Total synthesis of amorfrutin B via a Pd-catalyzed regioselective geranyl migration-decarboxylation-cycloaromatization cascade

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Abstract
A biomimetic total synthesis of amorfrutin B, a resorcylate with geranyl bibenzyl scaffold, has been completed in eight steps from 2,2,6-trimethyl-4H-1,3-dioxin-4-one. The key step utilized a highly regioselective Pd-catalyzed geranyl migration-decarboxylation-cycloaromatization cascade. The methodology should be of practical utility in the construction of geranyl bibenzyl scaffolds manifested in many natural products.

Keywords: Amorfrutin B, cascade, resorcylates, biomimetic reactions

Introduction

Molecules containing a bibenzyl unit were found to occur widely in natural products1-3 and display diversified biological activities such as antioxidant,4 antimicrobial,5 antifungal,6 antitumor,7 and cytotoxic.8 Within this class, amorfrutins were isolated in 1981 by Mitscher et al., from the ethanolic extracts of the fruits, stems, and leaves of Amorpha fruticosa, a shrub originating in North America, China and Korea.9,10 In addition to antimicrobial activities against G-positive and acid-fast microorganisms, amorfrutins were able to inhibit nuclear transcription factor-jB (NF-jB) activation and related gene expression, which is known to be related to several inflammatory diseases such as arthritis, asthma, bowel inflammation, and cancer.11 Recently this family of natural products has been discovered to exhibit antidiabetic activities.12 More specifically, amorfrutin B was identified as a partial agonist of peroxisome proliferator-activated receptor γ (PPARγ) with a considerably higher affinity and γ-selectivity than that of any other amorfrutins previously reported, and similar to that of the marketed drug rosiglitazone.13 Due to its physiological profiles remarkably different from current marketed PPARγ drugs, and the
predictable application prospects, this compound has found extensive research interest in many labs, for example, in pharmacodynamic and structure–activity relationship studies.\textsuperscript{14}

Several syntheses of geranyl bibenzyl derivatives have been reported, the majority of strategies utilizing two-step sequences: Wittig reaction followed by alkene hydrogenation,\textsuperscript{15} benzyllic metalation and subsequent alkylation\textsuperscript{16,17} from protected phenolic precursors, and more recently palladium catalyzed Sonogashira reaction of phenylacetylene and triflate precursor followed by alkyne hydrogenation.\textsuperscript{12} The geranyl moiety could be introduced by electrophilic aromatic alkylation with geraniol in the presence of BF\textsubscript{3}-OEt\textsubscript{2} as catalyst or by using regioselective metalation of the 2-position with n-BuLi or KH and subsequent alkylation with geranyl bromide or chloride.\textsuperscript{13,15,18} However, yields were typically low, with co-production of considerable amounts of O-geranylated product.\textsuperscript{13,15} Besides its geranyl bibenzyl scaffold, the molecule contains a 6-alkyl-2,4-dihydroxybenzoic acid (resorcylic acid) motif, which occurs in numerous natural products.\textsuperscript{19-22} Reported syntheses invariably require the use of protective groups and strong bases, subsequent alkylations giving low yields and poor regioselectivity.

**Results and Discussion**

In consideration of the fact that the molecule contains a resorcylic acid unit, we were inspired by the biomimetic synthesis of resorcylates using dioxinone chemistry, especially by Barrett’s elegant discovery of the cascade reaction.\textsuperscript{23-27} Herein, we report a full description and experimental details on a flexible strategy for the total synthesis of amorfrutin B, which was adapted from resorcylates biosynthesis and should be of practical utility.

