Total Synthesis of (±)-Kellermanoldione: Stepwise Cycloaddition of a Functionalized Diene and Allenoate

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ABSTRACT

The total synthesis of the diterpene kellermanoldione 1 is reported. Stepwise [4 + 2] cycloaddition of the ketal diene 8 and the allenoate 3 afforded the exo adduct 10x as the major product. It was converted into 1 via six steps, among them a key nonconjugative hydrolysis of a γ-methylene silyl enol ether.

Kellermanoldione 1 (Figure 1) is a labdane diterpene isolated from Brickellia kellermanii Grenm., a shrub which is reported to have potent antidiarrhetic properties and is used in Mexican folk medicine.1,2 No synthesis of this hydroxydione has appeared in the literature to date. Recently we reported the preparation of very hindered trimethyldecalin systems, involving a novel stepwise [4 + 2] cycloaddition of the very hindered diene 2 with the allene carboxylate 3 to give the [4 + 2] cycloadducts 4xn by a mechanism that proceeds via the cyclobutane 5, the initial [2 + 2] cycloadduct (Scheme 1).3 In addition, we have shown that certain labdane diterpenes lacking functionality in the A ring can be prepared using this exact cycloaddition, e.g., hedychilactone B.4 However, for this synthetic process to be generally useful it must be able to be performed with functional molecules since many di- and triterpenes have functionality in the A ring, usually oxygen at C3. We report here the total synthesis of 1 from the exo [4 + 2] cycloadduct 10x via a key nonconjugative hydrolysis of a γ-methylene silyl enol ether.

The required diene for the synthesis of these functionalized labdane diterpenes, the ketal silyl enol ether 8, was prepared by a direct route from 2,2,4-trimethylcyclohex-

Figure 1. Kellermanoldione.
ane-1,3-dione 6 via the known vinyl iodide 7 which has been used by Danishefsky in a synthesis of taxol derivatives (Scheme 2). The vinylolithium prepared from 7 was trapped with acetaldehyde and oxidized, and the silyl enol ether was prepared by the standard route to give the desired diene 8. Heating a neat mixture of the diene 8 with the allene carboxylate 3 (prepared in 64% yield by reaction of acetyl chloride with ethoxycarbonylmethylene phosphorane) at 110 °C for 14 days gave a separable mixture of three products, the [2 + 2] cycloadduct 9, the desired exo [4 + 2] cycloadduct 10x, and the endo adduct 10n in 7.2%, 26.5%, and 13.7% yield, respectively, with 32.4% of the recovered starting diene 8. The cyclobutane 9 could be converted into the same 2:1 ratio of 10x and 10n, resulting in a 39.2% overall yield of 10x based on recovered starting material.

The conversion of the adduct 10x into kellermanoldione 1 required two key steps, formation of the axial cyclo-

from methoxymethyltriphenylphosphonium iodide, prepared in two steps from methylal via reaction with trimethylsilyl iodide (TMSI) and triphenylphosphine, by reaction with n-butyllithium and addition of the aldehyde gave a mixture of stereoisomers of the enol methyl ether 14 in 51% yield. The exocyclic methylene remained untouched (Scheme 4). As expected, reduction of the decalone with DIBAL occurred from the less-hindered equatorial direction to give the desired axial alcohol 16 in quantitative yield. Very mild acidic hydrolysis of the methyl enol ether (aq. HCl in THF) afforded the keto aldehyde 17 in 84% yield. Attachment of the 3-furyl ketone unit to the side chain was all that was required to complete the synthesis. The 3-furyllithium species, prepared from commercially available 3-bromofuran, was added to the keto aldehyde 17 to afford chemoselectively the aldehyde adduct in fair yield. However, attempted selective oxidation of this benzylic alcohol using manganese dioxide proceeded rather poorly, and only very small amounts of kellermanoldione 1 could be obtained. Therefore we decided to examine a different sequence for the conversion of the key aldehyde 12 into the desired product 1.


We decided to reduce the number of steps of the synthesis and install the 3-furyl unit earlier. In particular, we wanted to see if the analogue of the enol ether 14 with the 3-furyl unit already in place could be prepared by an olefination process, since then that enol ether would not only serve as a protecting group for the aldehyde but also furnish the required 3-furyl ketone on hydrolysis. Since there were few examples of such enol ethers in the literature, we carried out some model studies (Scheme 5).

To the aldehydes 20ab was added diethyl phosphite\(^9\) followed by methylation of the alkoxide to give the methoxy phosphonates 21ab.\(^{10}\) Addition of benzaldehyde to the anion of 21ab afforded in good yield a mixture of the E and Z isomers of the methoxyalkenes 22ab which were hydrolyzed in good yields to the known ketones.

We then applied this route to the synthesis of kellermanoldione 1 (Scheme 6). Formation of the anion of the furyl methoxy phosphonate 21b with LDA and addition to the aldehyde 12 afforded the desired mixture of alkene stereoisomers 24EZ in 82% yield. Careful desilylation of the TBS enol ether using HF-pyridine at low temperature furnished the \(\beta,\gamma\)-unsaturated ketone 25 in 66% yield. No migration of the exocyclic double bond into the ring at either allylic position was observed. DIBAL reduction gave solely the axial alcohol as expected, and final hydrolysis of both the ketal and the enol ether afforded kellermanoldione 1 in 62% yield for the two steps. The spectroscopic data of the synthetic material, especially the proton and carbon NMRs, were identical to that reported in the literature for the natural product.\(^{1,11}\)

Thus, we have carried out the first total synthesis of the labdane diterpene kellermanoldione B 1 from the \([4 + 2]\) cycloadduct 10x formed in good yield via a stepwise cycloaddition of the functionalized very hindered diene 8 and the allenolate dienophile 3. The synthesis utilized a nonconjugative hydrolysis of a \(\gamma\)-methylene silyl enol ether and a novel introduction of the 3-furyl ketone unit. This is the first indication that functionalized trimethyldecalin systems can be prepared by this route using a stepwise \([4 + 2]\) cycloaddition. Further work on terpene synthesis is underway in our laboratories and will be reported in due course.


\(\text{(10) Compound 21a is known, while 21b is not. Roeschlaub, C. A.; Sammes, P. G. J. Chem. Soc., Perkin Trans. 2000, 1, 2243.}\)

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**Supporting Information Available:** Experimental procedures and proton and carbon NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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