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First Enantioselective Synthesis of (-)-Seiridin the Major Phytotoxic Metabolite of Seiridium Species Pathogenic for Cypress

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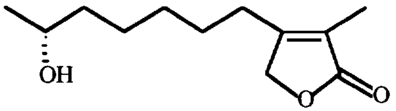
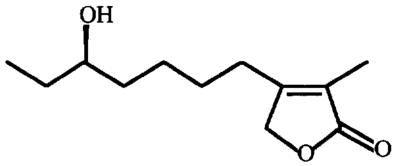
Abstract: the first enantioselective synthesis of seiridin, a phytotoxic dialkylsubstituted butenolide produced by three Seiridium species, fungi pathogenic for cypress, is described.The short sequence, which leads to optically pure compound **1**, would be useful to the obtaining of larger quantities of the compound for genetic selection of resistant cypress plants.

Seiridin **1**, together with its structural isomer isoseiridin **2**, are two phytotoxic 3,4-dialkylsubstituted $\Delta^{\alpha,\beta}$-butenolides produced *in vitro* by the three species of Seiridium, Seiridium cardinale, S. Cupressi and S. unicorne[1,2], fungi associated with the canker of cypress trees (Cupressus sempervirens) in the Mediterranean area.[3]



seiridin **1**



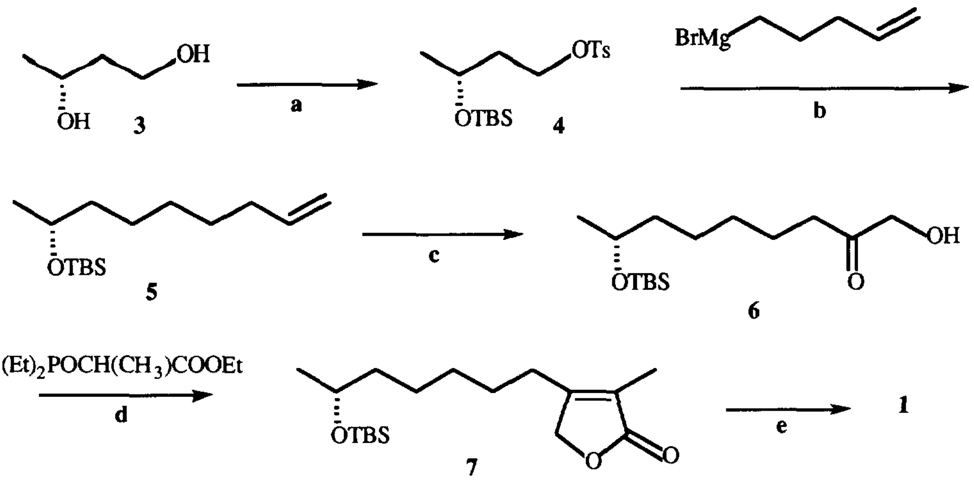
isoseiridin **2**

These two metabolites accumulate in the cultures of all the three fungi species, together with other phytotoxins.[4] Seiridines **1** and **2** are postulated to be involved in the cypress canker desease, a pathogenesis causing heavy loss to the nursery industry, to cypress plantation used for afforestation and wind-break and to ornamental cypresses.[3] Furthermore they show, amongst other things, hormone-like and antimicrobial biological activities.[5] Of the two substances seiridin **1** is the most abundant and also the more toxic metabolite.

Since seiridins are only available at very low levels, after a long process of purification of culture filtrates of Seiridium spp., a total enantioselective synthesis would allow the obtaining of more material as well as the definitive demonstration of the proposed structure. The synthetic compound could be used to obtain lines of cypresses resistant to canker desease through a program of genetic selection on cell liquid cultures of the host plant. Recently a stereoselective synthesis of the minor metabolite isoseiridin **2** was reported[6], although this involved several steps and with ee's not exceeding 88%.

The presence of a 3,4 alkyl substituted butenolide seemed to represent the major problem in the synthesis, since very few examples of this type of lactone were the object of previous studies and since of the rare presence in natural products of such unsaturated lactones.[7] Our choice was to build up the butenolide moiety by Wittig olefination or better via intramolecular reaction (see below).

The introduction of the correct chirality on the secondary alcoholic function (see scheme) can be easily accomplished starting with the commercially available enantio pure (3R) 1,3-butanediol **3**, which is easily transformed into the tosyl monoprotected derivative **4** (86%).



a.TsCl/DMAP/Et$_3$/CH$_2$Cl$_2$, then TBS-Cl/DMF/Imidazole, r.t. (86%). **b**. 5-bromo-1-pentene, Mg, Et$_2$0,Li$_2$CuCl$_4$, 5h, r.t., (57%). **c**. KMnO$_4$/CH$_3$COOH in aceton, r.t., 15 min, 53%). **d**.(Et)$_2$POCH(CH)$_3$COOEt,LiOH, molecular sieves, in THF, reflux, 24h, 63% . **e**. HF/CH$_3$CN, 1h, r.t. (99%).

The subsequent coupling (catalysed by Li$_2$CuCl$_4$)[8] of the appropiate Grignard reagent with **4** afforded, in reasonable yield, the olefin **5**. After several attempts, the oxidation of the double bond was best achieved with KMnO$_4$, CH$_3$COOH (catalytic) conditions[9], which afforded the ketol **6**.

The key olefination step leading to the compound **7**, after several attemps with different reaction conditions, was best carried out with the appropriate phosphonate and LiOH in the presence of molecular sieves, as recently reported.[10] In these conditions, presumably, at first the esterification of the alcohol function occurs, followed by the Wittig intramolecular olefination which leads, in reasonable yield, to the target compound **7**. This compound was then deprotected to seiridin **1**, as was clearly demonstrated comparing its NMR, IR, UV and optical rotation data with those of natural **1** recorded in the same conditions.[11]

In conclusion, the short synthetic sequence illustrated, not only demonstrates the correct structure of the naturally occurring seiridin **1**, but also provides large quantities of this compound for further studies on its biological activity, also in relation to its role in the pathogenesis affecting cypress.

References and Notes

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7. Although the butenolide moiety is frequently encountered in natural products only few examples of 3,4 dialkyl substitution have been reported. Interestingly from the same fungi other two related $\Delta^{\alpha,\beta}$-butenolides have been recently isolated:(see ref. 4)
8. Byon, C.Y.; Gut, M. and Toome, V. , *J. Org. Chem.,* **1991**, *46*, 3901.
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11. Optical rotation value for synthetic 1: $[\alpha]_D$= - 7.8 (c= 3.85%, in CHCl$_3$); natural 1:$[\alpha]_D$ = - 7.5 (c= 0.96%, in CHCl$_3$).

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