Ketoester 6 was synthesized in 3 steps from dioxinone 1 by following literature procedure.\textsuperscript{18} Regioselective acylation of ketoester 6 by Claisen condensation reaction with dihydrocinnamoyl chloride 8 in the presence of magnesium chloride and pyridine gave the corresponding diketoester–dioxinone 9 in a satisfactory yield. Subsequent reaction of diketoester–dioxinone 9 with Pd(PPh\textsubscript{3})\textsubscript{4} and cesium carbonate resulted in decarboxylative geranyl migration and formation of the resorcylate 10. Finally, phenol methylation of 10 and saponification of resulting 13 gave amorfrutin B.
Scheme 1. Synthesis of amorfrutin B (i) PhMe, 100 °C, 5 h, 89%; (ii) 3, isoamylene, CH₂Cl₂, r.t.; oxalyl chloride, DMF, 0 °C – r.t., 2.5 h; (iii) 5, TMSi₂NLi, THF, -78 °C, 3.5 h; 4, THF, -78 °C, 1.5 h, 53% over two steps; (iv) MgCl₂, pyridine, CH₂Cl₂, 0 °C, 1 h; 8, 0 °C, 1 h, 57%; (v) Pd(PPh₃)₄, Cs₂CO₃, THF, 0–25 °C, 18 h, 53%; (vi) MeI, Cs₂CO₃, THF, 25 °C, 12 h, 96%; (vii) KOH 48%, DMSO, 80 °C, 12 h, 80%.

The synthesis utilized a highly regioselective geranyl migration-decarboxylation-cycloaromatization cascade reaction as a key step. Naturally it would be very helpful to understand the mechanism of this important transformation. According to a recent paper, the cascade was proposed to proceed via an interesting intermolecular pathway: Pd(0)/base-assisted degeranylation from a second molecule; regioselective geranylation at C-3 center; and final decarboxylation to generate the precursor 16 for subsequent cycloaromatization. Geranyl-diketo-dioxinone 16 then readily undergoes intramolecular condensation to give 17 followed by dehydration to produce resorcylate 10. Though the published paper illustrated the transformation mechanism primarily based on a prenyl-diketo-dioxinone substrate and a considerable similarity is reasonably present between prenyl- and geranyl-diketo-dioxinone substrates, confirmative experimental evidence concerning this mechanism still needs to be found and reported in due course.
Scheme 2. Proposed mechanism for the key cascade transformation

Conclusions

The total synthesis of amorfrutin B has been accomplished in eight steps from dioxinone 1 in an overall yield of 11%. We have demonstrated the efficiency of a biomimetic approach and a Pd-catalyzed geranyl migration-decarboxylation-cycloaromatization cascade to the construction of geranyl bibenzyl scaffold. In addition, the mechanism of the key cascade transformation was proposed. Further total synthesis of other resorcylates and application of the methodology to medicinal chemistry will be reported in due course.
Experimental Section

**General.** All reactions were carried out in oven-dried glassware under N₂, using commercially supplied solvents and reagents unless otherwise stated. Column chromatography was carried out on silica gel, using flash techniques. Analytical thin layer chromatography was performed on pre-coated silica gel F₂₅₄ glass plates with visualization under UV light or by staining using either acidic vanillin, anisaldehyde or ninhydrin spray reagents. ¹H and ¹³C NMR spectra were respectively recorded at 600 MHz and 150 MHz with chemical shifts (δ) quoted in parts per million (ppm) and coupling constants (J) recorded in Hertz (Hz). High-resolution ESI mass spectra were obtained on quadrupole time-of-flight instrument (Q-Star-TOF) in the electrospray-ionization mode.

