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Facile Synthesis of Allixin and Its Related Compounds

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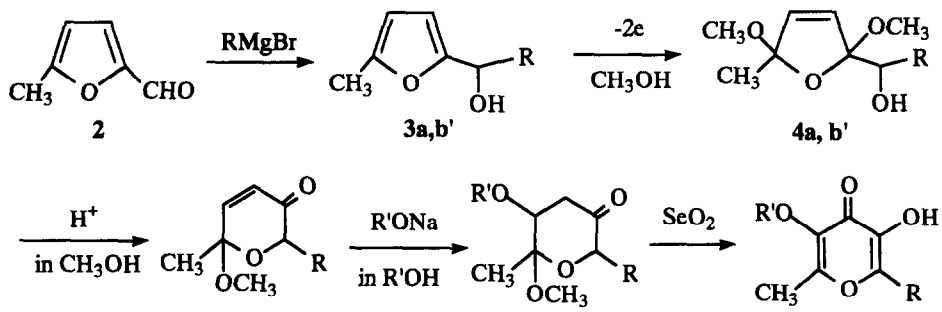
Abstract: Allixin was synthesized by a very convenient method which consisted of only five steps. The starting compound was 5-methylfurfural, and an electrochemical oxidation was involved as the key step in the method. © 1998 Elsevier Science Ltd. All rights reserved.

Allixin **1a**$_1$, 3-hydroxy-5-methoxy-6-methyl-2-pentyl-4*H*-pyran-4-one, is one of phytoalexins, first isolated from garlic by Kodera and Itakura *et al*,[1] and its activities such as antitumor effect have attracted much interest of many chemists.[2] However, a lack of synthetic methods for 2,6-dialkyl-3-hydroxy-5-methoxy-4*H*-pyran-4-ones might make it difficult to carry out a systematic study on a structure-activity relationship between the allixin related compounds and the activities. Our study has started from this viewpoint and succeeded in a synthesis of **1a**$_1$ and related compounds **1a**$_2$ and **1b**.[3] Our method is characterized by very short steps (*only 5 steps*) and the facile procedures. Although the yields at the last step has remained to be improved, we wish to describe herein our method preliminarily since there have recently been reported a total synthesis of **1a**$_1$ which consisted of 22 steps starting from D-mannose.[4]

Scheme 1 shows our method in which the starting compound was 5-methylfurfural **2**, a commercially available compound.



2 **3a,b'** **4a, b'** **5a, b'** **6a**$_1$, **a**$_2$, **b** **1a**$_1$, **a**$_2$, **b**

a : R=*n*-C_5H_{11} **b'** : R=*n*-C_4H_9

a$_1$: R=*n*-C_5H_{11}, R'=CH_3 **a**$_2$: R=*n*-C_5H_{11}, R'=C_2H_5 **b** : R=*n*-C_4H_9, R'=CH_3

Scheme 1

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A typical procedure is exemplified by a synthesis of **1a**$_1$ from **2**. At the first step was carried out an alkylation of **2** by a Grignard reagent. A solution of pentylmagnesium bromide in ether was added to **2** to afford **3a**. The second and third steps were key in our method. Electrochemical oxidation of **3a** in methanol containing NaBr afforded **4a**, which was transformed to **5a** by treating **3a** in methanol containing a catalytic amount of *p*-toluenesulfonic acid at rt. for 1 hr (**5a**; 82% yield from **2** without the isolation of **3a** and **4a**). The fourth and last steps were as follows. The Michael addition of methoxide anion to **5a** (1.5 equiv. $NaOCH_3/CH_3OH$ at rt. for 1.5hr) (66% yield) followed by the oxidation of the addition product **6a**$_1$ with selenium dioxide in toluene (refl. for 3h) yielded the desired allixin **1a**$_1$ (10% yield).[5] The overall yield was 5.4% (the overall yield in the method starting from mannose; 2.9%[6]). Also, allixin related compounds **1a**$_2$ and **1b** could be prepared by similar procedures. Those yields and ^{1}H NMR data at last three steps were described in references and notes 7 and 8.

In conclusion, our new method makes it possible to prepare a variety of 2,6-dialkyl-3-hydroxy-5-methoxy-4*H*-pyran-4-ones, which might be useful for investigation of structure-activity relationship of allixin related compounds. The improvement of yields at the last step and further synthesis of a variety of allixin derivatives are now under investigation.

