

Total Syntheses of Natural Furan Derivatives Rehmanones A, B, and C

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Abstract: The synthesis of naturally occurring furan derivatives rehmanones A, B, and C is described. Diverse alternative synthetic strategies were developed for the preparation of these natural products. Conjugate addition of a furan to captodative alkene 1-acetylvinyl 4-nitrobenzoate was carried out under Lewis acid catalysis to give the corresponding adduct, which was transformed into rehmanones B and C in three and two steps, respectively. They were also prepared by condensation of acetone with the key furan-2-carbaldehyde intermediates, which could be readily obtained from D-fructose. The bis-furan rehmanone A was not only obtained in a one-step procedure by a double condensation of acetone with 5-(methoxymethyl)furan-2-carbaldehyde, but by condensing the latter with rehmanone B in high overall yields.

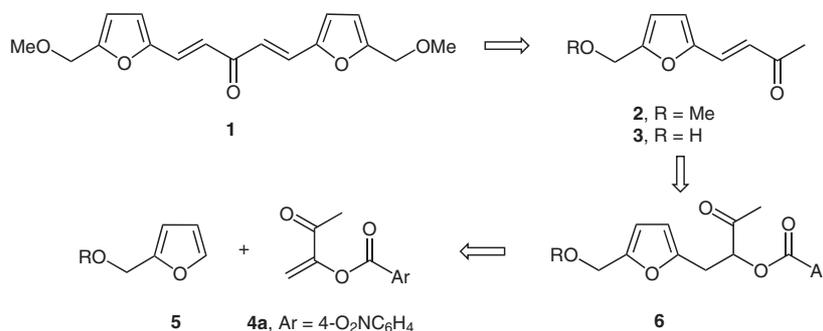
Key words: rehmanones A, B, and C, conjugate addition, captodative alkenes, Lewis acids, condensation

The naturally occurring furan derivatives rehmanone A (**1**), rehmanone B (**2**), and rehmanone C (**3**) have been recently isolated from the dried roots of *Rehmannia glutinosa*,¹ and **3** from *Salvia miltiorrhiza* Bunge (Labiatae).² These plants have been widely used in Chinese folk medicine for the treatment of menstrual disorders, insomnia, arthritis, and coronary heart affections, and also as a tonic.^{1,2} Compounds **1–3** have displayed significant biological activity, since **1** inhibited blood platelet aggregation and, also shown by **3**, promoted immune activity. Moreover, the latter activity is inhibited when **2** and **3** are tested at higher concentrations.¹ Therefore, an effective and versatile synthetic procedure for the synthesis of **1–3** is desirable. Herein we describe details of diverse synthetic strategies for the preparation of these attractive natural products.

A first synthetic approach to rehmanones B (**2**) and C (**3**) is depicted in Scheme 1. It starts from a conjugate addition of the correctly protected furfuryl alcohol **5** to the easily available captodative alkene **4a**, to yield adduct **6**, which could be transformed into the desired natural products. Additionally, compound **2** could react with a suitable substrate to give the bis-furan derivative rehmanone A (**1**).

Conjugate addition of nucleophiles to Michael acceptors constitutes a milestone reaction in organic synthesis for the β -functionalization of carbonyl compounds.³ Conjugate addition of heterocycles to electron-deficient alkenes has captured special attention due to the fact that this procedure can be an easy strategy for the functionalization of seminal heterocycles such as indoles, pyrroles, and imidazoles, among others.⁴ Although conjugate addition of an aryl ring⁵ or even some other heterocycles⁶ into a Michael acceptor promoted by Lewis acids has been somehow limited because of the difficulty in correctly activating the starting substrates, non-optimum reaction conditions, or the presence of undesired side products or mixtures of isomers, some successful examples have been reported.⁷ Previously, we reported the highly efficient Lewis acid promoted conjugate addition of substituted aryl compounds to captodative alkene **4a**, which proved to be more reactive than other electron-deficient alkenes.⁸

Consequently, furfuryl alcohol (**5a**) was protected with a methyl group to obtain **5b**, which could lead to natural product **2**, and with a benzyl or a trimethylsilyl group to yield derivatives **5c** and **5d**, respectively (Scheme 2). The latter may be deprotected as precursors of natural product **3**. When these furfuryl derivatives, **5b–d**, were treated in