**(E)-3-(3,7-Dimethylocta-2,6-dienyloxy)-3-oxopropanoic acid (3).** To a 50 mL round-bottle-flask were added Meldrum’s acid (1, 6.80 g, 47.0 mmol) and geraniol (2, 10.2 mL, 58.8 mmol) in toluene (5 mL). The mixture was refluxed with stirring for 5 h. After cooling to room temperature, aqueous ammonia (10 mL, 30%) was added and stirred for 10 min. EtOAc (30 mL) was then added, and the two phases were separated. The aqueous layer was acidified to pH~3 with 1 M HCl, and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with anhydrous MgSO₄ and subsequent rotary evaporation afforded 3 (10.04 g, 89%) as a pale yellow oil, sufficiently pure for the next step. An analytically pure sample (70%) was obtained by column chromatography as a colorless oil. Rₖ 0.27 (EtOAc/MeOH 10:1); FT-IR (KBr) ν max 1745, 1721, 1154, 980, 906, 827, 758 cm⁻¹; ¹H NMR (CDCl₃) δ 8.60 (brs, 1H), 5.35 (t, J = 7.3 Hz, 1H), 5.08 (t, J = 6.1 Hz, 1H), 4.70 (d, J = 7.2 Hz, 2H), 3.44 (s, 2H), 2.13-2.05 (m, 4H), 1.71 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H); ¹³C NMR (CDCl₃) δ 171.5, 166.9, 143.4, 131.8, 122.2, 117.4, 62.8, 40.8, 39.5, 26.2, 25.6, 17.6, 16.5. These spectroscopic details are consistent with literature data.²⁷

**(E)-3,7-Dimethylocta-2,6-dienyl 3-chloro-3-oxopropanoate (4).** Acid 3 (1.00 g, 4.16 mmol) in CH₂Cl₂ (5 mL) was added with stirring to a 25 mL round-bottle-flask containing isoamylene (4.4 mL, 41.6 mmol) at room temperature. After cooling to 0 °C, oxalyl chloride (0.50 mL, 5.72 mmol) and a drop of DMF were added sequentially. After stirring for 30 min at 0 °C and 2 h at room temperature, the mixture was rotary evaporated, and the residue was dried under vacuum to obtain the crude acid chloride 4 as a brown oil, to be used immediately at the next step.

**(E)-3,7-Dimethylocta-2,6-diyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-oxobutanoate (6).** To a solution of dioxinone 5 (0.9 mL, 6.25 mmol) in THF (2 mL) was added fresh lithium bis(trimethylsilyl) amide (6.7 mL, 6.7 mmol) at −78 °C under N₂. After stirring for 3.5 h, the crude acyl chloride 4 (1.08 g) in THF (2 mL) was added dropwise. After 1.5 h, saturated aqueous NH₄Cl (10 mL) was added to quench the reaction, and the mixture was allowed to warm to room temperature. Then Et₂O (10 mL) was added to dilute the solution, and the pH was adjusted to ~2 with HCl (1 M). The two phases were separated, and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic layers were dried with anhydrous MgSO₄, rotary evaporated,
and chromatographed on silica gel to obtain β-keto ester 6 (0.59 g, 53% over two steps from acid 3) as a yellow oil: Rf 0.22 (hexane/EtO 1:1); IR νmax 1720, 1377, 1271, 1201, 1016 cm⁻¹; ¹H NMR (CDCl₃) δ 5.36 (s, 1H), 5.35 (mc, 1H), 5.06 (mc, 1H), 4.67 (d, J = 7.2 Hz, 1H), 4.66 (d, J = 7.2 Hz, 1H), 3.51 (s, 2H), 3.50 (s, 2H), 2.10 – 2.05 (m, 4H), 1.70 (s, 9H), 1.67 (s, 3H), 1.59 (s, 3H); ¹³C NMR (CDCl₃) δ 195.7, 166.4, 163.6, 160.5, 143.6, 131.9, 123.5, 117.3, 107.3, 97.1, 62.6, 49.1, 46.9, 39.5, 32.2, 26.2, 25.7, 24.9, 17.7, 16.5; HRMS (ESI) m/z calc. C₂₀H₂₉O₆: [M + H]⁺ 365.1962; found 365.1978. These spectroscopic data are consistent with literature.²⁷

3-Phenylpropanoyl chloride (8). SOCl₂ (0.7 mL, 7.5 mmol) was added dropwise into a 25 mL round-bottle-flask containing 3-phenylpropanoic acid (1.0 g, 6.8 mmol) in CHCl₃ (10 mL). The mixture was refluxed for 3 h and rotary evaporated. Then the residue was dried under vacuum to obtain the crude acid chloride 8 for immediate use at the next step.

