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Synthesis of 3-alkyl-5-hydroxycyclohex-2-enones via aldolic addition/sulfinate elimination tandem reactions

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Abstract—The first synthesis of 3-alkyl-5-hydroxycyclohex-2-enones is reported. An intramolecular cyclization by means of an aldolic addition/sulfinate elimination tandem reactions, performed under mild basic conditions was the key step. © 2003 Elsevier Science Ltd. All rights reserved.

As a part of our work on the synthesis and biological evaluation of Bryophyte constituents,[1–3] we devoted chiefly to the preparation of prelunularin (**1**) (Fig. 1). This secondary metabolite isolated from *Ricciocarpos natans*,[4] showed a novel structural feature consisting of a 5-hydroxy-3-substituted-cyclohex-2-enone. Recently, Honda et al.[5] established the synthesis of 5-hydroxycyclohex-2-enone using an enantioselective deprotonation of a 1,3-*syn*-dihydroxy system as the key step, but none of the reported examples bore an alkyl group at the 3-position. Sato et al.[6] previously reported the synthesis of optically active 5-(tertbutyldimethylsiloxy)cyclohex-2-enone as well as its 6-substituted derivatives in eight steps with 17% overall yield.

Being a key intermediate in our synthesis of prelunularin, we embarked upon the synthesis of 3-alkyl-5-hydroxycyclohex-2-enones which, to the best of our knowledge, has not been reported in the literature.

The synthetic strategy was based on the formation of the α-sulfonylcarbanion derived from **4**[7] with *n*-butyllithium in anhydrous THF, followed by addition of the appropriated alkyl halides.[8,9] These alkylations provided the corresponding side chain at the 3-position of the target molecules. A second alkylation strategy proceeded in good-to-excellent yields using *t*-butyllithium and allyl bromide to obtain **6**. Further reductive ozonolysis of **6** afforded aldehyde **7**, which was unstable under standard acidic conditions required to perform the ketal deprotection. Using milder conditions (PPTS/acetone) we recovered only starting material. Therefore, we resorted to the protection of the carbonyl group with ethanedithiol in the presence of $BF_3{\cdot}Et_2O$. Interestingly, formation of the thioacetal proceed simultaneously with remotion of the ketal group to afford ketosulfone **8** according to Scheme 1. Treatment of **8** with $HgCl_2/CaCO_3$ in aqueous acetonitrile afforded ketoaldehydes **9**. The overall yield was 15 and 8% for **9a** and **9b**, respectively.

At this point we conceived compounds **9** as 'good holosynthons' (*holos* = global in Greek) according to Chanon's definition.[10] This concept focuses on a struc-

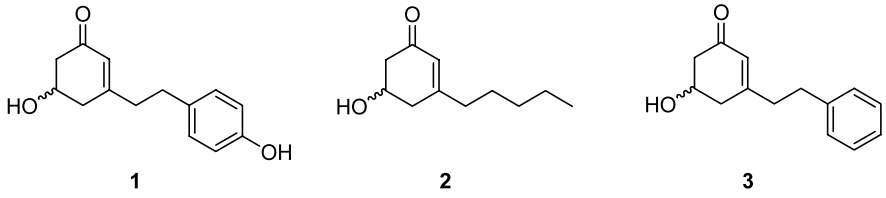

Figure 1. Structures of prelunularin **1** and analogs.