Scheme 1

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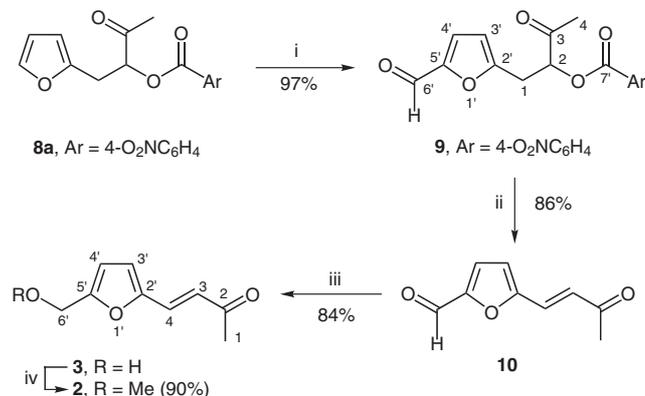
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the presence of **4a** with different Lewis acids (ZnCl_2 , $\text{BF}_3\cdot\text{OEt}_2$, AlCl_3) and solvents (CH_2Cl_2 , MeCN), and at various temperatures ($-70\text{ }^\circ\text{C}$, $20\text{ }^\circ\text{C}$), the starting materials were recovered. Compounds **5** tend to decompose when the temperature is increased, without any significant transformation into the desired products.

It is likely that the low reactivity of these substrates in the presence of Lewis acids was due to the deactivation of the furan ring by coordination of the catalyst with the OR substituent of compounds **5**,⁹ counterbalancing the activation by coordination with the Michael acceptor **4a**. This hypothesis seems to be supported by the fact that captodative alkene **4a** reacted with furan (**7**) in the presence of catalytic amounts of boron trifluoride–diethyl ether complex under mild conditions ($0\text{ }^\circ\text{C}$, 1 h) to give the corresponding adduct **8a** in moderate yield (60%) (Scheme 2). Moreover, captodative alkene **4b**, which is expected to be less reactive than **4a**,¹⁰ also undergoes the conjugate addition satisfactorily to furnish adduct **8b**. The yield of **8a** could be improved up to 85% by increasing the reaction temperature to $20\text{ }^\circ\text{C}$ and the reaction time to three hours.

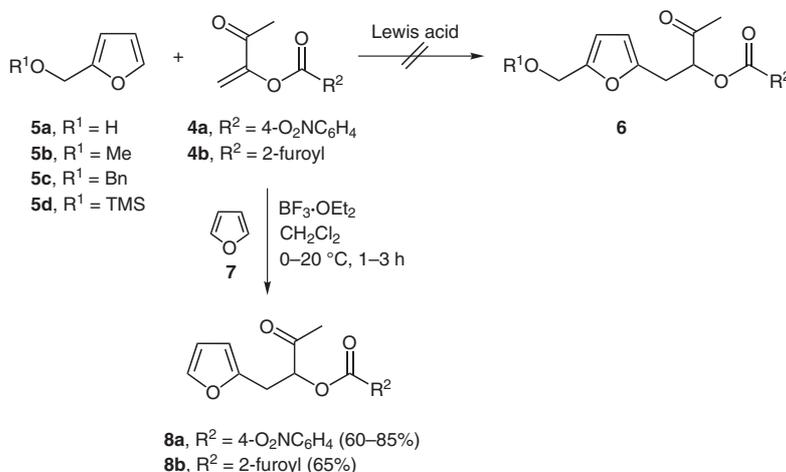
Once the furan ring was found to be functionalized with the butanone moiety, we decided to introduce the methoxy- or hydroxymethyl group to the heterocycle by formylation.¹¹ Thus, compound **8a** was treated with *N,N*-dimethylformamide/phosphoryl chloride for thirty minutes to give an excellent yield of the carbaldehyde derivative **9** (Scheme 3). Elimination of the 4-nitrobenzyloxy group was carried out by reaction of the latter with 1,5-diazabicyclo[4.3.0]non-5-ene at room temperature for two hours, to provide the α,β -unsaturated ketone **10** in good yield as a single *E*-stereoisomer.¹² The ^1H NMR of the crude mixture did not show any signal attributed to the *Z*-isomer. Reduction of the formyl group with sodium borohydride under standard conditions (MeOH, H_2O , r.t.) yielded a mixture of the desired product **3** and the product of reduction of both carbonyl groups. A more selective method resulted when using sodium borohydride and wet silica gel was used with dichloromethane as the solvent,¹³ since rehmanone C (**3**) was obtained as the main product in 84% yield (Scheme 3). Rehmanone B (**2**) was prepared

in 90% yield by methylation with methyl iodide of compound **3**, in the presence of sodium hydride as the base. In summary, the efficacy of this synthetic pathway led to the preparation of compounds **2** and **3** in 54% and 60% overall yields, respectively.¹⁴

