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

Hideyuki Sugimura *, Mao Kikuchi, Saori Kato, Wataru Sekita, Ikuo Sasaki

*Department of Chemistry and Biological Science, College of Science and Engineering, Aoyama Gakuin University, 5-10-1, Fuchinobe, Chuo-ku, Sagamihara-shi, 252-5258, Japan*

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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.



## 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.

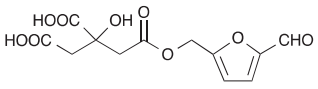
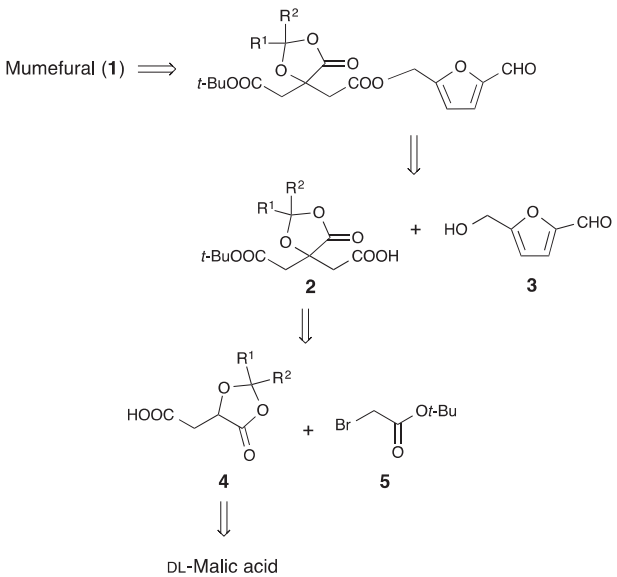



**Fig. 1.** Structure of mumefural (**1**).

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**).

* Corresponding author. E-mail address: sugimura@chem.aoyama.ac.jp (H. Sugimura).

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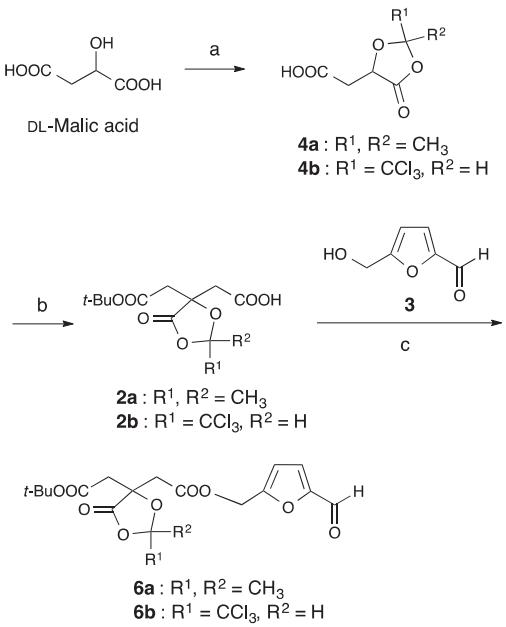
linkage and acid-sensitive furan ring in mumefural require that the protecting groups in the citric acid moiety are removable under mild reaction conditions. As shown in the structure of **2**, cyclic acetal protection was used for the internal carboxylic acid and hydroxy groups, and *tert*-butyl ester 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.

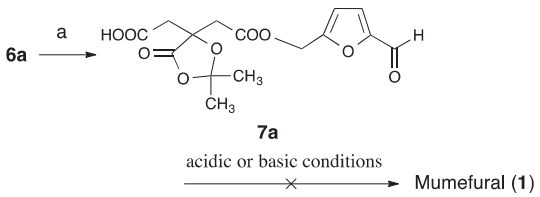
## 2. Results and discussion

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.

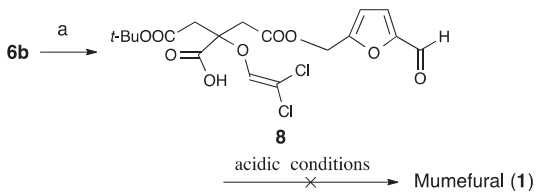



**Scheme 2.** Reagents and conditions: (a) Ref. 6 for **4a**, 84%; Ref. 7c for **4b**, 99% (*trans*:*cis*=6:1) (b) LiHMDS (2 equiv), THF, −78 °C, 1 h, then $BrCH_2CO_2t$-Bu to −10 °C, 3 h, 66% for **2a**, 58% for **2b** (as a single diastereomer) (c) **3** (1.2 equiv), DCC (1.1 equiv), DMAP (0.1 equiv), $CH_2Cl_2$, rt, 3 h, 69% for **6a**, 91% for **6b**.

