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

Chao Wang,*[a] Yajun Kong,[a] and Hongyun Qiao [b]

[a] *School of Material Science and Engineering, Southwest University of Science and Technology, Mianyang, Sichuan Province 621 010, China*

[b] *Research & Development Department, ChemPartner Inc., Zhangjiang Hi-Tech Park, Shanghai 201 203, China*

E-mail: cwang2004@gmail.com

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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-4*H*-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 products[1-3] 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

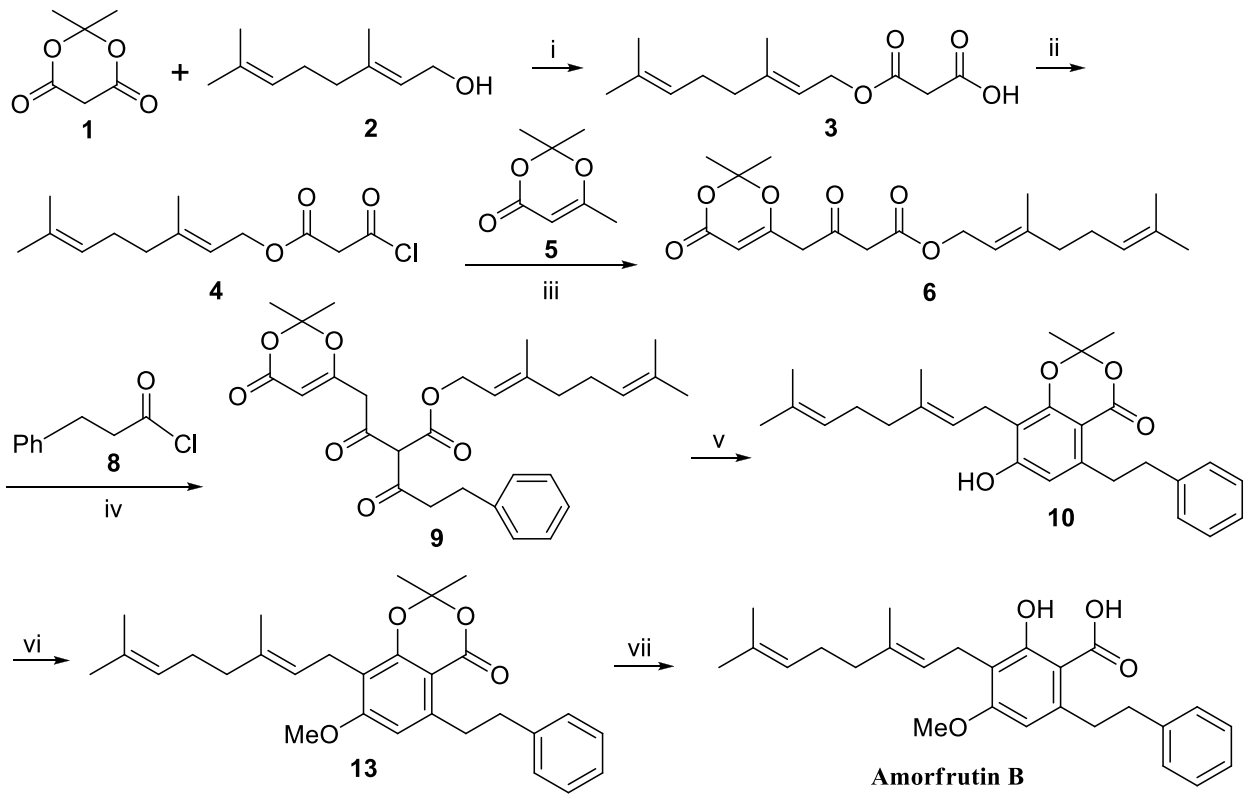
predictable application prospects, this compound has found extensive research interest in many labs, for example, in pharmacodynamic and structure–activity relationship studies.[14]

Several syntheses of geranyl bibenzyl derivatives have been reported, the majority of strategies utilizing two-step sequences: Wittig reaction followed by alkene hydrogenation,[15] benzylic metalation and subsequent alkylation[16,17] from protected phenolic precursors, and more recently palladium catalyzed Sonogashira reaction of phenylacetylene and triflate precursor followed by alkyne hydrogenation.[12] The geranyl moiety could be introduced by electrophilic aromatic alkylation with geraniol in the presence of BF_3-OEt_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.[13,15,18] However, yields were typically low, with co-production of considerable amounts of *O*-geranylated product.[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.[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

