHMDS, THF, −78°C, 1 h then CH_2O, aq. acetone, K_2CO_3, rt, 18 h, 42% [+ 19% **16**]; (h) H_2O_2, $NaHCO_3$, aq. THF, 4°C, 15 h, 73% [+ 20% **1**]

In conclusion, we have achieved the first total synthesis of (±)-1-desoxyhypnophilin **2** and developed a useful annulation protocol for the synthesis of cyclic enones. We are presently exploring the scope of the annulation sequence for the synthesis of other polycycles and exploring further its use in target oriented synthesis.

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