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3. Our method is based on a maltol synthesis exploited by one of authors: Shono, T.; Matsumura, Y. *Tetrahedron Lett.* **1976**, 1363-1364.
4. a) Fischer, E.; Oetker, R. *Ber.* **1913**, *46*, 4029-4040. b) Nicolaou, K.C.; Hwang, C.-K.; Duggan, M.E. *J.Am.Chem.Soc.* **1989**, *111*, 6682-6690.
5. Many unidentified products were formed.
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7. **3b'**; 88% yield. **5b'**; 63% yield from **3b'**. **6b**; 23% yield. **1b**; 7% yield. **6a**$_2$; 20% yield. **1a**$_2$; 9% yield.
8. **5a**: ^{1}H NMR (300MHz, $CDCl_3$): δ 0.90 (t, 3H, *J*=6.6Hz), 1.21-1.49 (m, 6H), 1.52 (s, 3H), 1.57 -1.73 (m, 1H), 1.88-2.06 (m, 1H), 3.35 (s, 3H), 4.27 (dd, 1H, *J*=8.3, 3.5Hz), 6.00 (d, 1H, *J*= 10.1Hz), 6.75 (d, 1H, *J*=10.1Hz). **5b'**: ^{1}H NMR (200MHz, $CDCl_3$): δ 0.92 (t, 3H, *J*=6.5Hz), 1.20-1.80 (m, 5H), 1.53 (s, 3H), 1.90-2.07 (m, 1H), 3.35 (s, 3H), 4.27 (dd, 1H, *J*=8.0, 3.0Hz), 6.00 (d, 1H, *J*=10.0Hz), 6.76 (d, 1H, *J*=10.0Hz). **6a**$_1$: ^{1}H NMR (300MHz, $CDCl_3$): δ 0.88 (t, 3H, *J*=6.6Hz), 1.20- 1.65 (m, 7H), 1.44 (s, 3H), 1.70-1.90 (m, 1H), 2.61 (dd, 1H, *J*=15.9, 5.0Hz), 2.83 (dd, 1H, *J*=15.9, 3.9Hz), 3.35 (s, 3H), 3.39 (s, 3H), 3.50 (dd, 1H, *J*=5.0, 3.9Hz), 3.88 (dd, 1H, *J*=8.7,3.8Hz). **6a**$_2$: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J*=6.0Hz), 1.18 (t, 3H, *J*=7.0Hz), 1.22-1.68 (m, 7H), 1.44 (s, 3H), 1.74 -1.93 (m, 1H), 2.56 (dd, 1H, *J*=15.0, 7.0Hz), 2.80 (dd, 1H, *J*=15.0, 4.0Hz), 3.33 (s, 3H), 3.41-3.70 (m, 3H), 3.87 (dd, 1H, *J*=10.0, 4.0Hz). **6b**: ^{1}H NMR (300M Hz, $CDCl_3$): δ 0.90 (t, 3H, *J*=7.1Hz), 1.23-1.62 (m, 5H), 1.44 (s, 3H), 1.76-1.91 (m, 1H), 2.60 (dd, 1H, *J*=15.9, 5.0Hz), 2.82 (dd, 1H, *J*= 15.9, 3.6Hz), 3.34 (s, 3H), 3.39 (s, 3H), 3.50 (t, 3H, *J*= 3.6, 5.0Hz), 3.87 (dd, 1H, *J*=8.4, 3.9Hz). **1a**$_2$: ^{1}H NMR (300MHz, $CDCl_3$): δ 0.90 (t, 3H, *J*=6.6Hz), 1.08-1.41 (m, 4H), 1.34 (t, 3H, *J*=7.0 Hz), 1.59-1.73 (m, 2H), 2.33 (s, 3H), 2.67 (t, 2H, *J*=7.5Hz), 4.16 (q, 2H, *J*=7.0Hz), 6.24 (bs, 1H). **1b**: ^{1}H NMR (200MHz, $CDCl_3$): δ 0.95 (t, 3H, *J*=7.1Hz), 1.2-1.50 (m, 2H), 1.54-1.74 (m, 2H), 2.34 (s, 3H), 2.67 (t, 2H, *J*=7.5Hz), 3.88 (s, 3H), 6.36 (bs, 1H).