Keywords: 3-alkyl-5-hydroxycyclohex-2-enones; tandem reactions; prelunularin analogs.
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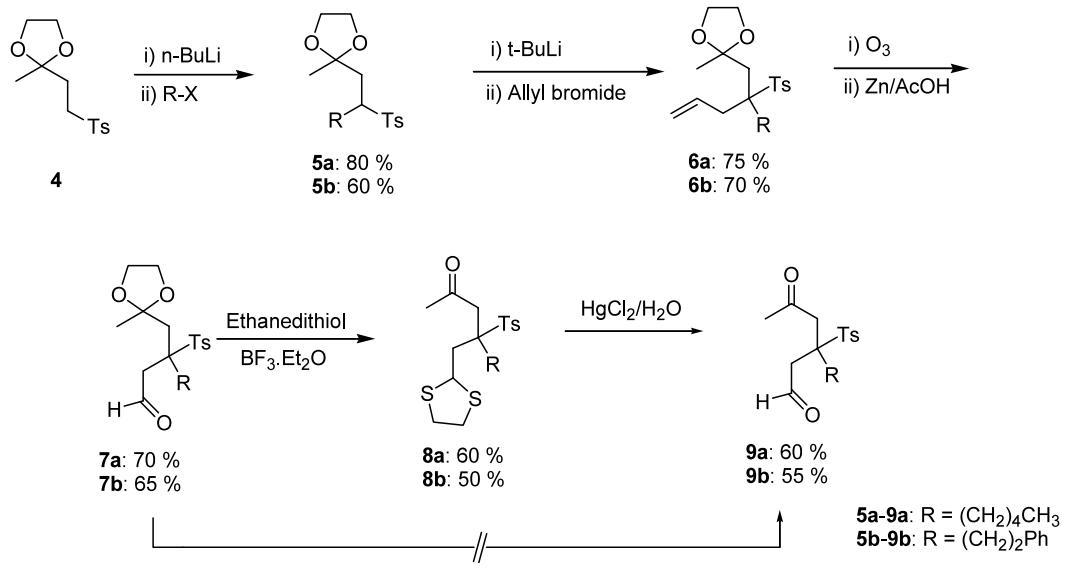
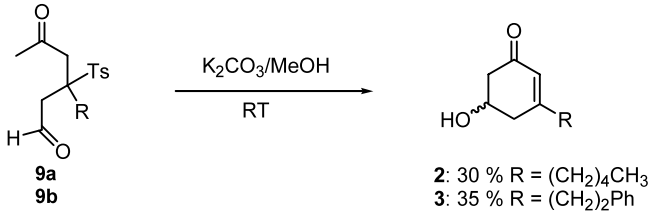


Scheme 1. Preparation of compound **9a** and **9b**.

tural entity specifically designed to make a major change of complexity and/or similarity possible in a one pot reaction.

The intramolecular cyclization was accomplished as shown in Scheme 2 by means of an aldolic addition/sulfinate elimination tandem reactions. The ketoaldehyde **9a** was dissolved in anhydrous methanol and treated with K_2CO_3 (1 equiv.) at room temperature for 5 h† to afford **2**[11] in 30% yield as a racemic mixture. We also isolated the corresponding 3-pentylphenol (15%) due to rapid aromatization of **2** under such conditions. We attempted to replace potassium carbonate by triethylamine at room temperature or LDA at −78°C in THF, but no reaction was observed. Using K_2CO_3, the ketoaldehyde **9b** afforded **3**[12] in 35% yield. In this case, the corresponding 3-phenetylphenol was not isolated.

In conclusion, we have prepared previously unreported 5-hydroxy-3-substituted-cyclohex-2-enones in six steps.



Scheme 2. Preparation of compound **2** and **3**.

† Preparation of **2** (or **3**): **9a** or **9b** (0.23 mmol) was dissolved in 8 mL of anhydrous methanol and potassium carbonate (0.46 mmol) was added. The mixture was stirred for 5 h at room temperature and poured onto 10 mL of water. The aqueous layer was extracted with ethyl acetate (3×20 mL). The combined extracts were washed with brine, dried over sodium sulfate and the solvent was removed under reduced pressure to give a yellow oil. The residue was purified by flash chromatography (silica gel, hexanes:ethyl acetate 4:6) to give **2** (or **3**) as a colorless oil.

This synthesis proved to be simple and efficient to produce the required structures. Currents efforts in our laboratory are directed to the total synthesis of prelunularin based on this procedure.

Acknowledgements

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11. Compound **2**: ^1H NMR ($CDCl_3$, 400 MHz) δ 5.95 (s, 1H), 4.31 (m, 1H), 2.70 (dd, $J=16.2$ Hz and $J=4.1$ Hz, 1H), 2.62 (dd, $J=17.6$ Hz and $J=4.4$ Hz, 1H), 2.47 (dd,

$J=16.2$ and $J=8.9$ Hz, 1H), 2.41 (dd, $J=17.6$ Hz and $J=7.3$ Hz, 1H), 2.26 (t, $J=7.5$ Hz, 2H), 1.54 (m, 2H), 1.33 (m, 4H), 0.92 (t, $J=6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.2, 163.2, 126.2, 67.3, 46.8, 38.9, 38.3, 31.7, 26.9, 22.7, 14.3.

12. Compound **3**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.97 (s, 1H), 4.31 (m, 1H), 2.86 (m, 2H), 2.70 (dd, $J=16.3$ Hz and $J=3.7$ Hz, 1H), 2.60 (m, 3H) 2.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.2, 161.9, 140.8, 129.0, 129.6, 126.8, 126.6, 67.1, 46.7, 39.9, 39.0, 33.6.