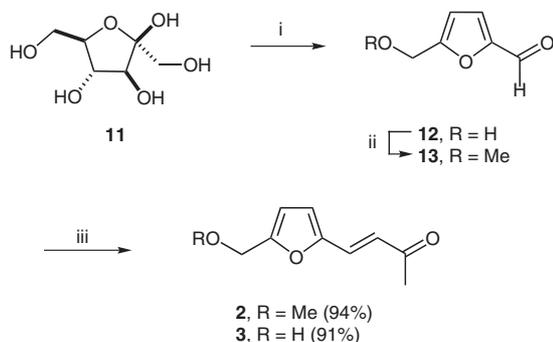


Scheme 3 Reagents and conditions: (i) DMF, POCl_3 , CH_2Cl_2 , $40\text{ }^\circ\text{C}$, 30 min; (ii) DBN, THF, r.t., 2 h; (iii) NaBH_4 , wet silica gel, CH_2Cl_2 , r.t., 20 min; (iv) MeI, NaH, THF, r.t., 2 h.

An alternative strategy was also pursued for the synthesis of rehmanone B (**2**), which involved an aldol condensation between the preformed furanyl scaffold and the carbonylic synthon in order to introduce the (*E*)-butenone side chain. Thus, the direct condensation between the 5-substituted furaldehyde **13** and acetone in the presence of sodium hydroxide led to the desired product **2** in high yield (Scheme 4). Substituted furan compound **13** was prepared in two steps, through an acid-catalyzed transformation of D-fructose (**11**) into furaldehyde **12**,¹⁵ which was methylated with methyl iodide, and sodium hydride as the base, to give **13** in 64% overall yield (Scheme 4). The shortness and effectiveness of this strategy prompted us to use it also for the synthesis of rehmanone C (**3**). Thus, condensation of **12** with acetone under the same reaction conditions led to **3** in comparable overall yield (62%) to that obtained for **2** (60%), and in only two steps starting from **11** (Scheme 4).



Scheme 2



Scheme 4 Reagents and conditions: (i) H_2SO_4 , DMSO, 110 °C, 48 h, 68%; (ii) MeI, NaH, THF, r.t., 16 h, 94%; (iii) acetone (2 equiv), NaOH, r.t., 24 h.

The total synthesis of rehmanone A (**1**) was carried out through three related approaches. The first one started from rehmanone B (**2**) via a condensation reaction with furfuryl compound **13** under mild basic conditions to furnish **1** in quantitative yield (Scheme 5). The second approach was inspired by the fact that **1** has a symmetrical structure. Therefore, by condensing 2.0 equivalents of **13** with 1.0 equivalent of acetone in the presence of sodium hydroxide, natural rehmanone A (**1**) was obtained in 67% yield (Scheme 5). Finally, the third pathway consisted of a condensation of **12** with acetone to give the bis-condensing product **14**, which was methylated with methyl iodide to give **1** in 18% overall yield (Scheme 5). NMR spectral data assignment of rehmanones A–C, **1**–**3**, was supported by HMQC and HMBC experiments, and is in agreement with those reported.^{1,2}

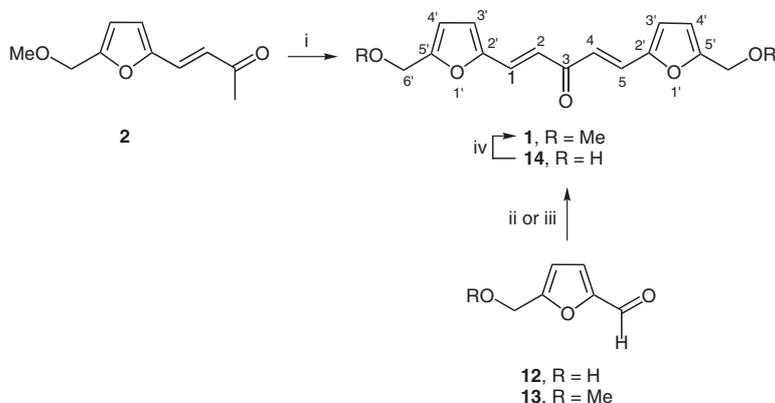
In conclusion, we have described an efficient total synthesis of rehmanones B (**2**) and C (**3**) via the key steps of 2,5-bis-functionalization of furan (**7**) by Lewis acid catalyzed conjugate addition to captodative alkene **4a**, followed by formylation. An alternative and shorter strategy was also developed by condensing acetone with the 2,5-disubstituted furanic compounds **12** and **13** to give **3** and **2**, respectively, in high overall yields. By using the concept of molecular symmetry, the first total synthesis of rehmanone A (**1**) was carried out in one step by bis-aldol condensation of acetone with two molecules of **13**. In