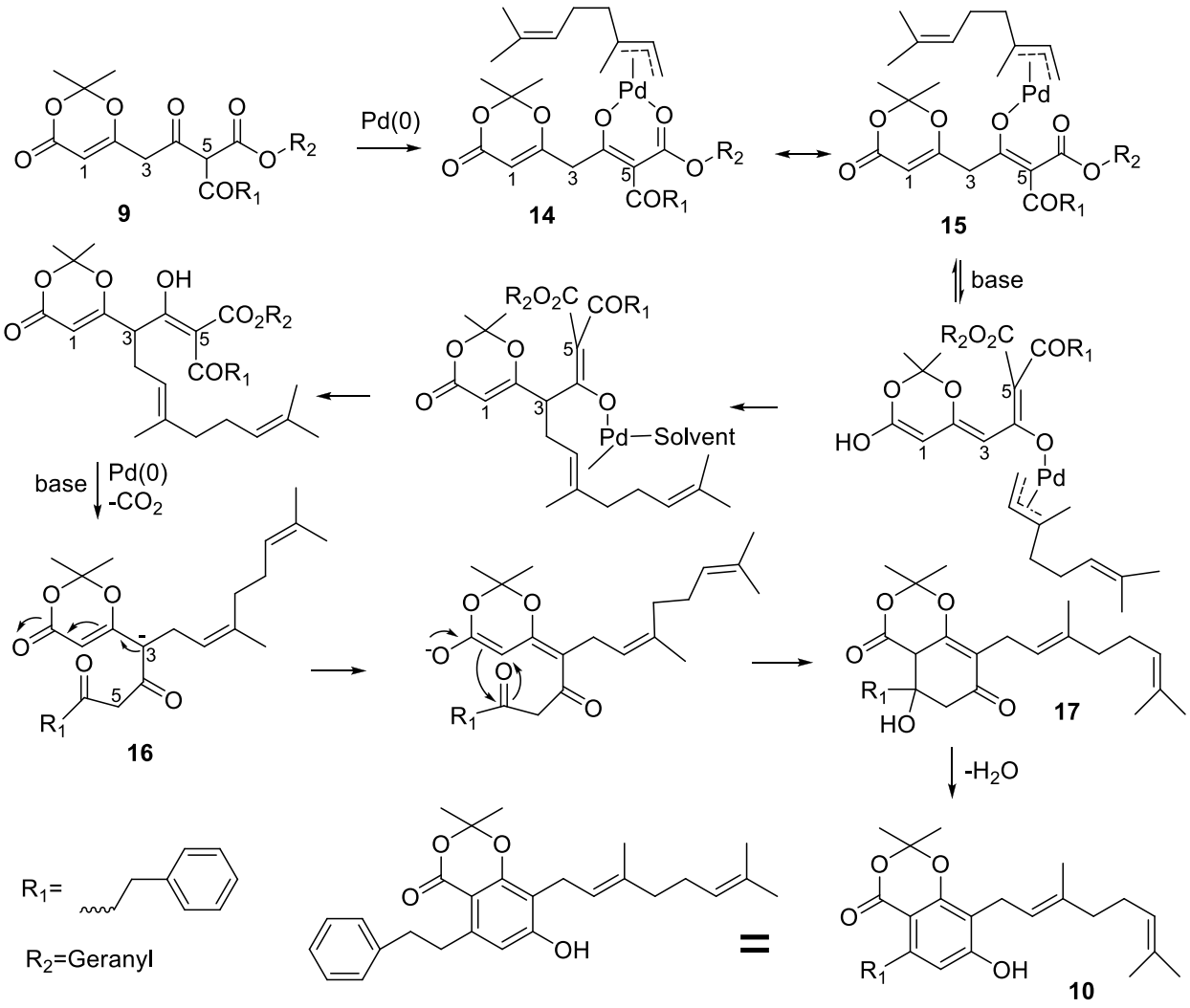
In consideration of the fact that the molecule contains a resorcylic acid unit, we were inspired by the biomimetic synthesis of resorcylates using dioxinone chemistry, especially by Barrett's elegant discovery of the cascade reaction.[23-27] Herein, we report a full description and experimental details 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.[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 $Pd(PPh_3)_4$ 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, CH_2Cl_2, r.t.; oxalyl chloride, DMF, 0 °C – r.t., 2.5 h; (iii) **5**, $TMSi_2NLi$, THF, -78 °C, 3.5 h; **4**, THF, -78 °C, 1.5 h, 53% over two steps; (iv) $MgCl_2$, pyridine, CH_2Cl_2, 0 °C, 1 h; **8**, 0 °C, 1 h, 57%; (v) $Pd(PPh_3)_4$, Cs_2CO_3, THF, 0–25 °C, 18 h, 53%; (vi) MeI, Cs_2CO_3, 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.[23-27] Naturally it would be very helpful to understand the mechanism of this important transformation. According to a recent paper,[28] 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[28] 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 N_2, 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 F_{254} glass plates with visualization under UV light or by staining using either acidic vanillin, anisaldehyde or ninhydrin spray reagents. ^{1}H and ^{13}C 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 $MgSO_4$, 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. R_f 0.27 (EtOAc/MeOH 10:1); FT-IR (KBr) ν_{max} 1745, 1721, 1154, 980, 906, 827, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 CH_2Cl_2 (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-dienyl 4-(2,2-dimethyl-4-oxo-4*H*-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 N_2. 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 NH_4Cl (10 mL) was added to quench the reaction, and the mixture was allowed to warm to room temperature. Then Et_2O (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 Et_2O (3 × 10 mL). The combined organic layers were dried with anhydrous $MgSO_4$, 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: R_f 0.22 (hexane/Et_2O 1:1); IR ν_{max} 1720, 1377, 1271, 1201, 1016 cm^{-1}; ^1H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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. $C_{20}H_{28}O_6$: $[M + H]^+$ 365.1962; found 365.1978. These spectroscopic data are consistent with literature.[27]

