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A stereoselective synthesis of (+)-malyngolide via a ring-closing olefin metathesis

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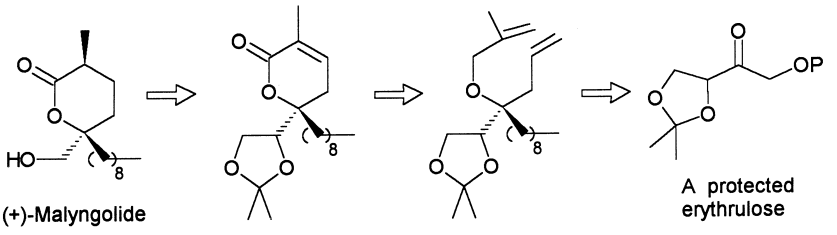
Abstract

A very short and stereoselective synthesis of the non-natural enantiomer of malyngolide from L-erythrulose is described. Key features of the synthesis are the Felkin–Anh diastereoselective allylation of a poly-oxygenated ketone and the allylation/metathesis/allylic oxidation protocol recently described by our group.

Keywords: malyngolide; ring-closing metathesis; diastereoselective allyltin addition.

(–)-Malyngolide is a naturally ocurring δ-lactone isolated from the alga *Lyngbya majuscula* Gomont and displays antibiotic activity against pathogenic species belonging to genera such as *Staphylococcus*, *Mycobacterium*, *Pseudomonas* and other related genera.[1] Total syntheses of this metabolite, both of the naturally occurring enantiomer and of its antipode (+)-malyngolide, have been previously published by other groups, including two very recent ones by Hoppe, Tanaka and their respective co-workers.[2] In the present communication, we present another approach to (+)-malyngolide based on our recently described methodology of sequential allylation/metathesis/allylic oxidation.[3] The starting material is L-erythrulose, currently developed by our group as a useful C_4 chiron.[4] Our retrosynthetic analysis of (+)-malyngolide is shown in Scheme 1.



Scheme 1.

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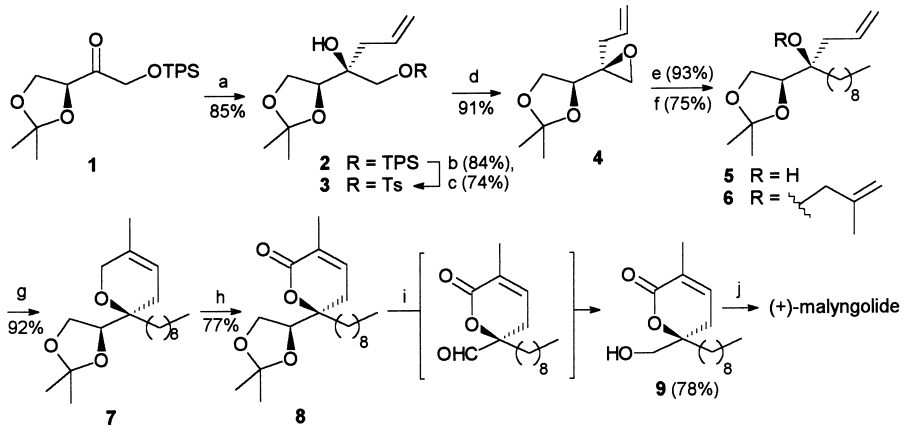
The synthetic sequence depicted above relies on a stereoselective nucleophilic allylation of a suitably protected erythrulose derivative. This has previously been achieved for 3,4-di-*O*-benzyl erythrulose derivatives under conditions of chelation control.[4] Unfortunately, the synthetically much more convenient erythrulose acetals[5] were found to decompose in the presence of certain Lewis acids or to react unstereoselectively under other allylation conditions.[6] After extensive experimentation, we found that treatment of the silylated L-erythrulose acetonide **1**[5] (Scheme 2, TPS=*t*-butyldiphenylsilyl) with allyl tri-*n*-butyltin in the presence of the mild Lewis acid $MgBr_2 \cdot Et_2O$[7] furnished allylcarbinol **2** as an essentially single stereoisomer in a very good chemical yield. Unexpectedly, the configuration of the new stereogenic centre corresponded to that predicted by the Felkin–Anh model and was thus opposite to that which was expected from a chelation control.[4,8] Desilylation of **2** and subsequent tosylation afforded **3**, which was treated with base to yield epoxide **4**. Nucleophilic opening of the oxirane ring with an in situ generated *n*-octylcuprate reagent[9] gave rise to the tertiary carbinol **5**, which was then *O*-alkylated with methallyl chloride. This provided ether **6**, which was then exposed to ring-closing metathesis conditions[3] in the presence of Grubbs benzylidene ruthenium catalyst.[10] Dihydropyran **7** was formed in an excellent 92% yield. Allylic oxidation with the CrO_3/3,5-DMP complex[3] yielded the α,β-unsaturated δ-lactone **8**, which was then subjected to oxidative cleavage of the dioxolane ring with periodic acid in Et_2O.[11] The intermediate aldehyde was not purified but immediately reduced with $NaBH_4$ in isopropanol to yield dehydromalyngolide **9**.[12] Lactone **9** was then stereoselectively converted into (+)-malyngolide by catalytic hydrogenation.[13] The described physical and spectral properties of both malyngolide and its dehydro derivative were coincident with those of our products.[2,14]



Scheme 2. Reaction conditions: (a) allylSnBu$_3$, MgBr$_2$, CH_2Cl_2, –40°C. (b) TBAF, THF, RT. (c) TsCl, NEt_3, DMAP, CH_2Cl_2, Δ. (d) KH, THF, RT. (e) Me(CH$_2$)$_7$MgI, CuI, THF, –30°C. (f) KH, methallyl chloride, THF, Δ. (g) 3% PhCH=RuCl$_2$(PCy$_3$)$_2$, CH_2Cl_2, Δ. (h) CrO_3/3,5-DMP, CH_2Cl_2, –20°C. (i) H_5IO_6, Et_2O, RT, then $NaBH_4$ (1.2 equiv.)/*i*PrOH, 0°C. (j) H_2, Pd/C (Ref. 13).

A derivative of the commercially available L-erythrulose was the starting material in the synthesis of (+)-malyngolide described above. A key step was the stereoselective nucleophilic allylation of its carbonyl group under nonchelation (Felkin–Anh) control. The synthesis of the naturally occurring (–)-malyngolide therefore requires either D-erythrulose derivatives as the starting material,[15] or stereoselective allylations of L-erythrulose derivatives to be performed

under chelation control.[4,16] Both possibilities are currently being explored by our group and the results will be reported in due course.

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