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LETTERS

A Short Synthesis of α-Herbertenol featuring The Use of a Dihydropyranone as a 1,5-Diketone Synthon.

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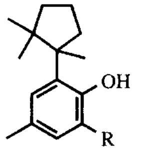
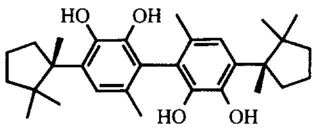
Abstract: The paper describes a short synthesis of α-herbertenol. Key features are the addition of dihyropyranone **5** to an aryllithium to give 1,5-diketone **7**; a titanium(0) mediated cyclisation of **7** to diol **8** and a sequential methylation of **8** to herbertenol methyl ether **9**. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Cyclisation; Diones; Lactones; Lithium and compounds; Natural products; Terpenes and terpenoids; Titanium and compounds.

α-Herbertenol **1**, an isocuparane sesquiterpene found in a wide variety of liverworts,[1-3] has attracted considerable attention due to its unusual structure and anti-fungal activity.[3-5] More recently, two related natural products, herbertenediol **2**[1,6] and mastigophorene A **3**,[7] have come to prominence due to their potent anti-lipid peroxidation activity and interesting neurotrofic properties (they accelerate neurite sprouting and network formation).[6,7] These factors, together with our interest in natural products containing aromatic ring systems,[8] led us to embark on a total synthesis programme directed towards the herbertanes. In this *Letter* we report a short, total synthesis of α-herbertenol **1** that features the use of a dihydropyranone as a 1,5-diketone synthon (Scheme 1).



1 R = H
2 R = OH



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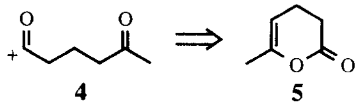

Scheme 1

Our synthesis of α-herbertenol began with the addition of dihydropyran **5** to a cooled, THF solution of the organolithium derived from **6**. Quenching the reaction with trimethylsilyl chloride after 15 min at -78°C, followed by an acidic work up, gave 1,5-diketone **7** in 77% yield. A low valent titanium induced intramolecular pinacolic coupling reaction then transformed **7** into diol **8**[9] which in turn was converted into α-herbertenol methyl ether **9** through exposure to dimethyltitanium dichloride.[10] Finally, deprotection of the phenol with boron tribromide[4] gave a synthetic sample of α-herbertenol **1** which displayed spectral characteristics identical to those reported for the natural product (Scheme 2).

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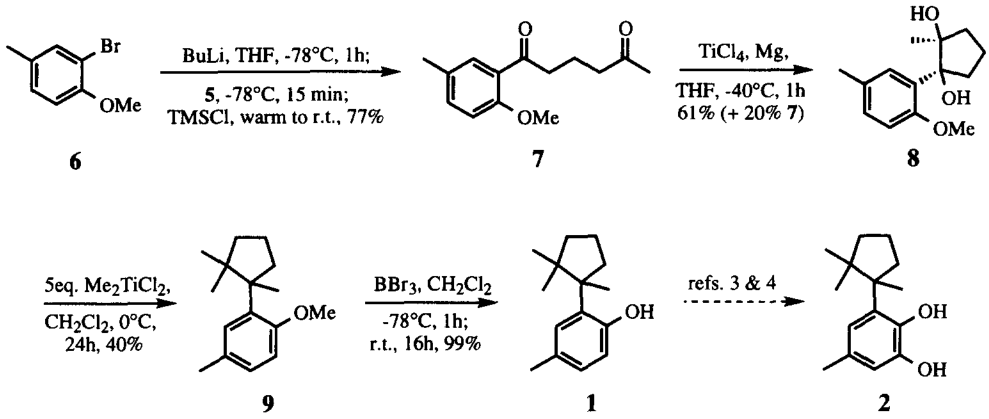

Scheme 2

In conclusion, we have developed a new strategy for the synthesis of 1,5-diketones involving the addition of a dihydropyranone to an organolithium reagent. The reaction has been used as a key step in a synthesis of the isocuparane natural product α-herbertenol **1**. Additionally, the work constitutes a formal total synthesis of herbertenediol **2** as this compound has been prepared by oxidation of α-herbertenol.[3,4] We are currently applying the methodology to a synthesis of mastigophorene A.

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