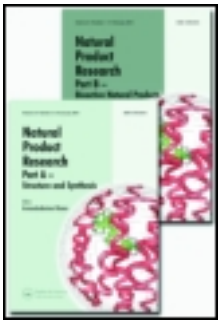

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# Total synthesis of the natural succinate derivative of 5-(hydroxymethyl)furfural isolated from the Noni fruit (*Morinda citrifolia*)

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Three alternative synthetic routes for the synthesis of naturally occurring *n*-butyl (5-formylfuran-2-yl)methyl succinate (**1**) are described. One of them started from furfuryl alcohol (**4**), and the other two synthetic strategies started from 5-(hydroxymethyl)furfural (**6**), which could be readily obtained from D-fructose. One of the latter involved a two-step reaction sequence: esterification of **6** with succinic anhydride (**5**) and esterification of the resultant *mono*-succinate **2** with *n*-butyl bromide, to give **1** in 85% overall yield. The second, a one-pot two-step synthesis, consisted of treating **6** with **5** followed by the addition of *n*-butyl bromide to afford the desired natural product **1** in 85% yield.

**Keywords:** *n*-butyl (5-formylfuran-2-yl)methyl succinate; 5-(hydroxymethyl)furfural; D-fructose; succinic anhydride; *Morinda citrifolia* L.

## 1. Introduction

A broad range curative potential has been attributed to *Morinda citrifolia* L. (Wang et al., 2002), commonly known as Noni fruit, in oriental traditional and folk medicine, including therapeutic effects such as analgaesic, antimicrobial, antifungal, anti-inflammatory, antioxidant, antitumour, antiviral, anthelmintic, hypotensive, and immunomodulator effects, among others (Pak-Dek, Abdul-Hamid, Osman, & Soh, 2008; Wang, Anderson, Nowicki, & Jensen, 2008; Wang et al., 2002; Zhang, Wei, Shi, & Liu, 2007). It has been reported that Noni fruit juice inhibits tumour growth by immune system stimulation (Hirazumi & Furusawa, 1999), and extends the life of mice into which a Lewis pulmonary carcinoma has been implanted (Hirazumi, Furusawa, Chou, & Hokama, 1994). The nutritional value of Noni fruit juice has also been well documented (Bui, Bacic, & Pettolino, 2006; West, Tolson, Vest, Jensen, & Lundell, 2006). Phytochemical studies of this fruit have revealed the presence of many metabolites, including coumarins, flavones, iridoids, polysaccharides, anthraquinones and phenolic compounds, exhibiting potent pharmacological effects (Deng et al., 2007; Kamiya et al., 2008; Pawlus & Kinghorn, 2008; Potterat & Hamburger, 2007). Recently, new compounds have been isolated and structurally characterised (Lin, Ni, Huang, Sheu, & Chen, 2007; Siddiqui, Sattar,

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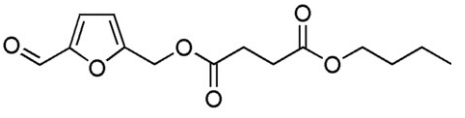
Begum, Gulzar, & Ahmad, 2007; Takashima et al., 2007; West & Zhou, 2008), among them the furan derivative *n*-butyl (5-formylfuran-2-yl)methyl succinate (**1**) (Samoylenko et al., 2006). Owing to its potential biological activity and its use as a chemical marker to control the quality of the commercial juice of the Noni fruit (Samoylenko et al., 2006), an effective and short synthesis of **1** is highly desirable. Therefore, a synthetic study of **1** is described herein, in which three approaches have been developed.