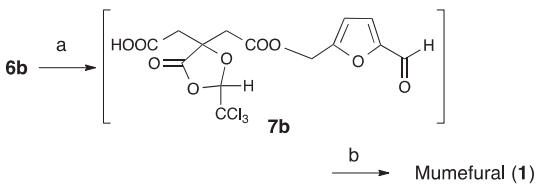
Deprotection of compounds **6a**,**b** was then performed. Treatment of **6a** with 50% $CF_3CO_2H$ in $CH_2Cl_2$ gave the terminal carboxylic acid **7a** in 90% yield. However, hydrolysis of the acetal protection from **7a** under a variety of both acidic and basic conditions resulted in the formation 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% $CF_3CO_2H/CH_2Cl_2$ at rt for 3 h followed by hydrolysis of the resultant cyclic acetal **7b** with aqueous 70% $CH_3CO_2H$ at 100 °C for 16 h afforded mumefural in 68% yield (Scheme 5).




**Scheme 3.** Reagents and conditions: (a) 50% $CF_3CO_2H/CH_2Cl_2$, rt, 4 h, 92%.




**Scheme 4.** Reagents and conditions: (a) Zn, THF/1 M $KH_2PO_4$ aq, rt, 3 h, 74%.




**Scheme 5.** Reagents and conditions: (a) 50% $CF_3CO_2H/CH_2Cl_2$, rt, 1 h (b) 70% $CH_3CO_2H$ 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 $^{13}C$ NMR chemical shifts do not match their reported values partly (see Table 1).[1] In our $^{13}C$ NMR spectrum, there is no peak around 110.0 ppm; instead, there is a peak at 123.2 ppm. The well-established $^{13}C$ NMR chemical shifts of HMF[10] are also shown in Table 1. In addition, the $^{13}C$ 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

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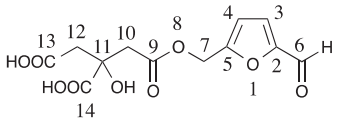
**Table 1**
Comparison of the $^{13}C$ NMR data for mumefural obtained in this work with those reported by Chuda et al.




| Position | Mumefural[a] | Mumefural (Ref. 1)[b] | HMF (Ref. 10)[c] |
|---|---|---|---|
| 2 | 153.9 | 154.0 | 152.1 |
| 3 | ***123.2*** | ***113.4*** | 122.7 |
| 4 | ***113.4*** | ***110.0*** | 109.9 |
| 5 | 156.3 | 156.4 | 160.4 |
| 6 | 178.6 | 178.5 | 177.4 |
| 7 | 58.6 | 58.6 | 57.6 |
| 10 | 43.2 | 43.2 | — |
| 11 | 73.7 | 73.5 | — |
| 12 | 43.5 | 43.5 | — |
| 13 | 171.7 | 171.5 | — |
| 14 | 174.8 | 174.7 | — |

[a] Recorded in acetone-$d_6$ at 125 MHz.
[b] Recorded in acetone-$d_6$ at 75 MHz.
[c] Recorded in $CDCl_3$ at 100 MHz.

addition, because of high diastereoselectivity observed in the alkylation of **2b**, enantiomerically pure mumefural will be obtained when D- or L-malic acid is used as the starting material. Moreover, because the mumefural exhibits significant pharmacological activity, the specific biological activities of optically active mumefural are of particular interest, and their synthesis is currently under investigation in our laboratory.

## 4. Experimental section

### 4.1. Materials and methods

All experiments were performed in well-dried glassware fitted with rubber septa under argon atmosphere. Solvents and commercially available chemicals were purified by standard methods or used as purchased. Analytical TLC was performed on silica gel plates 60 $F_{254}$ (Merck Co.). Flash column chromatography was performed on silica gel 60A (Kanto Co.). IR spectra were recorded on a JASCO FTIR-4100A spectrometer as thin film. NMR spectra were recorded on a JEOL JMN-500II spectrometer in $CDCl_3$ or acetone-$d_6$ with TMS as the internal standard. HRMS was obtained using a Thermo Scientific Exactive spectrometer (ESI).

