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SEQUENTIAL [2,3]WITTIG AND CLAISEN REARRANGEMENT: A FACILE SYNTHETIC METHOD FOR (\underline{e} , \underline{e})-4,7-ALKADIENALS AND -ALKADIENOIC ACIDS. A NEW FORMAL SYNTHESIS OF ($\underline{+}$)-CERULENIN

Koichi MIKAMI, Naoyuki KISHI, and Takeshi NAKAI*

Department of Chemical Technology, Tokyo Institute of Technology, Meguro-ku, Tokyo 152

The regioselective [2,3]Wittig rearrangement of bis-allylic ethers followed by the Claisen rearragement permits ready access to (\underline{E} , \underline{E})-4,7-alkadienals and -alkadienoic acids. The versatility of the sigmatropic sequence is demonstrated within the context of a new formal synthesis of (\pm)-cerulenin possessing an interesting spectrum of biological activities.

Recently we have found¹⁾ that the Wittig rearrangement of unsymmetrical bis-allylic ethers (1) proceeds exclusively in the [2,3]sigmatropic fashion and affords the single regioisomer of 1,5-dien-3-ols (2) arising from the exclusive lithiation on the less substituted allylic moiety as shown in Scheme I. To access further the synthetic utility of the genuine [2,3]Wittig rearrangement, we have developed²⁾ new sigmatropic sequences triggered by this rearrangement which include the tandem [2,3]Wittig-oxy-Cope sequence as depicted in Scheme I. Scheme I



In a continuation of these studies, we now wish to report another new sigmatropic sequence in which the [2,3]Wittig rearrangement is followed by the Claisen rearrangements (Scheme II). This sigmatropic sequence provides a very convenient method for the stereocontrolled synthesis of functionalized (<u>E</u>, <u>E</u>)-1,4-dienes which are frequently found in natural products and synthetic intermediates thereof.

In this work, 1,5-dien-3-ols (2) obtained via the [2,3]Wittig rearrangement of 1 were subjected to the three modifications of the Claisen rearrangement³⁾ to afford the 1,4-dienes



with different functionalities (Scheme II).⁴⁾ First, we found that the standard Claisen rearrangement⁵⁾ of 2 afforded the 4,7-alkadienal (3). Thus 2a was heated at 140°C in ethyl vinyl ether in the presence of mercury(II) acetate giving (\underline{E} , \underline{E})-4,7-nonadienal (3a) in 56% yield.⁶⁾ Secondly, the orthoester Claisen modification⁷⁾ of 2 yielded the alkadienoate (4). For example, a mixture of 2b and ethyl orthoacetate was heated at 140°C in the presence of propionic acid producing exclusively the (\underline{E} , \underline{E})-isomer of ethyl 4,7-tridecadienoate (4b) in 86% yield.⁸⁾ Thirdly, the acetate of 2 was subjected to the ester enolate Claisen modification⁹⁾ to yield the dienoic acid (5). Thus a solution of the acetate of 2c in THF was treated successively with lithium diisopropylamide and chlorotrimethylsilane at -78°C and the mixture was then heated at 70°C to afford, after hydrolysis, (\underline{E})-4,6-dimethyl-4,7-octadienoic acid (5c) in 79% yield.¹⁰

The present approach to functionalized 1,4-dienes offers several advantages, as compared with previous methods; ¹¹⁾(a) a broad variety of the starting ethers are easily available via the Williamson reaction using the phase transfer catalyst, (b) the procedure is operationally quite simple, (c) the geometry of the two olefinic bonds in the product can be fully controlled through the highly <u>E</u> selective [2,3]Wittig¹⁾ and the Claisen rearrangements,³⁾ and (d) the remarkable flexibility inherent in this approach permits the preparations of a variety of 1,4-dienes with different functionalities.

With the successful development of a facile route to functionalized (\underline{E} , \underline{E})-1,4-dienes, our efforts were next directed toward the total synthesis of cerulenin ($\underline{6}$) isolated from

Cephalosporium caerulens.¹²⁾ Cerulenin was shown to have both antibiotic and antifungal activity and to inhibit the biosynthesis of lipids and steroids.¹²⁾ Recent studies^{13a-c)} on the total synthesis of 6 have shown that (\underline{E} , \underline{E})-4,7-nonadienal (3a) (or the dienol) serves as the side-chain component which has been prepared via tedious, lengthy sequences of reactions starting with less accessible acetylenic alcohols. With a satisfactory quantity of 3a in hand, we set out to develop a new, more facile method for conversion of 3a to the butenolide \underline{Z} since \underline{Z} (or the epoxylactone) is the most widely used precursor of 6.¹³⁾ Scheme III outlines the newly developed sequence which relies primarily on the synthetic procedure recently reported by Uda and co-workers.¹⁴⁾



Dienal 3a was first converted to epoxide § in 88% yield¹⁵⁾ via the standard ylide procedure.¹⁶⁾ Then, § was added to a solution of the dilithium salt in THF generated from phenylthioacetic acid and lithium diisopropylamide (2 equiv) giving the hydroxy acid 9 which on warming in benzene closed to lactone 10 in 82% yield.¹⁷⁾ Oxidation of 10 with MCPBA at -78°C followed by thermolysis of the resulting sulfoxide in refluxing toluene furnished the desired butenolide \mathcal{I} in 76% yield.¹⁸⁾ Since \mathcal{I} has been elaborated to § in three simple steps,^{13a)} the synthesis of \mathcal{I} constitutes a new formal synthesis of (±)-cerulenin. Notably, the straightforward synthesis of \mathcal{I} , coupled with the easy availability of 3a, makes the overall process an attractive method of choice for the relatively large scale synthesis of (±)-cerulenin.





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