addition, a convergent and highly efficient synthesis of **1** was also reported by reacting rehmanone B (**2**) with furfural derivative **13**. Although the overall efficiency in the synthesis of **2** and **3** was more practical starting from D-fructose, the development of diverse synthetic methodologies for the preparation of natural products **1**–**3**, including the isolation of a series of intermediates and precursors, will allow us to synthesize a large variety of derivatives with the aim of searching for higher bioactivity than that shown by the natural furan compounds. This is currently in process and the results will be reported in due course.

Melting points (uncorrected) were determined with an Electrothermal capillary melting point apparatus. IR spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury (300 MHz) instrument, with CDCl_3 as the solvent and TMS as internal standard. MS and HRMS spectra were obtained in EI (70 eV) or FAB^+ modes on Thermo-Finnigan Polaris Q and on Jeol JMS-AX 505 HA spectrometers, respectively. 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, visualized by a long- and short-wavelength UV lamps. 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 Na. DMF, CH_2Cl_2 , and EtOAc were distilled over CaH_2 prior to use. DMSO and acetone were dried by distillation after treatment with 4 Å molecular sieves. Et_3N was freshly distilled from NaOH. All other reagents were used without further purification. Alkenes **4a** and **4b**,¹⁶ and furfuryl protected alcohols **5b–d**,¹⁷ were prepared as reported.

1-(Furan-2-ylmethyl)-2-oxopropyl 4-Nitrobenzoate (**8a**); Typical Procedure

To a stirred soln of **4a** (1.0 g, 4.26 mmol) in anhyd CH_2Cl_2 (2 mL), at 0 °C under N_2 , was added dropwise **7** (0.35 g, 5.1 mmol). The mixture was cooled to –78 °C and $\text{BF}_3 \cdot \text{OEt}_2$ (0.028 g, 0.2 mmol) was added dropwise and it was stirred at r.t. for 3 h. H_2O (2 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 15 mL) and washed with aq sat. NaHCO_3 until neutral. The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, 30 g, hexane–EtOAc– CH_2Cl_2 , 9:0.5:0.5) to give **8a** (1.1 g, 85%) as a pale yellow solid; mp 75–77 °C (hexane–EtOAc, 1:1); R_f = 0.47 (hexane–EtOAc, 1:1).



Scheme 5 Reagents and conditions: (i) **13**, NaOH, EtOH, r.t., 48 h, 99%; (ii) **13** (2.0 equiv), acetone (1.0 equiv), NaOH, r.t., 24 h, 67% of **1**; (iii) **12** (2.0 equiv), acetone (1.0 equiv), NaOH, r.t., 2 h, 60% of **14**; (iv) MeI, NaH, THF, r.t., 24 h, 30%.

IR (CH₂Cl₂): 1726, 1530, 1349, 1104 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 2.21 (s, 3 H, CH₃CO), 3.34 (d, *J* = 9.0 Hz, 2 H, H1), 5.56 (t, *J* = 9.0 Hz, 1 H, H2), 6.18 (br d, *J* = 3.0 Hz, 1 H, H3'), 6.32 (dd, *J* = 3.0, 1.5 Hz, 1 H, H4'), 7.35 (d, *J* = 1.5 Hz, 1 H, H5'), 8.17–8.34 (m, 4 H, ArH).

¹³C NMR (75 MHz, CDCl₃): δ = 26.6 (CH₃CO), 29.4 (C1), 77.8 (C2), 108.1 (C3'), 110.6 (C4'), 123.6 (ArH), 130.9 (ArH), 134.6 (Ar), 142.2 (C5'), 149.2 (C2'), 150.8 (Ar), 163.9 (ArCO₂), 203.6 (CH₃CO).

MS: *m/z* (%) = 303 ([M]⁺, 1), 150 (90), 136 (100), 121 (66), 104 (49), 94 (53), 81 (43), 76 (28).

Anal. Calcd for C₁₅H₁₃NO₆: C, 59.41; H, 4.32; N, 4.62. Found: C, 59.66; H, 4.41; N, 4.81.

