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

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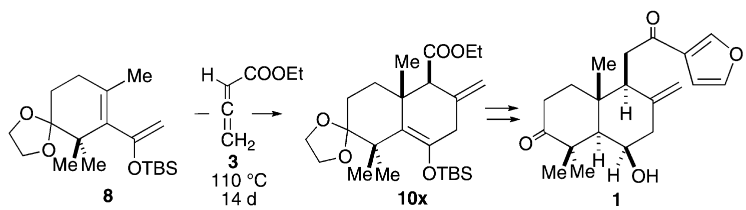
ABSTRACT



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.

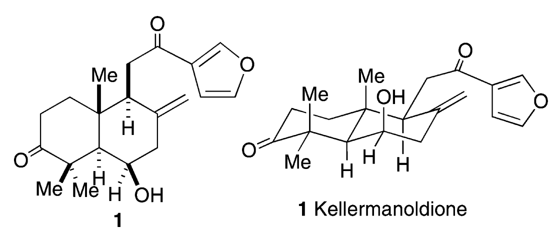


Figure 1. Kellermanoldione.

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-

(1) Ortega, A.; Salazar, I.; Gaviño, R.; Maldonado, E. *Phytochemistry* **1997**, *44*, 319.
(2) For recent syntheses of diterpenes, see: (a) Williams, D. R.; Walsh, M. J.; Miller, N. A. *J. Am. Chem. Soc.* **2009**, *131*, 9038. (b) Schnabel, C.; Hiersemann, M. *Org. Lett.* **2009**, *11*, 2555. (c) Boukouvalas, J.; Wang, J.-X. *Org. Lett.* **2008**, *10*, 3397. (d) Marcos, I. S.; Castaneda, L.; Basabe, P.; Diez, D.; Urones, J. G. *Tetrahedron* **2008**, *64*, 10860. (e) Aslaoui, J.; Li, H.; Morin, C. *Tetrahedron Lett.* **2005**, *46*, 1713.
(3) Jung, M. E.; Murakami, M. *Org. Lett.* **2006**, *8*, 5857.
(4) Jung, M. E.; Murakami, M. *Org. Lett.* **2007**, *9*, 461.

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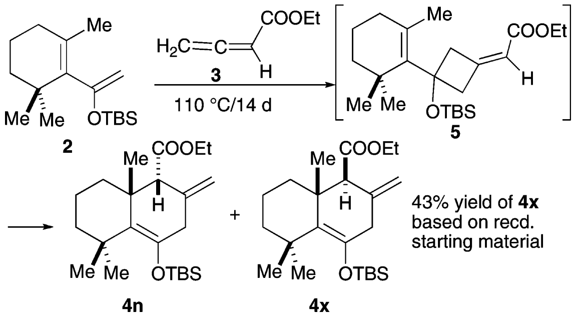
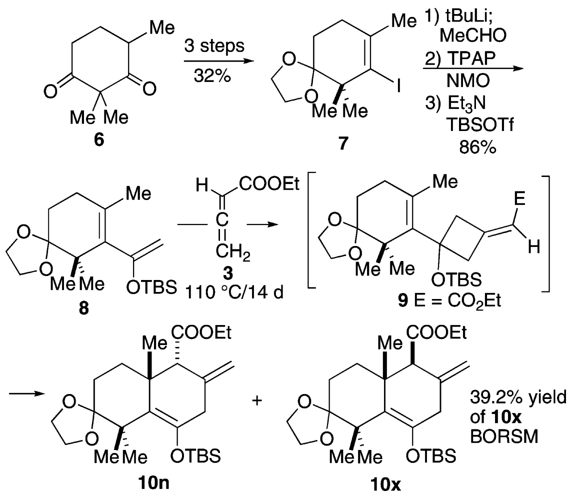
Scheme 1



ane-1,3-dione **6** via the known vinyl iodide **7** which has been used by Danishefsky in a synthesis of taxol derivatives[5] (Scheme 2). The vinyllithium prepared from **7** was

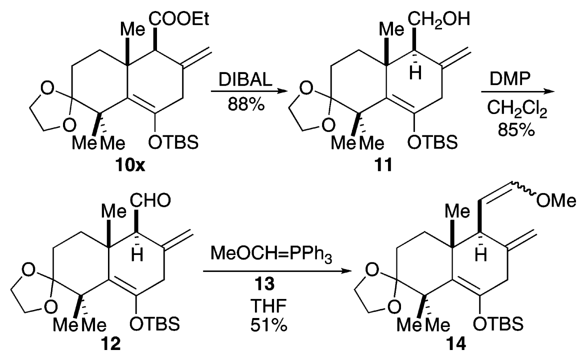
Scheme 2



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 ethoxycarbonylmethylenephosphorane)[6] 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 cyclohexanol without moving the exomethylene unit into the more stable endocyclic position and installation of the 3-furyl ketone. We used the same technique that had worked in our earlier synthesis of hedychilactone B;[3] namely, reduction of the ester of **10x** with DIBAL afforded in 88% yield the alcohol **11**, which was oxidized under Dess-Martin periodinane conditions to afford the aldehyde **7** in 85% yield (Scheme 3). Formation of the ylide **13**