### 4.2. 2-(4-(2-(*tert*-Butoxy)-2-oxoethyl)-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (2a)

To a solution of **4a**[6] (2.68 g, 15.4 mmol) in THF (150 mL) was added LiHMDS (32.2 mL, 32.2 mmol, 1.0 M in THF) dropwise over a period of 20 min at −78 °C and stirred for 1 h. After addition of *t*-butyl bromoacetate (4.5 mL, 31 mmol) over a period of 5 min, the temperature was raised to −10 °C over a period 3 h. The resulting solution was partitioned between EtOAc and 1 M HCl and extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (hexane:EtOAc=1:1) to give **2a** (2.92 g, 66%) as a yellow syrup. IR (neat) 3545, 3211, 2985, 1793, 1736, 1378, 1298, 1218, 1162, 936 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$=1.47 (s, 9H), 1.62 (s, 3H), 1.64 (s, 3H), 2.80 (d, *J*=10.0 Hz, 1H), 2.91 (d, *J*=16.0 Hz, 1H), 2.98 (d, *J*=16.0 Hz, 1H), 3.12 (d, *J*=16.9 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$=27.5, 27.7, 28.0, 41.2, 42.4, 77.7, 82.1, 111.1, 167.8, 172.6, 174.2; HRMS (ESI) *m/z* calcd for $C_{13}H_{20}O_7Na$ 311.1101, found $[M+Na]^+$ 311.1100.

### 4.3. 2-(4-(2-(*tert*-Butoxy)-2-oxoethyl)-5-oxo-2-(trichloromethyl)-1,3-dioxolan-4-yl)acetic acid (2b)

To a solution of **4b**[7c] (2.64 g, 10.0 mmol) in THF (100 mL) was added LiHMDS (21 mL, 21 mmol, 1.0 M in THF) dropwise over a period of 20 min at −78 °C and stirred for 1 h. After addition of *t*-butyl bromoacetate (2.2 mL, 15 mmol) over a period of 5 min, the temperature was raised to 0 °C over a period 3 h. The resulting solution was partitioned between EtOAc and 1 M HCl and extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (hexane:EtOAc=1:1) to give **2b** (2.19 g, 58%) as a yellow solid. IR (KBr) 3426, 2984, 2938, 1827, 1716, 1379, 1334, 1252, 1194, 1068, 856, 648, 632 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$=1.48 (s, 9H), 2.89 (d, *J*=16.0 Hz, 1H), 3.04 (d, *J*=17.8 Hz, 1H), 3.09 (d, *J*=16.0 Hz, 1H), 3.51 (d, *J*=17.8 Hz, 1H), 5.95 (s, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$=28.1, 41.2, 41.6, 78.8, 83.1, 96.3, 105.2, 168.8, 171.0, 172.9; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}O_7Cl_3Na$ 398.9776, found $[M+Na]^+$ 398.9777.

### 4.4. *tert*-Butyl 2-(4-(2-((5-formylfuran-2-yl)methoxy)-2-oxoethyl)-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)acetate (6a)

To a solution of **2a** (1.35 g, 4.7 mmol), 5-hydroxymethylfurfural (0.66 g, 5.2 mmol), and 4-dimethylaminopyridine (0.20 g, 1.64 mmol) in dichloromethane (20 mL) was added dicyclohexylcarbodiimide (1.06 g, 5.2 mmol) at rt and stirred for 3 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was extracted with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (hexane:EtOAc=3:1) to give **6a** (1.28 g, 69%) as a dark yellow syrup. IR (neat) 2983, 2941, 1795, 1739, 1684, 1526, 1377, 1226, 936 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$=1.46 (s, 9H), 1.58 (s, 3H), 1.62 (s, 3H), 2.79 (d, *J*=16.0 Hz, 1H), 2.91 (d, *J*=16.0 Hz, 1H), 2.92 (d, *J*=16.0 Hz, 1H), 3.13 (d, *J*=16.0 Hz, 1H), 5.17 (s, 2H), 6.61 (d, *J*=4.0 Hz, 1H), 7.21 (d, *J*=4.0 Hz, 1H), 9.65 (s, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$=27.6, 27.7, 28.0, 41.1, 42.4, 58.3, 77.8, 82.1, 111.0, 112.9, 121.7, 152.9, 154.7, 167.7, 168.2, 172.4, 177.8; HRMS (ESI) *m/z* calcd for $C_{19}H_{24}O_9Na$ 419.1313, found $[M+Na]^+$ 419.1311.