1-(Furan-2-ylmethyl)-2-oxopropyl Furan-2-carboxylate (8b)

Following the typical procedure for **8a** using a mixture of **4b** (0.3 g, 1.67 mmol), **7** (0.566 g, 8.33 mmol), and BF₃·OEt₂ (0.024 g, 0.17 mmol) in anhyd CH₂Cl₂ (5 mL) with stirring at r.t. for 1 h, to give **8b** (0.27 g, 65%) as a pale yellow oil; *R*_f = 0.32 (hexane–EtOAc, 8:2).

IR (CH₂Cl₂): 1721, 1577, 1472, 1394, 1361, 1297, 1175, 1115, 1015, 765 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 2.17 (s, 3 H, CH₃CO), 3.18–3.32 (m, 2 H, H1), 5.47 (dd, *J* = 6.8, 5.6 Hz, 1 H, H2), 6.13–6.17 (m, 1 H, H3'), 6.28 (dd, *J* = 3.2, 1.7 Hz, 1 H, H4'), 6.53 (dd, *J* = 3.4, 1.7 Hz, 1 H, H4''), 7.23 (dd, *J* = 3.4, 0.9 Hz, 1 H, H3''), 7.32 (dd, *J* = 1.7, 0.9 Hz, 1 H, H5'), 7.61 (dd, *J* = 1.7, 0.9 Hz, 1 H, H5'').

¹³C NMR (75 MHz, CDCl₃): δ = 26.6 (C4), 29.4 (C1), 76.8 (C2), 107.9 (C3'), 110.4 (C4'), 112.0 (C4''), 119.0 (C3''), 141.9 (C5'), 143.6 (C2''), 147.0 (C5''), 149.4 (C2'), 157.6 (CO₂), 204.5 (CO).

MS: *m/z* (%) = 249 ([M + H]⁺, 1), 231 (1), 136 (17), 95 (83), 94 (70), 81 (27), 53 (34), 43 (100).

HRMS (FAB): *m/z* [M + H]⁺ calcd for C₁₃H₁₂O₅: 249.0763; found: 249.0762.

1-(5-Formylfuran-2-ylmethyl)-2-oxopropyl 4-Nitrobenzoate (9)

A soln of anhyd DMF (0.2 g, 2.7 mmol) and POCl₃ (0.403 g, 2.63 mmol) was stirred at 0 °C for 10 min and at r.t. for 20 min under N₂. To this was added dropwise **8a** (0.81 g, 2.67 mmol) in anhyd CH₂Cl₂ (2 mL) at 0 °C. The mixture was stirred at r.t. for 10 min, then at 40 °C for 30 min. H₂O (2 mL) was added and aq 2 M NaOH was added dropwise until neutral. The mixture was diluted with CH₂Cl₂ (20 mL), the organic layer was washed with H₂O (2 × 20 mL) and dried (Na₂SO₄), and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, 30 g, hexane–EtOAc, 8:2) to give **9** (0.86 g, 97%) as a pale yellow solid; mp 94–95 °C (hexane–EtOAc, 9:1); *R*_f = 0.49 (hexane–EtOAc, 1:1).

IR (CH₂Cl₂): 1724, 1674, 1522, 1399, 1341, 1271, 1103, 1025, 719 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 2.27 (s, 3 H, CH₃CO), 3.31–3.49 (m, 2 H, H1), 5.62 (dd, *J* = 7.4, 5.3 Hz, 1 H, H2), 6.40 (d, *J* = 3.5 Hz, 1 H, H3'), 6.31 (d, *J* = 3.5 Hz, 1 H, H4'), 8.34–8.18 (m, 4 H, ArH), 9.56 (s, 1 H, CHO).

¹³C NMR (75 MHz, CDCl₃): δ = 26.5 (C4), 29.4 (C1), 77.1 (C2), 111.2 (C3'), 122.8 (C4'), 123.7 (C10'), 131.0 (C9'), 134.1 (C8'), 150.8 (C11'), 152.5 (C5'), 156.4 (C2'), 163.8 (C7'), 177.0 (C6'), 202.9 (C3).

Anal. Calcd for C₁₆H₁₃NO₇: C, 58.01; H, 3.96; N, 4.23. Found: C, 58.07; H, 4.00; N, 4.18.