**1**

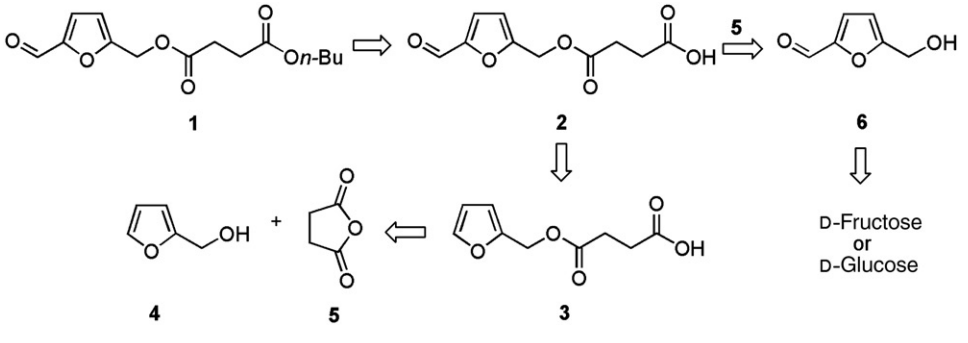


## 2. Results and discussion

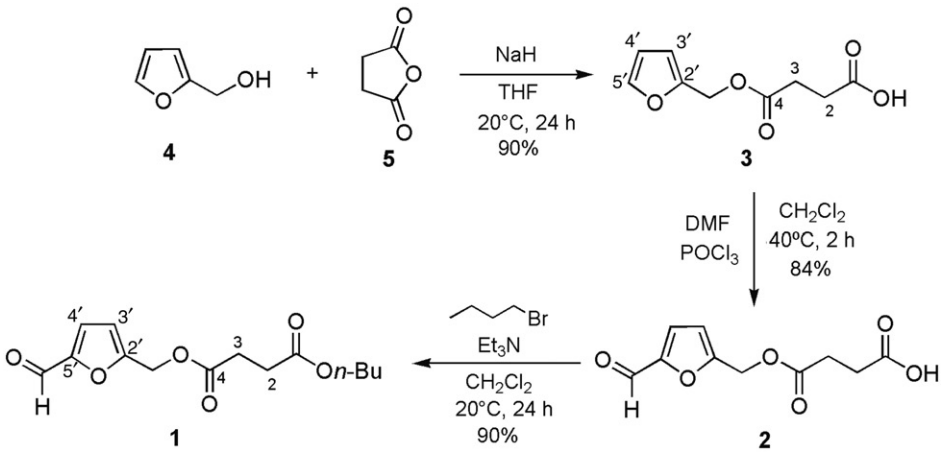
A retrosynthetic analysis of the preparation of **1** is depicted in Scheme 1. The last step of any of the possible routes involved the esterification of the key precursor **2** with the proper alcohol or alkyl halide. The first approach was considered to reach compound **2** by a formylation of the furan derivative **3**, which in turn may be obtained by an esterification reaction between furfuryl alcohol (**4**) and succinic anhydride (**5**). For the second approach, the key starting material might be 5-(hydroxymethyl)furfural (**6**), which by treatment with **5** may furnish *mono*-succinate **2**. A third and shorter pathway may be carried out: the transformation of **6** into **1** in a single reaction, without isolation of **2**.

The first synthesis was started by the esterification of furfuryl alcohol (**4**) with succinic anhydride (**5**) under mild basic conditions (NaH, 20°C, 24 h) to give ester **3** in good yield (90%) (Scheme 2). Upon formylation of the latter under Vilsmeier–Haack reaction conditions, furancarboxylic acid **2** was obtained in 84% (Garber, Jones, & Robinson, 1961; Ono, Tadata, Harumi, & Isshiki, 1999). Although the preparation of **1** was carried out by acid-catalysed esterification in the presence of *n*-butyl alcohol, the yield was low (52%). A better procedure consisted of the treatment of **2** with 1-bromobutane, promoted by triethylamine at room temperature, to afford the desired natural product in 90% yield.

