# Practical synthesis of mumefural, a component of Japanese apricot juice concentrate

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ABSTRACT

A practical four-step method for the synthesis of mumefural from malic acid is described. The key step of this method involves the alkylation of acetal-protected malic acid with bromoacetate, followed by condensation with 5-(hydroxymethyl)furfural. Some of the $^{13}$C NMR data for our products differed from those previously reported, and further analysis indicated that the previously reported assignments were partly erroneous.

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## 1. Introduction

Mumefural (**1**, see Fig. 1), a simple monoester of 5-(hydroxymethyl)furfural (HMF, **3**) and citric acid, is known to improve human blood fluidity.[1] It also exhibits potent multiple inhibitory effects on the pandemic influenza A (H1N1) virus.[2] It may be isolated from Japanese apricot juice concentrate as a racemate but is not detected in the fresh fruit, suggesting that it is produced artificially during the processing of the fruit. Suzuki et al. have been reported a thermal condensation process for the production of mumefural directly from fructose and citric acid;[2] however an appropriate synthetic route that could be employed to supply sufficient material for thorough biological screening has not yet been reported. Therefore, we herein report the development of a practical synthetic method for mumefural in consideration of the ability to perform on a gram-scale.
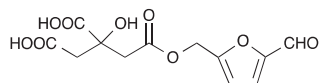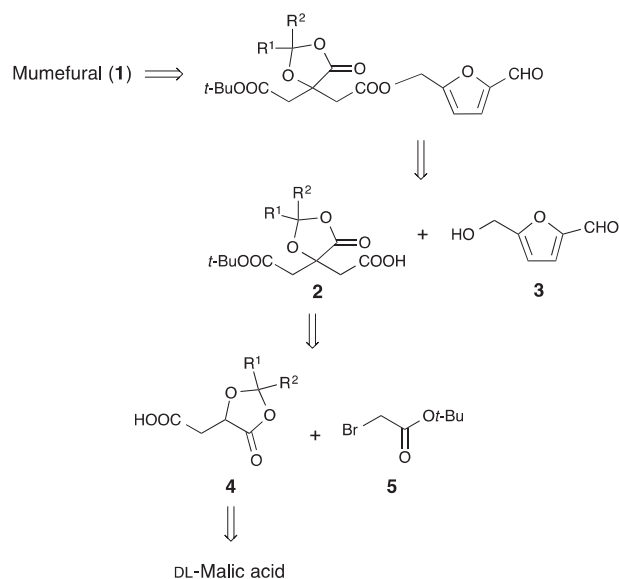


**Fig. 1.** Structure of mumefural (**1**).

Retrosynthetic analysis of mumefural suggested a route that proceeds via condensation of the appropriately protected citric acid derivative **2** and HMF (**3**), as shown in Scheme 1. The ester



**Scheme 1.** Retrosynthetic analysis of mumefural (**1**).

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linkage and acid-sensitive furan ring in mumefural require that the protecting groups in the citric acid moiety are removable under mild reaction conditions. As shown in the structure of **2**, cyclic acetal protection was used for the internal carboxylic acid and hydroxy groups, and *tert*-butyl ester protection was used for one of the terminal carboxylic acids because both these protecting groups can be removed under mildly acidic conditions without cleavage of the internal ester bond. The protected citric acid **2** is prepared through the α-alkylation of acetal-protected malic acid **4** with *t*-butyl bromoacetate (**5**) according to precedent studies by Tietze et al.[3] and Barrett et al.[4] Because mumefural is a racemic compound, inexpensive DL-malic acid was used as the starting material in this study. However, based on Seebach's concept of the self-regeneration of stereogenic centers,[5] optically active **4** may be prepared starting from D- or L-malic acid, facilitating an enantioselective synthesis of mumefural for future studies.

## 2. Results and discussion

Our investigation began with the preparation of two cyclic acetal-protected malic acids, **4a,b** based on previously reported procedures[6,7] (see Scheme 2). The conversion of **4a,b** into citrate derivatives **2a,b** was achieved by deprotonation with lithium hexamethyldisilazide in THF at −78 °C for 1 h. After addition of *t*-butyl bromoacetate, the temperature was raised to −10 °C over 3 h. These conditions, reported by Tietze et al.[3] as an improvement of the original procedure developed by Seebach,[8] afforded **2a,b** in moderate yields, and with high diastereoselectivity for **2b**.[9] Ester formation between citrate **2a,b** and HMF mediated by DCC afforded the protected mumefural **6a,b** in good yields.
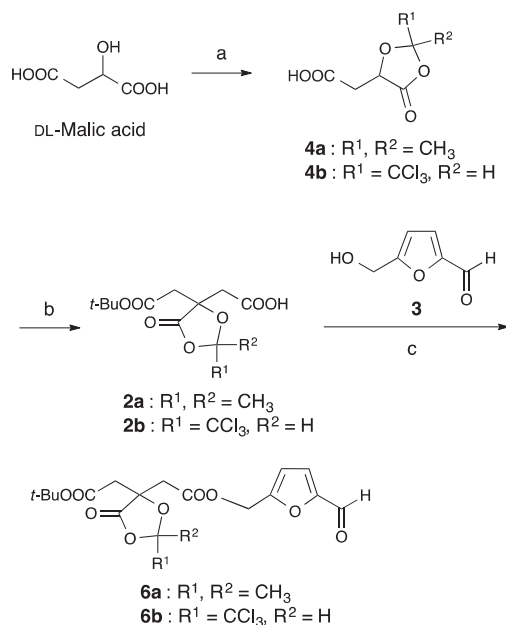