(E)-5-(3-Oxobut-1-enyl)furan-2-carbaldehyde (10)

To a stirred soln of **9** (0.24 g, 0.73 mmol) in anhyd THF (10 mL), at 20 °C under N₂, was added dropwise DBN (0.179 g, 1.46 mmol). The mixture was stirred at r.t. for 2 h, filtered through Celite, and washed with THF (10 mL). The solvent was removed under vacuum and the residue was extracted with CH₂Cl₂ (2 × 15 mL) and washed with aq 1 M HCl (2 × 20 mL) and H₂O until neutral. The organic layer was dried (Na₂SO₄) and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, 10 g, hexane–EtOAc, 8:2) to give **10** (0.103 g, 86%) as a pale yellow solid; mp 110–111 °C (hexane–EtOAc, 8:2) [Lit.¹² 110–111 °C]; *R*_f = 0.49 (hexane–EtOAc, 1:1).

IR (CH₂Cl₂): 1671, 1618, 1498, 1400, 1361, 1260, 1217, 1174, 1041, 970, 813, 774 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 2.37 (s, 3 H, CH₃CO), 6.80 (d, *J* = 3.6 Hz, 1 H, H4), 6.91 (d, *J* = 16.2 Hz, 1 H, H8), 7.27 (d, *J* = 3.6 Hz, 1 H, H3), 7.31 (d, *J* = 16.2 Hz, 1 H, H7), 9.68 (s, 1 H, CHO).

¹³C NMR (75 MHz, CDCl₃): δ = 28.4 (CH₃CO), 116.2 (C4), 122.3 (C3), 127.7 (C7), 128.4 (C8), 152.9 (C2), 155.1 (C5), 177.7 (CHO), 197.2 (CH₃CO).

HRMS (EI): *m/z* [M]⁺ calcd for C₉H₈O₃: 164.0473; found: 164.0474.

Rehmanone C (3)^{12,14}

Method A: To a stirred mixture of **10** (0.119 g, 0.73 mmol) in CH₂Cl₂ (2 mL) and silica gel (230–400 mesh) (0.146 g, 2.43 mmol) impregnated with H₂O (0.044 g, 30% in weight), at r.t. under N₂, was added dropwise NaBH₄ (0.014 g, 0.37 mmol). The mixture was stirred at 20 °C for 20 min, filtered through Celite, and washed with CH₂Cl₂ (10 mL). The solvent was removed under vacuum and the residue was extracted with CH₂Cl₂ (2 × 20 mL) and washed with aq sat. NaHCO₃ (2 × 20 mL) and then with H₂O until neutral. The organic layer was dried (Na₂SO₄) and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, 10 g, hexane–EtOAc, 8:2) to give **3** (0.1 g, 84%) as a pale yellow oil.

Method B: To a stirred soln of **12** (0.5 g, 4.0 mmol) in EtOH (20 mL) and acetone (0.5 g, 8.6 mmol), at r.t. under N₂, was added dropwise 10% aq NaOH (3.2 mL). The mixture was stirred at r.t. for 24 h and the solvent was removed under vacuum. The residue was dissolved in CH₂Cl₂ (50 mL) and washed with 5% aq HCl (2 × 25 mL) and then with H₂O until neutral. The aqueous layer was washed with CH₂Cl₂ (2 × 25 mL), the combined organic extracts were dried (Na₂SO₄) and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, 20 g, hexane–EtOAc, 8:2) to give **3** (0.6 g, 91%) as a pale yellow oil; *R*_f = 0.31 (hexane–EtOAc, 1:1).

IR (film): 3393, 1662, 1623, 1574, 1362, 1266, 1181, 1091, 967, 798 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 2.31 (s, 3 H, CH₃CO), 4.64 (s, 2 H, H6'), 6.39 (d, *J* = 3.3 Hz, 1 H, H4'), 6.59 (d, *J* = 15.9 Hz, 1 H, H3), 6.62 (d, *J* = 3.3 Hz, 1 H, H3'), 7.22 (d, *J* = 15.9 Hz, 1 H, H4).

¹³C NMR (75 MHz, CDCl₃): δ = 28.0 (CH₃CO), 57.6 (C6'), 110.5 (C4'), 116.6 (C3'), 124.1 (C3), 129.3 (C4), 150.8 (C2'), 157.3 (C5'), 198.3 (CH₃CO).

HRMS (EI): *m/z* [M]⁺ calcd for C₉H₁₀O₃: 166.0630; found: 166.0630.