Recently, we have described the synthesis of furan natural compounds rehmanones A–C through several routes, including that which starts from **6** (Quiroz-Florentino, Aguilar, Santoyo, Díaz, & Tamariz, 2008). The latter is a natural metabolite isolated from *Gastrodia elata*, which shows significant anti-platelet activity (Pyo, Jin, Koo,




Scheme 1. Retrosynthetic analysis of *n*-butyl (5-formylfuran-2-yl)methyl succinate (**1**).




Scheme 2. Synthetic approach to **1** starting from furfuryl alcohol (**4**).

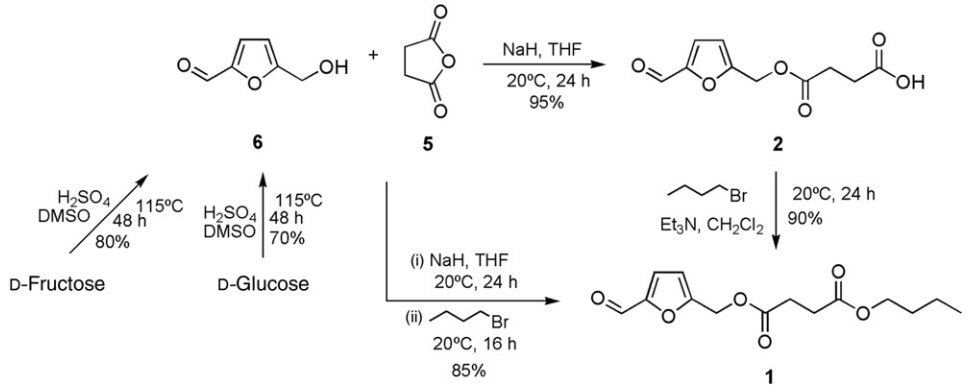


& Yun-Choi, 2004). It has also recently attracted strong and deep interest for its value as a natural versatile and key synthon in fine-chemical industry (Taarning, Nielsen, Egeblad, Madsen, & Christensen, 2007), and mainly as a promising precursor to produce biomass-derived automotive fuels, as a renewable energy source, and an industrial chemical feedstock (Kamm, 2007; Mascal & Nikitin, 2008; Román-Leshkov, Barrett, Liu, & Dumesic, 2007; Yong, Zhang, & Ying, 2008). It has been efficiently prepared in a single step by acidic treatment of D-fructose (Halliday, Young, & Grushin, 2003). We have found that in the reaction of the latter with sulphuric acid in DMSO at 110°C for 48 h, the furfural compound **6** is obtained in 68% yield (Quiroz-Florentino et al., 2008). However, we herein optimised this method by slightly increasing the temperature (115°C) and keeping the same reaction conditions to afford **6** in 80% yield (Scheme 3). Moreover, **6** rose in 70% yield by treating D-glucose, as the starting carbohydrate (Goswami, Dey, & Jana, 2008), with a solution of 10 mol% of sulphuric acid in DMSO (115°C, 48 h).

Once having the furfural moiety of the target molecule in our hands, its conversion into the natural product took place through a sequence of two steps, under similar conditions to the previous approach. Thus, the reaction of **6** with succinic anhydride (**5**) in the presence of sodium hydride provided the mono-ester acid derivative (**2**) in excellent yield (95%) (Scheme 3), which by treatment with 1-bromobutane and triethylamine furnished the desired product (**1**) in 90% yield.

In spite of the fact that compound **1** was prepared in fairly good overall yield (68%) starting from D-fructose, we decided to improve the strategy by shortening the conversion of **6** into **1** in a one-pot two-step procedure. Thus, after performing the reaction between **5** and **6** under identical conditions as shown in Scheme 3, a solution of 1-bromobutane was added to the reaction mixture, which was maintained under stirring at room temperature for 24 h to give **1** in 85% yield (Scheme 3). Although this second synthetic pathway provided an identical overall yield (starting from D-fructose) of **1** (68%) to that of the previous route, the methodology was shortened and the workup was simplified.