**Scheme 2.** Reagents and conditions: (a) Ref. 6 for **4a**, 84%; Ref. 7c for **4b**, 99% (*trans*:*cis*=6:1) (b) LiHMDS (2 equiv), THF, −78 °C, 1 h, then BrCH₂CO₂*t*-Bu to −10 °C, 3 h, 66% for **2a**, 58% for **2b** (as a single diastereomer) (c) **3** (1.2 equiv), DCC (1.1 equiv), DMAP (0.1 equiv), CH₂Cl₂, rt, 3 h, 69% for **6a**, 91% for **6b**.

Deprotection of compounds **6a,b** was then performed. Treatment of **6a** with 50% CF₃CO₂H in CH₂Cl₂ gave the terminal carboxylic acid **7a** in 90% yield. However, hydrolysis of the acetal protection from **7a** under a variety of both acidic and basic conditions resulted in the formation of HMF alone as an isolable product (Scheme 3). This

indicates that cleavage of the ester linkage between the citric moiety and HMF occurs preferentially over deprotection. Next, we attempted to remove the trichloroethylidene acetal of **6b** by treatment with zinc dust in an aqueous phosphate buffer, yielding β-elimination product **8** (Scheme 4). Removal of the dichlorovinyl ether moiety in compound **8** was attempted under several different acidic conditions, resulting in hydrolysis of the *t*-butyl ester alone. After several attempts at hydrolysis of **6b** under acidic or basic conditions, we found that treatment of **6b** with 50% CF₃CO₂H/CH₂Cl₂ at rt for 3 h followed by hydrolysis of the resultant cyclic acetal **7b** with aqueous 70% CH₃CO₂H at 100 °C for 16 h afforded mumefural in 68% yield (Scheme 5).
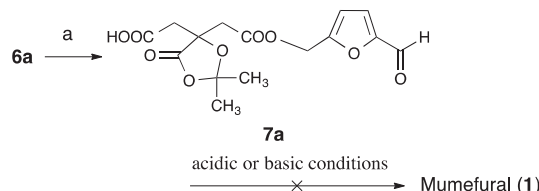


**Scheme 3.** Reagents and conditions: (a) 50% CF₃CO₂H/CH₂Cl₂, rt, 4 h, 92%.
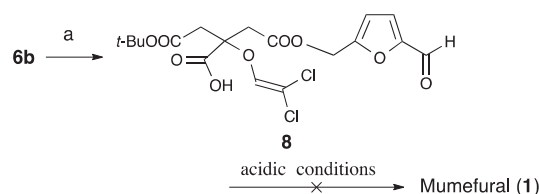


**Scheme 4.** Reagents and conditions: (a) Zn, THF/1 M KH₂PO₄ aq, rt, 3 h, 74%.
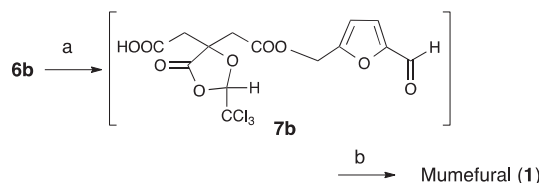


**Scheme 5.** Reagents and conditions: (a) 50% CF₃CO₂H/CH₂Cl₂, rt, 1 h (b) 70% CH₃CO₂H aq, 100 °C, 16 h, 68% from **6b** in two steps.

The ¹H NMR chemical shifts and coupling constants of our product perfectly matched the values reported for this compound by Chuda et al.; however, the ¹³C NMR chemical shifts do not match their reported values partly (see Table 1).[1] In our ¹³C NMR spectrum, there is no peak around 110.0 ppm; instead, there is a peak at 123.2 ppm. The well-established ¹³C NMR chemical shifts of HMF[10] are also shown in Table 1. In addition, the ¹³C NMR peaks of acetylated HMF (Ac-HMF, 5-acetoxymethyl-furfural) appear at 20.8 (Ac), 57.9, *112.7*, *121.8*, 153.0, 155.6, 170.5 (Ac), and 178.0 ppm,[11] revealing a high degree of similarity in the values for the HMF moieties in mumefural and Ac-HMF. These data indicate that 123.2 ppm is the correct chemical shift for C-3 and that 113.4 ppm is correct for C-4, not C-3. Thus, the C-3 and C-4 chemical shifts reported by Chuda et al. appear to be erroneous.

## 3. Conclusion

In conclusion, we achieved the total synthesis of mumefural in four steps and 35% overall yield from DL-malic acid via acetal **4b**. This synthetic route provides practical access to mumefural in the gram-scale quantities needed for thorough biological screening. In