### 4.5. *tert*-Butyl 2-(4-(2-((5-formylfuran-2-yl)methoxy)-2-oxoethyl)-5-oxo-2-(trichloromethyl)-1,3-dioxolan-4-yl)acetate (6b)

To a solution of **2b** (2.10 g, 5.6 mmol), 5-hydroxymethylfurfural (0.85 g, 6.7 mmol), and 4-dimethylaminopyridine (54 mg, 0.44 mmol) in dichloromethane (30 mL) was added dicyclohexylcarbodiimide (1.26 g, 6.1 mmol) at rt and stirred for 3 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was extracted with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (hexane:EtOAc=2:1) to give **6b** (2.46 g, 91%) as a white solid. IR (neat) 2981, 2938, 1820, 1723, 1685, 1525, 1370, 1189, 1154, 1008, 822, 636 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$=1.47 (s, 9H), 2.86 (d, *J*=15.5 Hz, 1H), 3.01 (d, *J*=17.8 Hz, 1H), 3.05 (d, *J*=15.5 Hz, 1H), 3.48 (d, *J*=17.8 Hz, 1H), 5.16 (d, *J*=13.5 Hz, 1H), 5.22 (d, *J*=13.5 Hz, 1H), 5.91 (s, 1H), 6.61 (d, *J*=3.4 Hz, 1H), 7.20 (d, *J*=3.4 Hz, 1H), 9.64 (s, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$=28.1, 41.2, 41.6, 58.5, 78.8, 83.1, 96.3, 105.1, 113.0, 121.6, 153.0, 154.6, 167.2, 168.8, 170.9, 177.9; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}O_9Cl_3Na$ 506.9987, found $[M+Na]^+$ 506.9985.

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### 4.6. 2-(4-(2-((5-Formylfuran-2-yl)methoxy)-2-oxoethyl)-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (7a)

To a solution of **6a** (0.30 g, 0.67 mmol) in dichloromethane (1.8 mL) was added trifluoroacetic acid (1.8 mL) at 0 °C and stirred at rt for 4 h. After addition of toluene (20 mL), the solvents was removed under reduced pressure, and the residue was purified by column chromatography ($CHCl_3$: MeOH=19:1) to give **7a** (0.21 g, 92%) as a yellow syrup. IR (neat) 3523, 3004, 2941, 1793, 1740, 1682, 1389, 1291, 1224, 1127, 935 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$=1.59 (s, 3H), 1.61 (s, 3H), 2.93 (d, $J$=16.0 Hz, 1H), 2.95 (d, $J$=16.0 Hz, 1H), 3.10 (d, $J$=16.0 Hz, 1H), 3.15 (d, $J$=16.0 Hz, 1H), 5.18 (s, 2H), 6.62 (d, $J$=4.0 Hz, 1H), 7.22 (d, $J$=4.0 Hz, 1H), 9.64 (s, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$=27.6, 27.7, 41.0, 41.2, 58.4, 77.5, 111.5, 113.1, 121.9, 152.9, 154.7, 168.1, 172.2, 173.4, 178.0; HRMS (ESI) $m/z$ calcd for $C_{15}H_{16}O_9Na$ 363.0687, found $[M+Na]^+$ 363.0687.

### 4.7. 4-(*tert*-Butoxy)-2-((2,2-dichlorovinyl)oxy)-2-(2-((5-formylfuran-2-yl)methoxy)-2-oxoethyl)-4-oxobutanoic acid (8)

To a solution of **6b** (0.23 g, 0.47 mmol) in THF (1.6 mL) was added aqueous 1M $KH_2PO_4$ (0.32 mL) and zinc dust (0.31 g) at rt and stirred for 3 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography ($CHCl_3$:MeOH=9:1) to give **8** (0.16 g, 74%) as a dark yellow syrup. IR (neat) 3491, 2981, 2938, 1737, 1680, 1525, 1370, 1157, 966, 734 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$=1.45 (s, 9H), 2.94 (d, $J$=16.0 Hz, 1H), 3.09 (d, $J$=16.0 Hz, 1H), 3.11 (d, $J$=16.0 Hz, 1H), 3.20 (d, $J$=16.0 Hz, 1H), 5.16 (d, $J$=13.2, 1H), 5.20 (d, $J$=13.2 Hz, 1H), 6.62 (d, $J$=4.0 Hz, 1H), 6.96 (s, 1H), 7.24 (d, $J$=4.0 Hz, 1H), 9.61 (s, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$=28.0, 41.0, 42.1, 58.5, 80.9, 82.7, 108.2, 112.9, 122.4, 138.4, 152.8, 155.1, 168.6(×2), 168.8, 178.1; HRMS (ESI) $m/z$ calcd for $C_{18}H_{20}O_9Cl_2Na$ 473.0377, found $[M+Na]^+$ 473.0377.