Structures of the intermediates **2** and **3** and final product **1** were characterised by NMR spectroscopy, high-resolution mass spectrometry or elemental analysis. The recorded spectral data for **1** are in agreement with those reported for the natural product (Samoylenko et al., 2006).




Scheme 3. Synthetic approaches to **1** starting from D-fructose or D-glucose.



In summary, we have described an efficient total synthesis of *n*-butyl (5-formylfuran-2-yl) methyl succinate (**1**) through a mono-esterification of furan derivative **6** with succinic anhydride (**5**), followed by a second esterification with 1-bromobutane. A shorter strategy was developed by doing both esterifications in a single step in a high overall yield. In addition, a longer but also efficient alternative synthetic pathway of **1** was also described, via the preparation of furan carboxylic acid **3**, starting from furfuryl alcohol (**4**), followed by formylation and final esterification, to afford compound **1** in three steps and a 68% overall yield.

## 3. Experimental section

Melting points (uncorrected) were determined with an Electrothermal capillary melting point apparatus. IR spectra were recorded on a Perkin–Elmer 2000 spectrophotometer. $^{1}H$ and $^{13}C$ NMR spectra were recorded on Varian Mercury (300 MHz) and Varian VNMR System (500 MHz) NMR instruments, with $CDCl_3$ as the solvent and TMS as internal standard. High-resolution mass spectra (HRMS) were obtained in electron impact (EI) (70 eV) mode on a Jeol JSM-GCMate II spectrometer. Microanalyses were performed by M-H-W Laboratories (Phoenix, AZ). Analytical TLC was carried out using E. Merck silica gel 60 $F_{254}$ coated 0.25 plates, visualised by a long- and short-wavelength UV lamp. Flash column chromatography was performed over Natland International Co. silica gel (230–400 mesh). All air moisture sensitive reactions were carried out under $N_2$ using oven-dried glassware. THF was freshly distilled over sodium, and $CH_2Cl_2$ over $CaH_2$, prior to use. DMSO was not dried. $Et_3N$ was freshly distilled from NaOH. All other reagents were used without further purification.

### 3.1. *Procedures*

#### 3.1.1. *4-[(Furan-2′-yl)methoxy]-4-oxobutanoic acid (**3**)*

To a stirred solution of **4** (0.51 g, 5.2 mmol) in anhydrous THF (6 mL) at 0°C under $N_2$, NaH (0.15 g, 6.25 mmol) was added. The reaction mixture was stirred for 20 min at 4°C, then succinic anhydride (**5**) (1.04 g, 10.4 mmol) was added in one portion and the stirring was continued at room temperature for 24 h. The solvent was removed under vacuum and

the residue was dissolved with $CH_2Cl_2$ (40 mL) and washed with water (2 × 40 mL). The organic layer was dried ($Na_2SO_4$) and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (32 g, hexane/EtOAc, 7 : 3) to give 0.93 g (90%) of **3** as a colourless oil. $R_f$ 0.29 (hexane : EtOAc, 6 : 4); IR (film): $\nu_{max}$ 3800–2290, 1738, 1714, 1503, 1410, 1380, 1349, 1229, 1164, 1016, 998, 919, 823, 750 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 2.62–2.71 (m, 4H, $CH_2CH_2CO_2H$), 5.02 (s, 2H, $CH_2O$), 6.36 (dd, $J = 3.5$, 2.0 Hz, 1H, H-3′), 6.41 (dd, $J = 3.5$, 1.0 Hz, 1H, H-4′), 7.42 (dd, $J = 2.0$, 1.0 Hz, 1H, H-5′); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 28.7 ($CH_2CO_2$), 28.8 ($CH_2CO_2$), 58.4 ($CH_2O$), 110.5 (C-3′ or C-4′), 110.7 (C-4′ or C-3′), 143.3 (C-5′), 149.2 (C-2′), 171.8 ($O_2C$-1), 178.1 ($O_2C$-4); HRMS (EI, $[M]^+$) $m/z$ Anal. Calcd for $C_9H_{10}O_5$: 198.0528; found: 198.0528.

