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

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**Scheme 1**

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the presence of 4a with different Lewis acids (ZnCl₂, BF₃·OEt₂, AlCl₃) and solvents (CH₂Cl₂, MeCN), and at various temperatures (−70 °C, 20 °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, counterbalancing the activation by coordination with the Michael acceptor 4a. This hypothesis seems to be supported by the fact that captodative alkene 4b reacted with furan (7) in the presence of catalytic amounts of boron trifluoride–diethyl ether complex under mild conditions (0 °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, 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 °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. 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-nitrobenzoyloxy 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 a,β-unsaturated ketone 10 in good yield as a single E-stereoisomer. 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, H₂O, 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 as the solvent, 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.

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 carboxylic 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, 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 from 11 (Scheme 4).

Scheme 2
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 yield (Scheme 5). The second approach was inspired by the fact that 1 has a symmetrical structure. Therefore, by condensing 2.0 equivalents of 1 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-condensation 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 HMCO 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-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. \(^1\)H 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 Thermofinnigan 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 (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\(_2\)Cl\(_2\), 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\(_3\)N was freshly distilled from NaOH. All other reagents were used without further purification. Alkenes \(^4\)a and \(^4\)b, \(^1\) and furfuryl protected alcohols \(^5\)b–d, \(^1\) 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\(_2\)Cl\(_2\) (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 BF\(_3\)OEt\(_2\) (0.028 g, 0.2 mmol) was added dropwise and it was stirred at r.t. for 3 h. H\(_2\)O (2 mL) was added and the mixture was extracted with CH\(_2\)Cl\(_2\) (2 × 15 mL) and washed with aq sat. NaHCO\(_3\) until neutral. The organic layer was dried (Na\(_2\)SO\(_4\)) and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, 30 g, hexane–EtOAc–CH\(_2\)Cl\(_2\), 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 4 Reagents and conditions: (i) \(\text{H}_2\text{SO}_4\), DMSO, 110 °C, 48 h, 68%; (ii) MeI, NaH, THF, r.t., 16 h, 94%; (iii) acetone (2 equiv), NaOH, r.t., 24 h.

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%.
(E)-5-(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]; Rf = 0.49 (hexane–EtOAc, 1:1).

IR (CH2Cl2): 1711, 1618, 1498, 1400, 1364, 1301, 1273, 1257, 1234, 1178, 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).


Rehmehano C (3)1,2,4

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; Rf = 0.31 (hexane–EtOAc, 1:1).

IR (film): 3393, 1662, 1623, 1574, 1376, 1262, 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 (C13), 129.3 (C4), 150.8 (C2'), 157.3 (C5'), 198.3 (CH3CO).

HRMS (EI): m/z [M+H]+ calcd for C10H9O4: 166.0630; found: 166.0630.

Rehmehano B (2)1,4

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
Celeste and washed with CH₂Cl₂ (10 mL). The solvent was removed under vacuum, the residue was dissolved in CH₂Cl₂ (10 mL), washed with aq sat. NaHCO₃ (2 × 10 mL) and then with brine until neutral. The organic layer was dried (Na₂SO₄) 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; Rf = 0.25 (hexane–EtOAc, 8:2).

IR (CH₂Cl₂): 1687, 1665, 1616, 1576, 1360, 1257, 1183, 1091, 1021, 968 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 2.32 (s, 3 H, CH₃CO), 4.42 (s, 2 H, H6), 6.42 (d, J = 3.6 Hz, 1 H, H5), 6.63 (d, J = 3.3 Hz, 1 H, H3), 7.25 (d, J = 16.0 Hz, 1 H, H4).

13C NMR (75 MHz, CDCl₃): δ = 58.2 (MeO), 66.5 (CH₂O), 112.0 (C6), 154.4 (C5), 197.7 (CO).


5-(Hydroxymethyl)furan-2-carbaldehyde (11)15

A stirred soln of NaH (60% in mineral oil, 0.16 g, 6.7 mmol) in anhyd THF (1 mL), MeI (1.112 g, 7.9 mmol) was added, and the mixture was stirred 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 thorough Celite and washed with THF (10 mL). The solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, 30 g, hexane–EtOAc, 9:1) to give 12 (0.5 g, 3.57 mmol) as a pale yellow gum; Rf = 0.31 (hexane–EtOAc, 1:1).

IR (film): 3648, 1648, 1620, 1575, 1384, 1258, 1179, 1089, 1022, 973, 801 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 3.42 (s, 6 H, 2 MeO), 4.45 (s, 4 H, 2 CH₃O), 6.43 (d, J = 3.3 Hz, 2 H, H4⁴), 6.65 (d, J = 3.3 Hz, 2 H, H3⁴), 6.92 (d, J = 15.6 Hz, 2 H, H2, H4), 7.44 (d, J = 15.6 Hz, 2 H, H1, H5).

13C NMR (75 MHz, CDCl₃): δ = 58.2 (MeO), 66.5 (CH₂O), 112.0 (C4), 116.7 (C3), 123.3 (C2, C4), 129.1 (C1), 151.6 (C2), 154.5 (C5), 188.1 (CO).


(1AE,4E)-1,5-Bis[5-(hydroxymethyl)furan-2-yl]pent-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 N₂ for 2 h to give 14 (0.27 g, 60%) as a pale yellow oily solid; Rf = 0.10 (hexane–EtOAc, 1:1).

IR (KBr): 3375, 1616, 1554, 1383, 1346, 1182, 1073, 1089, 1022, 973, 801 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 2.87 (br s, 2 H, OH), 4.61 (s, 4 H, 2 CH₂O), 6.40 (d, J = 3.3 Hz, 2 H, H4⁴), 6.60 (d, J = 3.3 Hz, 2 H, H3⁴), 6.89 (d, J = 15.6 Hz, 2 H, H2, H4), 7.43 (d, J = 15.6 Hz, 2 H, H1, H5).

13C NMR (75 MHz, CDCl₃): δ = 56.7 (CH₂OH), 109.8 (C4), 116.8 (C3), 122.3 (C2, C4), 128.9 (C1, C5), 150.5 (C2'), 157.9 (C5'), 187.8 (CO).


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