Rehmanone B (2)^{1,14}

Method A: To a stirred soln of NaH (60% in mineral oil, 0.028 g, 0.84 mmol) in anhyd THF (10 mL), at r.t. under N₂, was added dropwise **3** (0.14 g, 0.84 mmol) in anhyd THF (5 mL). The mixture was stirred at r.t. for 2 min, MeI (0.12 g, 0.84 mmol) was added, and the mixture was stirred at r.t. for 2 h. The mixture was filtered through

Celite and washed with CH_2Cl_2 (10 mL). The solvent was removed under vacuum, the residue was dissolved in CH_2Cl_2 (10 mL), washed with aq sat. NaHCO_3 (2×10 mL) and then with brine until neutral. The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, 30 g, hexane–EtOAc, 9:1) to give **2** (0.137 g, 90%) as a pale yellow oil.

Method B: Following method B for the preparation of **3**, a mixture of **13** (0.5 g, 3.57 mmol), acetone (0.5 g, 8.6 mmol) in EtOH (20 mL), and 10% aq NaOH (3 mL) was stirred at r.t. for 24 h to give **2** (0.61 g, 94%) as a pale yellow oil; $R_f = 0.25$ (hexane–EtOAc, 8:2).

IR (CH_2Cl_2): 1687, 1665, 1616, 1576, 1360, 1257, 1183, 1091, 1021, 968, 798 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): $\delta = 2.32$ (s, 3 H, CH_3CO), 3.40 (s, 3 H, MeO), 4.42 (s, 2 H, H_6'), 6.42 (d, $J = 3.3$ Hz, 1 H, H_4'), 6.63 (d, $J = 3.3$ Hz, 1 H, H_3'), 6.64 (d, $J = 16.0$ Hz, 1 H, H3), 7.25 (d, $J = 16.0$ Hz, 1 H, H_4).

^{13}C NMR (75 MHz, CDCl_3): $\delta = 27.9$ (CH_3CO), 58.1 (MeO), 66.3 (C_6'), 111.8 (C_4'), 116.3 (C_3'), 124.1 (C3), 129.1 (C4), 150.9 (C_2'), 154.4 (C_5'), 197.7 (CH_3CO).

HRMS (FAB): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{10}\text{H}_{13}\text{O}_3$: 181.0865; found: 181.0858.

5-(Hydroxymethyl)furan-2-carbaldehyde (**12**)¹⁵

A stirred soln of **11** (2.0 g, 0.011 mol) in anhyd DMSO (9 mL) and concd (98%) H_2SO_4 (0.108 g, 1.1 mmol) was heated to 110 °C for 48 h. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with H_2O until neutral. The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, 60 g, hexane–EtOAc, 7:3) to give **12** (0.95 g, 68%) as a pale yellow oil; $R_f = 0.31$ (hexane–EtOAc, 1:1).

IR (CH_2Cl_2): 3346, 1674, 1522, 1436, 1401, 1280, 1191, 1023, 966, 953, 812, 780, 770 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): $\delta = 4.65$ (d, $J = 0.6$ Hz, 2 H, CH_2OH), 6.53 (d, $J = 3.6$ Hz, 1 H, H_4), 7.27 (d, $J = 3.6$ Hz, 1 H, H3), 9.55 (s, 1 H, CHO).

^{13}C NMR (75 MHz, CDCl_3): $\delta = 56.4$ (CH_2OH), 109.2 (C4), 123.1 (C3), 151.4 (C2), 161.3 (C5), 177.1 (CHO).

5-(Methoxymethyl)furan-2-carbaldehyde (**13**)

To a stirred suspension of NaH (60% in mineral oil, 0.16 g, 6.7 mmol) in anhyd THF (2 mL), at r.t. under N_2 , was added dropwise **12** (0.5 g, 4.0 mmol) in anhyd THF (5 mL). The mixture was stirred at r.t. for 2 min, MeI (1.12 g, 7.9 mmol) was added, and the mixture was stirred at r.t. for 16 h. The mixture was filtered through Celite and washed with THF (10 mL). The solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2 (40 mL), washed with aq sat. NaHCO_3 (2×30 mL), and then brine until neutral. The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, 30 g, hexane–EtOAc, 8:2) to give **13** (0.52 g, 94%) as a pale yellow oil; $R_f = 0.27$ (hexane–EtOAc, 8:2).

IR (CH_2Cl_2): 2924, 2854, 1670, 1520, 1457, 1384, 1084, 753 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): $\delta = 3.43$ (s, 3 H, MeO), 4.50 (s, 2 H, CH_2O), 6.53 (d, $J = 3.6$ Hz, 1 H, H_4), 7.22 (d, $J = 3.6$ Hz, 1 H, H3), 9.63 (s, 1 H, CHO).