(E)-3,7-Dimethylocta-2,6-dienyl 2-(2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acetyl)-3-oxo-5-phenylpentanoate (9). Dioxinone 6 (200 mg, 0.55 mmol) in CH₃Cl₂ (2 mL) was added with stirring to MgCl₂ (52 mg, 0.55 mmol) and pyidine (0.1 mL, 1.1 mmol) in CH₂Cl₂ (2 mL) at 0 °C. After 1 h, 3-phenylpropanoyl chloride 8 (110 mg, 0.68 mmol) was added dropwise. The mixture was stirred at 0 °C for 1 h, and then brine (10 mL) was added to dilute the solution. The two phases were separated and the aqueous was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried with anhydrous MgSO₄, rotary evaporated and column chromatographed to afford diketoester-dioxinone 9 (155 mg, 57%) as a yellow oil: Rf 0.15 (Et₂O/hexane 1:1); FT-IR (KBr) νmax 1726, 1643, 1569, 1392, 1357, 1272, 1253, 1204, 1175, 1031, 900 cm⁻¹; ¹H NMR (CDCl₃) δ 7.28 - 7.19 (m, 5H), 5.38 (m, 1H), 5.35 (s, 1H), 5.28 (s, 1H), 5.05 (mc, 1H), 4.73 (d, J = 7.4 Hz, 2H), 3.69 (s, 2H), 3.04 - 2.95 (m, 4H), 2.07 - 2.05 (m, 4H), 1.71 - 1.59 (s, 15H); ¹³C NMR (CDCl₃) δ 197.5, 192.5, 165.2, 165.1, 160.8, 140.3, 129.0, 128.5 (2C), 128.3 (2C), 128.2, 123.5, 117.4, 108.7, 107.2, 96.5, 62.0, 61.8, 42.7, 39.5, 39.3, 32.2, 31.7, 26.2, 25.7, 24.9, 17.7, 16.5; HRMS (ESI) m/z calc. C₂₉H₃₆O₇: [M + Na]⁺ 519.2359; found 519.2378.

(E)-8-(3,7-Dimethylocta-2,6-dienyl)-7-hydroxy-2,2-dimethyl-5-phenethyl-4H-1,3-benzo-oxin-4-one (10). Pd(PPh₃)₄ (8.0 mg, 0.007 mmol) and Cs₂CO₃ (75 mg, 0.21 mmol) were stirred in THF (1 mL) for 10 min at 0 °C. Dioxinone 9 (30 mg, 0.06 mmol) in THF (1 mL) was added dropwise into the solution. Then the mixture was allowed to stand 18 h at 25 °C before brine (10 mL) was added. The mixture was then acidified to pH ~2 with HCl (1 M). The two phases were separated and the aqueous was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with anhydrous MgSO₄, rotary evaporated and column chromatographed to afford resorcylate 10 (14 mg, 53%) as a white solid. mp 134 - 136 °C (from hexane). Rf 0.28 (hexane/EtOAc 5:1); FT-IR (KBr) νmax 1725, 1684, 1593, 1515, 1297, 1211, 903 cm⁻¹; ¹H NMR (CDCl₃) δ 7.31 - 7.23 (m, 5H), 6.40 (s, 1H), 5.21 (t, J = 7.2 Hz, 1H), 5.06 (t, J = 7.2 Hz, 1H), 3.34 (d, J = 7.3 Hz, 1H), 3.33 (d, J = 7.3 Hz, 1H), 2.98 - 2.88 (m, 4H), 2.10 - 2.05 (m, 4H), 1.80 (s, 6H), 1.69 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H); ¹³C NMR (CDCl₃) δ 160.2, 156.2, 152.4, 146.3, 141.9, 140.2, 132.1, 128.7 (2C), 128.6 (2C), 128.3, 126.4, 125.8, 122.8, 120.8, 113.2, 104.7, 87.4, 72.2, 62.6, 49.1, 46.9, 39.5, 32.2, 26.2, 25.7, 24.9, 17.7, 16.5; HRMS (ESI) m/z calc. C₂₉H₃₆O₇: [M + Na]⁺ 519.2359; found 519.2378.
39.7, 37.5, 36.7, 30.7, 26.4, 25.7, 22.7, 21.9, 17.7, 16.2; HRMS (ESI) m/z calc. C_{28}H_{34}O_{4}: [M + H]^+ 435.2535; found 435.2545.