### 3.1.2. *5-(Hydroxymethyl)furan-2-carbaldehyde (**6**)*

3.1.2.1. *Method A*. A solution of D-fructose (1.0 g, 5.6 mmol) in DMSO (5 mL) and concentrated (98%) $H_2SO_4$ (0.055 g, 0.56 mmol) was stirred at 20°C for 30 min. The flask was provided with a Dean–Stark trap and a condenser, the mixture was heated at 115°C for 48 h, diluted with EtOAc (20 mL) and stirred at 20°C for 20 min. The mixture was filtered over Celite, and the solvent was removed under high vacuum. The residue was purified by column chromatography over silica gel (30 g, hexane : EtOAc, 7 : 3), to give 0.56 g (80%) of **6** as a pale yellow oil (Quiroz-Florentino et al., 2008).

3.1.2.2. *Method B*. A solution of D-glucose (1.0 g, 5.6 mmol) in DMSO (5 mL) and concentrated (98%) $H_2SO_4$ (0.055 g, 0.56 mmol) was stirred at 20°C for 30 min. The flask was provided with a Dean–Stark trap and a condenser, the mixture was heated at 115°C for 48 h, diluted with EtOAc (20 mL) and stirred at 20°C for 20 min. The mixture was filtered over Celite, and the solvent was removed under high vacuum. The residue was purified by column chromatography over silica gel (30 g, hexane : EtOAc, 7 : 3), to give 0.49 g (70%) of **6** as a pale yellow oil. $R_f$ 0.31 (hexane : EtOAc, 1 : 1).

### 3.1.3. *4-[(5′-Formylfuran-2′-yl)methoxy]-4-oxobutanoic acid (**2**)*

3.1.3.1. *Method A*. A solution of dry DMF (0.22 g, 3.01 mmol) and $POCl_3$ (0.461 g, 3.03 mmol) in dry $CH_2Cl_2$ (1 mL) was stirred at 0°C for 30 min, then at room temperature for 20 min under $N_2$. To this mixture, **3** (0.50 g, 2.53 mmol) in dry $CH_2Cl_2$ (4 mL) was added dropwise. The mixture was stirred at 40°C for 2 h, diluted with $CH_2Cl_2$ (40 mL) and $H_2O$ (20 mL) was added, then a 2.0 M aqueous solution of NaOH was added dropwise till it becomes neutral. The organic layer was washed with $H_2O$ (2 × 20 mL), dried ($Na_2SO_4$), and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (30 g, hexane : EtOAc, 8 : 2), to give 0.48 g (84%) of **2** as colourless amorphous crystals.

3.1.3.2. *Method B*. To a stirred solution of **6** (0.66 g, 5.24 mmol) in dry THF (6 mL) at 0°C under $N_2$, NaH (0.15 g, 6.25 mmol) was added. The reaction mixture was stirred at 4°C for 20 min, then succinic anhydride (1.04 g, 10.4 mmol) was added in one portion and the stirring was continued at room temperature for 24 h. The solvent was removed under vacuum, and the residue was dissolved with $CH_2Cl_2$ (40 mL) and washed with water

($2 \times 40$ mL). The organic layer was dried ($Na_2SO_4$) and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (32 g, hexane : EtOAc, 7 : 3), to give 1.13 g (95%) of **2** as colourless amorphous crystals. M.p. 84–85°C; $R_f$ 0.25 (hexane : EtOAc, 6 : 4); IR (film): $\nu_{max}$ 3330–2550, 1731, 1699, 1674, 1533, 1407, 1344, 1258, 1233, 1208, 1169, 940 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 2.66–2.73 (m, 4H, $CH_2CH_2CO_2H$), 5.17 (s, 2H, $CH_2O$), 6.59 (d, $J = 3.8$ Hz, 1H, H-3′), 7.21 (d, $J = 3.8$ Hz, 1H, H-4′), 9.64 (s, 1H, CHO); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 28.6 ($CH_2CO_2$), 28.7 ($CH_2CO_2$), 58.1 ($CH_2O$), 112.6 (C-3′), 121.7 (C-4′), 152.8 (C-5′), 155.2 (C-2′), 171.5 ($O_2C$-1), 177.2 ($O_2C$-4), 177.9 (CHO). Anal. Calcd for $C_{10}H_{10}O_6$: C, 53.10; H, 4.46. Found: C, 53.03; H, 4.73.