^{13}C NMR (75 MHz, CDCl_3): $\delta = 58.7$ (MeO), 66.5 (CH_2O), 111.1 (C4), 121.8 (C3), 152.6 (C2), 158.2 (C5), 177.7 (CHO).

Rehmanone A (**1**)¹

Method A: To a stirred soln of **2** (0.2 g, 1.1 mmol) in EtOH (10 mL) and **13** (0.16 g, 1.14 mmol) in EtOH (10 mL), at r.t. under N_2 , was

added dropwise 10% aq NaOH (1 mL). The mixture was stirred at r.t. for 48 h, the solvent removed under vacuum. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with 5% aq HCl (2×25 mL) and then H_2O until neutral. The aqueous layer was washed with CH_2Cl_2 (2×25 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, 20 g, hexane–EtOAc, 95:5) to give **1** (0.33 g, 99%) as a pale yellow gum.

Method B: To a stirred soln of **13** (0.5 g, 3.57 mmol) in EtOH (20 mL) and acetone (0.10 g, 1.72 mmol), at r.t. under N_2 , was added dropwise 10% aq NaOH (3 mL). The mixture was stirred at r.t. for 24 h and then the solvent was removed under vacuum. The residue was dissolved with CH_2Cl_2 (50 mL) and washed with 5% aq HCl (2×25 mL) and then H_2O until neutral. The aqueous layer was washed with CH_2Cl_2 (2×25 mL), the combined organic extracts were dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, 20 g, hexane–EtOAc, 95:5) to give **1** (0.72 g, 67%) as a pale yellow gum.

Method C: Following the method of preparation of **13**, a mixture of NaH (0.03 g, 1.25 mmol) in anhyd THF (1 mL), MeI (1.112 g, 0.79 mmol), and **14** (0.1 g, 0.36 mmol), at r.t. under N_2 , was stirred for 24 h, to give **1** (0.033 g, 30%) as a pale yellow gum; $R_f = 0.53$ (hexane–EtOAc, 1:1).

IR (film): 1648, 1620, 1575, 1384, 1258, 1179, 1089, 1022, 973, 801 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): $\delta = 3.42$ (s, 6 H, 2 MeO), 4.45 (s, 4 H, 2 CH_2O), 6.43 (d, $J = 3.3$ Hz, 2 H, H_4'), 6.65 (d, $J = 3.3$ Hz, 2 H, H_3'), 6.92 (d, $J = 15.6$ Hz, 2 H, H_2 , H_4), 7.44 (d, $J = 15.6$ Hz, 2 H, H_1 , H_5).

^{13}C NMR (75 MHz, CDCl_3): $\delta = 58.2$ (MeO), 66.5 (CH_2O), 112.0 (C_4'), 116.7 (C_3'), 123.3 (C2, C4), 129.1 (C1, C5), 151.6 (C_2'), 154.5 (C_5'), 188.1 (CO).

HRMS (FAB): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{17}\text{H}_{18}\text{O}_5$: 303.1232; found: 303.1241.

(1E,4E)-1,5-Bis[5-(hydroxymethyl)furan-2-yl]penta-1,4-dien-3-one (**14**)

Following method B for the preparation of **1**, a mixture of **12** (0.208 g, 1.65 mmol) in EtOH (20 mL) and acetone (0.05 g, 0.86 mmol) and 10% aq NaOH (1 mL) was stirred at r.t. under N_2 for 2 h to give **14** (0.27 g, 60%) as a pale yellow oily solid; $R_f = 0.10$ (hexane–EtOAc, 1:1).

IR (KBr): 3375, 1616, 1554, 1524, 1383, 1346, 1182, 1117, 1073, 1015, 975, 798 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): $\delta = 2.87$ (br s, 2 H, OH), 4.61 (s, 4 H, CH_2OH), 6.40 (d, $J = 3.3$ Hz, 2 H, H_4'), 6.60 (d, $J = 3.3$ Hz, 2 H, H_3'), 6.89 (d, $J = 15.6$ Hz, 2 H, H_2 , H_4), 7.43 (d, $J = 15.6$ Hz, 2 H, H_1 , H_5).

^{13}C NMR (75 MHz, CDCl_3): $\delta = 56.7$ (CH_2OH), 109.8 (C_4'), 116.8 (C_3'), 122.3 (C2, C4), 128.9 (C1, C5), 150.5 (C_2'), 157.9 (C_5'), 187.8 (CO).

HRMS (FAB): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{15}\text{H}_{15}\text{O}_5$: 275.0919; found: 275.0929.

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