Scheme 3

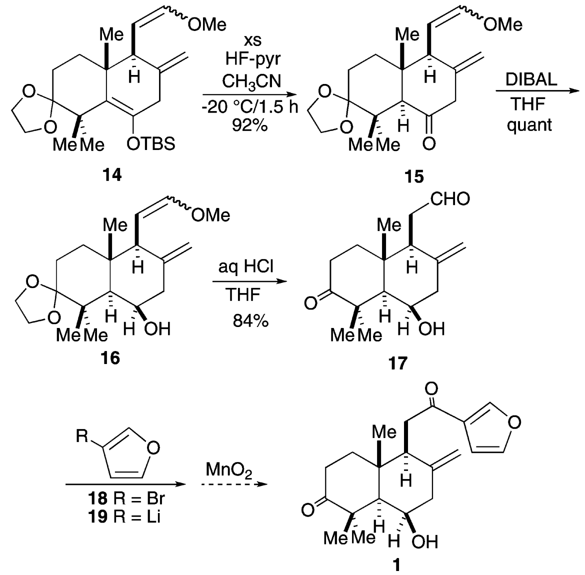


from methoxymethyltriphenylphosphonium iodide,[7] prepared in two steps from methylal via reaction with trimethylsilyl iodide (TMSI) and triphenylphosphine, by reaction with *n*-butyllithium and addition of the aldehyde gave a mixture of stereoisomers of the enol methyl ether **14** in 51% yield. The ketal functionality survived all of these transformations without any problems.

The key step of hydrolysis of the silyl enol ether without concomitant conjugation of the exocyclic methylene unit was effected by the use of conditions shown to work in our earlier system. Thus careful treatment of **14** with HF-pyridine in acetonitrile at low temperature afforded a 92% yield of the desired *trans*-decalone **15** in which 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,[8] 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**.

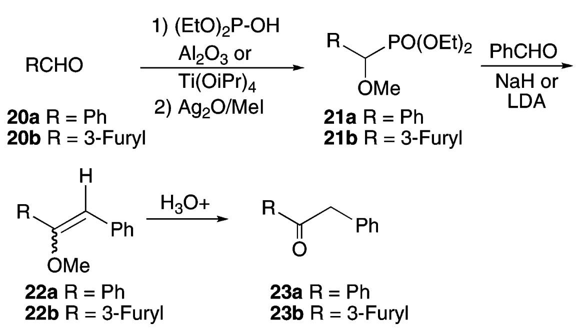
(5) Di Grandi, M. J.; Jung, D. K.; Krol, W. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 4989–92.
(6) Paik, Y. H.; Dowd, P. *J. Org. Chem.* **1986**, *51*, 2910.
(7) Jung, M. E.; Mazurek, M. A.; Lim, R. M. *Synthesis* **1978**, 588–90.
(8) (a) Collins, M. A.; Tanis, S. P. "3-Lithiofuran," e-EROS Encyclopedia of Reagents for Organic Synthesis (2001). (b) Chen, C.-L.; Sparks, S. M.; Martin, S. F. *J. Am. Chem. Soc.* **2006**, *128*, 13696.

Scheme 4



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).

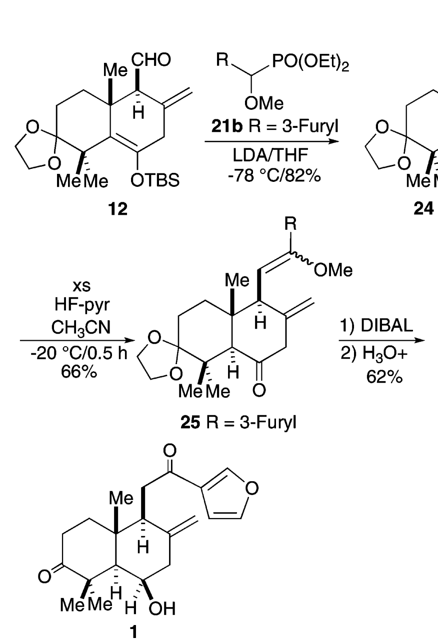
Scheme 5



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 **24*EZ*** in 82% yield. Careful desilylation of the TBS enol ether using HF-pyridine at low temperature furnished the β,γ-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]

Scheme 6



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 allenoate dienophile **3**. The synthesis utilized a nonconjugative hydrolysis of a γ-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.

(9) (a) Texier-Boullet, F.; Foucaud, A. *Synthesis* **1982**, 916. (b) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *J. Chem. Soc., Perkin Trans.* **1997**, *1*, 1527.

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

(11) We thank Professor E. Maldonado of the Universidad Nacional Autonoma de Mexico for providing the spectroscopic data.

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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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