### 3.1.4. n-*Butyl (5′-formylfuran-2′-yl)methyl succinate (**1**)*

3.1.4.1. *Method A*. To a solution of **2** (0.105 g, 0.465 mmol) in dry $CH_2Cl_2$ (1.5 mL) at room temperature under $N_2$, $Et_3N$ (0.06 g, 0.59 mmol) was added, followed by addition of 1-bromobutane (0.075 g, 0.55 mmol). The mixture was stirred at room temperature for 24 h and extracted with water ($2 \times 20$ mL). The aqueous layer was extracted with $CH_2Cl_2$ ($2 \times 20$ mL). The combined organic layers were dried over $Na_2SO_4$, and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (12 g, hexane : EtOAc, 9 : 1), to give 0.118 g (90%) of **1** as a colourless oil.

3.1.4.2. *Method B*. To a stirred solution of **6** (0.66 g, 5.24 mmol) in dry THF (6 mL), at 0°C under $N_2$, NaH (0.15 g, 6.25 mmol) was added. The reaction mixture was stirred at 4°C for 20 min, then **5** (1.04 g, 10.4 mmol) was added in one portion, and the stirring was continued at room temperature for 24 h. Then, 1-bromobutane (0.86 g, 6.29 mmol) was added and the mixture was stirred at room temperature for 16 h. The mixture was extracted with water ($2 \times 20$ mL) and $CH_2Cl_2$ ($2 \times 20$ mL), the organic layers were combined, dried over $Na_2SO_4$ and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (32 g, hexane : EtOAc, 7 : 3), to give 1.26 g (85%) of **1** as a colourless oil. $R_f$ 0.27 (hexane/EtOAc, 8 : 2); IR (film): $\nu_{max}$ 2964, 1738, 1683, 1526, 1407, 1350, 1270, 1203, 1156, 1021, 950, 813 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 0.93 (t, $J = 7.2$ Hz, 3H, $O(CH_2)_3CH_3$), 1.30–1.43 (m, 2H, $O(CH_2)_2CH_2CH_3$), 1.55–1.65 (m, 2H, $OCH_2CH_2Et$), 2.58–2.75 (m, 4H, $CH_2CH_2CO_2nBu$), 4.09 (t, 2H, $J = 6.6$ Hz, $OCH_2(CH_2)_2CH_3$), 5.16 (s, 2H, $CH_2O$), 6.59 (d, $J = 3.3$ Hz, 1H, H-3′), 7.21 (d, $J = 3.3$ Hz, 1H, H-4′), 9.64 (s, 1H, CHO); $^{13}C$ NMR (75.4 MHz, $CDCl_3$): $\delta$ 13.6 ($O(CH_2)_3CH_3$), 19.0 ($O(CH_2)_2CH_2CH_3$), 28.8 ($CH_2CO_2$), 28.9 ($CH_2CO_2$), 30.5 ($OCH_2CH_2Et$), 58.0 ($CH_2O$), 64.7 ($OCH_2(CH_2)_2CH_3$), 112.5 (C-3′), 121.6 (C-4′), 152.8 (C-5′), 155.3 (C-2′), 171.7 (C-1), 172.1 (C-4), 177.8 (CHO); HRMS (EI, $[M]^+$) $m/z$ Anal. Calcd for $C_{14}H_{18}O_6$: 282.1103; found: 282.1111.

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