### 4.8. Mumefural (1)

To a solution of **6b** (88 mg, 0.18 mmol) in $CH_2Cl_2$ (0.5 mL) was added $CF_3CO_2H$ (0.5 mL) at 0 °C. The reaction mixture was stirred at rt for 3 h. After the solvent was removed under reduced pressure, the residue was dissolved in aqueous 70% $CH_3CO_2H$ solution (1.8 mL). The resulting mixture was stirred at 100 °C for 16 h and concentrated under reduced pressure. The residue was purified by dry silica gel chromatography ($CHCl_3$:MeOH=19:1, $CHCl_3$:MeOH:$HCO_2H$=19:1:0.05 to 9:1:0.05) to give **1** (37 mg, 68%) as a dark brown syrup. IR (neat) 3427, 1737, 1673, 1525, 1405, 1199 $cm^{-1}$; $^1H$ NMR (500 MHz, acetone-$d_6$): $\delta$=2.87 (d, $J$=16.0 Hz, 1H), 2.93 (d, $J$=15.5 Hz, 1H), 2.96 (d, $J$=16.0 Hz, 1H), 3.01 (d, $J$=15.5 Hz, 1H), 5.19 (s, 2H), 6.76 (d, $J$=3.4 Hz, 1H), 7.40 (d, $J$=3.4 Hz, 1H), 9.64 (s, 1H); $^{13}C$ NMR (125 MHz, acetone-$d_6$): $\delta$=43.2, 43.5, 58.6, 73.6, 113.4, 123.2, 153.9, 156.3, 169.8, 171.7, 174.8, 178.5; HRMS (ESI) $m/z$ calcd for $C_{12}H_{12}O_9Na$ 323.0374, found $[M+Na]^+$ 323.0372.

*4.8.1. Gram-scale reaction.* To a solution of **6b** (2.58 g, 5.32 mmol) in $CH_2Cl_2$ (16 mL) was added $CF_3CO_2H$ (16 mL) at 0 °C. The reaction mixture was stirred at rt for 3 h. After the solvent was removed under reduced pressure, the residue was dissolved in aqueous 70% $CH_3CO_2H$ solution (50 mL). The resulting mixture was stirred at 100 °C for 16 h and concentrated under reduced pressure. The residue was purified by dry silica gel chromatography ($CHCl_3$:MeOH=19:1, $CHCl_3$:MeOH:$HCO_2H$=19:1:0.05 to 9:1:0.05) to give **1** (0.77 g, 49%) along with **7b** (1.02 g, 45%), which was again treated with aqueous 70% $CH_3CO_2H$ in the same manner above to give **1** (0.33 g). Thus, **1** was obtained in total 1.10 g (69% yield).

## Acknowledgements

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## Supplementary data

Supplementary data (copies of $^1H$ and $^{13}C$ NMR spectra of compounds **2a**, **2b**, **6a**, **6b**, and **1**) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.10.026.

## References and notes

1. Chuda, Y.; Ono, H.; Ohnishi-Kameyama, M.; Matsumoto, K.; Nagata, T.; Kikuchi, Y. *J. Agric. Food Chem.* **1999**, *47*, 828–831.
2. Sriwilaijaroen, N.; Kadowaki, A.; Onishi, Y.; Gato, N.; Ujike, M.; Odagiri, T.; Tashiro, M.; Suzuki, Y. *Food Chem.* **2011**, *127*, 1–9.
3. El Bialy, S. A. A.; Braun, H.; Tietze, L. F. *Eur. J. Org. Chem.* **2005**, 2965–2972.
4. Goldup, S. M.; Pilkington, C. J.; White, A. J. P.; Burton, A.; Barrett, A. G. M. *J. Org. Chem.* **2006**, *71*, 6185–6191.
5. For a review, see: Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 2708–2748.
6. Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2004**, *126*, 12432–12440.
7. (a) Shih, H.; Rankin, G. O. *Synthesis* **1989**, 866–867; (b) Rankin, G. O.; Sun, H.; McCain, B.; Hubbard, J. L.; Chai, M. *Synthesis* **2002**, 2165–2167; (c) Fujimoto, Y.; Ukita, T.; Miyagawa, H.; Tsurushima, T.; Irie, H.; Nishimura, K.; Ueno, T. *Biosci. Biotechnol. Biochem.* **1994**, *58*, 1627–1631.
8. Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313–1324.
9. Attempt to determine the relative stereochemistry of **2b** by direct spectroscopic analysis using NOESY experiments provided inconclusive results. The confirmation of the stereochemistry through derivatization of **2b** and the application to the enantioselective synthesis will be the subject of a future publication.
10. Wei, Z.; Liu, Y.; Thushara, D.; Ren, Q. *Green Chem.* **2012**, *14*, 1220–1226.
11. Coelho, J. A. S.; Trindade, A. F.; André, V.; Duarte, M. T.; Veiros, L. F.; Afonso, C. A. M. *Org. Biomol. Chem.* **2014**, *12*, 9324–9328.