(E)-8-(3,7-Dimethylocta-2,6-dienyl)-7-methoxy-2,2-dimethyl-5-phenethyl-4H-1,3-benzodioxin-4-one (13). Phenol 10 (20 mg, 0.046 mmol), MeI (12μL, 0.2 mmol) and Cs_{2}CO_{3} (54 mg, 0.17 mmol) in THF (2 ml) were stirred at 25 °C for 12 h before reaction was quenched with H_{2}O (1 mL). The two phases were separated and the aqueous was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried with anhydrous MgSO_{4}, rotary evaporated and column chromatographed to afford 13 (20 mg, 96%) as a white solid. mp 95 - 97 °C (from hexane). R_{f} 0.42 (EtOAc/hexane 1:7); ^{1}H NMR (CDCl_{3}) δ 7.23 - 7.15 (m, 5H), 6.32 (s, 1H), 5.12 (t, J = 7.2 Hz, 1H), 4.98 (t, J = 7.2 Hz, 1H), 3.78 (s, 3H), 3.27 (d, J = 7.3 Hz, 1H), 3.25 (d, J = 7.3 Hz, 1H), 2.90 - 2.80 (m, 4H), 2.02 - 1.97 (m, 4H), 1.72 (s, 6H), 1.60 (s, 3H), 1.52 (s, 6H); ^{13}C NMR (CDCl_{3}) δ 160.3, 156.3, 152.4, 146.5, 141.9, 140.3, 132.1, 128.7 (2C), 128.4 (2C), 126.5, 125.9, 122.9, 120.8, 113.3, 104.7, 56.4, 39.8, 37.4, 36.9, 30.9, 26.5, 25.7, 22.9, 22.1, 17.8, 16.3; HRMS (ESI) m/z calc. C_{29}H_{36}O_{4}: [M + H]^+ 449.2692; found 449.2680.

Amorfrutin B. Aqueous KOH (48%, 28 mg KOH, 0.50 mmol) was added dropwise to lactone 13 (20 mg, 0.045 mmol) in DMSO (2 mL) and the mixture was heated at 80 °C for 12 h. Upon cooling, the mixture was acidified to pH ~1 with HCl (1 M). The two phases were separated and the aqueous was extracted with EtOAc (2 × 5 mL). The combined organic layers were dried with anhydrous MgSO_{4}, rotary evaporated and column chromatographed to afford amorfrutin B (14.7 mg, 80%) as a white sticky solid: R_{f} 0.38 (EtOAc/hexane 1:1); ^{1}H NMR (CDCl_{3}) δ 7.21 - 7.13 (m, 5H), 6.29 (s, 1H), 5.16 (t, J = 7.1 Hz, 1H), 4.98 (t, J = 7.1 Hz, 1H), 3.89 (s, 3H), 3.97 (d, J = 7.3 Hz, 1H), 3.01 - 2.97 (m, 4H), 2.01 - 1.96 (m, 4H), 1.72 (s, 3H), 1.60 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (CDCl_{3}) δ 157.7, 155.5, 141.8, 141.3, 137.9, 131.8, 128.5 (2C), 128.3 (3C), 125.9, 123.9, 122.1, 112.7, 108.9, 103.6, 55.7, 39.7, 38.0, 37.7, 26.5, 25.7, 22.1, 17.7, 16.1; HRMS (ESI) m/z calc. C_{26}H_{32}O_{4}: [M + H]^+ 409.2379; found 409.2388. These spectroscopic data are consistent with literature. \(^9\)

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