3-Phenylpropanoyl chloride (**8**). $SOCl_2$ (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 $CHCl_3$ (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-4*H*-1,3-dioxin-6-yl)acetyl)-3-oxo-5-phenylpentanoate (**9**). Dioxinone **6** (200 mg, 0.55 mmol) in CH_2Cl_2 (2 mL) was added with stirring to $MgCl_2$ (52 mg, 0.55 mmol) and pyridine (0.1 mL, 1.1 mmol) in CH_2Cl_2 (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 $MgSO_4$, rotary evaporated and column chromatographed to afford diketoester-dioxinone **9** (155 mg, 57%) as a yellow oil: R_f 0.15 (Et_2O/hexane 1:1); FT-IR (KBr) ν_{max} 1726, 1643, 1569, 1392, 1357, 1272, 1253, 1204, 1175, 1031, 900 cm^{-1}; ^1H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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. $C_{29}H_{36}O_7$: $[M + Na]^+$ 519.2359; found 519.2378.

(*E*)-8-(3,7-Dimethylocta-2,6-dienyl)-7-hydroxy-2,2-dimethyl-5-phenethyl-4*H*-1,3-benzodioxin-4-one (**10**). $Pd(PPh_3)_4$ (8.0 mg, 0.007 mmol) and Cs_2CO_3 (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 $MgSO_4$, rotary evaporated and column chromatographed to afford resorcylate **10** (14 mg, 53%) as a white solid. mp 134 - 136 °C (from hexane). R_f 0.28 (hexane/EtOAc 5:1); FT-IR (KBr) ν_{max} 1725, 1684, 1593, 1515, 1297, 1211, 903 cm^{-1}; ^1H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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,

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-4*H*-1,3-benzodioxin-4-one (**13**). Phenol **10** (20 mg, 0.046 mmol), MeI (12μL, 0.2 mmol) and Cs_2CO_3 (54 mg, 0.17 mmol) in THF (2 ml) were stirred at 25 °C for 12 h before reaction was quenched with H_2O (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, 128.8 (2C), 128.7 (2C), 128.4, 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), 3.69 (s, 3H), 3.32 (d, *J* = 7.3 Hz, 1H), 3.31 (d, *J* = 7.3 Hz, 1H), 2.81 - 2.77 (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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