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Unified total synthesis of amorfrutins A and C via the Claisen rearrangement

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ABSTRACT

A concise, unified total synthesis of the two prenylated aromatic polyketides amorfrutins A and C, which exhibit various medicinally important biological profiles such as antimicrobial, PPARγ modulating and quorum sensing inhibitory activities, has been achieved from commercially available 3,5-dimethoxybenzaldehyde in 38% and 10% overall yields through nine and ten steps, respectively. The key transformation for the synthesis of amorfrutin A was the Claisen rearrangement of a mono-*O*-(1,1-dimethylallyl)resorcinol derivative to install the C3-prenyl substituent, while that for the synthesis of amorfrutin C was the double Claisen rearrangement of a di-*O*-(1,1-dimethylallyl)resorcinol derivative to introduce the two prenyl groups at the C3 and C5 positions all at once.

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Amorfrutin; total synthesis; Claisen rearrangement; Amorpha fruticosa; Glycyrrhiza acanthocarpa

Amorfrturin A (**1**) (Figure 1) is a polyketide–terpenoid hybrid meroterpene isolated first from the bastard indigobush *Amorpha fruitcosa* [1] and later from the two perennial herbs *Glycyrrhiza acanthocarpa* [2] and *G. foetida* [3]. It belongs to the amorfrutin family of natural products [4] and structurally features a salicylic acid nucleus substituted at the C3, C4, and C6 positions with a prenyl, a methoxy, and a 2-phenylethyl group, respectively. The fully substituted aromatic compound amorfrutin C (**2**), a congener of amorfrutin A (**1**) with an additional prenyl substituent at the C5 position, is also a member of this family recently discovered from *G. foetida* [5]. Until now, a variety of biological activities have been reported for **1, 2**, and other members of this family, including antimicrobial [1,6], NF-κB (nuclear transcription factor-κB) inhibitory [7], PPARγ (peroxisome proliferator-activated receptor gamma) modulating [3,8–10], anti-HCV (hepatitis C virus) [11], and quorum sensing inhibitory properties [12]. These medicinally important biological activities of amorfrutins coupled with their unique poly-substituted aromatic architectures have prompted considerable synthetic efforts toward **1** and **2**, which culminated in six total syntheses of amorfrutin A (**1**) [8,11–16] as well as two total syntheses of amorfrutin C (**2**) [17,18].

The previously reported total syntheses of **1** can be categorized into 2 types according to the method to install the C3-prenyl substituent (Scheme 1(a)): *C*-prenylation of resorcinol derivative **A** ($R^1 = CO_2Me$, CO_2Et, or CHO) (method 1) and Pd(0)-catalyzed migratory prenylation–aromatization of substituted dioxinone **D** (method 2). The *C*-prenylation of **A** gave desired *C*-prenylation product **B** in moderate yields of 38–58% together with substantial amounts of *O*-prenylated byproduct **C** [8,11,12,14]. The indirect conversion of **A** (R = CO_2Me) into **B** via montmorillonite K10-catalyzed rearrangement of **C**, which could be prepared *O*-selectively from **A** in 92% yield, also resulted in a modest yield of 38% over two steps [16]. The unique and efficient decarboxylative prenyl migration–aromatization approach (method 2) successfully converted **D** into desired product **E** in 62% isolated yield [13]. As for amorfrutin C (**2**), the Sauer group employed base-induced condensation between **F** and **G** to obtain 56% yield of **H** with two prenyl groups properly and efficiently installed (Scheme 1(b)) [17]. In Xie's synthesis of **2**, the two prenyl groups were introduced into *m*-dibromobenzene derivative **I** in a stepwise manner, but the yield of the two-step sequence leading to **K** via **J** was 36%, leaving room for improvement [18].

The preceding studies were, as described above, directed toward the synthesis of each of amorfrutins A and C, and no strategy enabling the synthesis of the two natural products in a unified manner has been reported so far. In this article, we describe a unified total synthesis of the two amorfrutins using the Claisen rearrangement as the key reaction.

Results and discussion

Our retrosynthetic analysis of amorfrutins A (**1**) and C (**2**) is outlined in Scheme 2. The target molecule **1** would be obtainable via the Claisen rearrangement of aryl ether **3a** bearing a 1,1-dimethylallyl (reverse-prenyl) group [19] on the oxygen atom at the C2 position, while the 3,5-diprenylated congener **2** would be derived through the double Claisen

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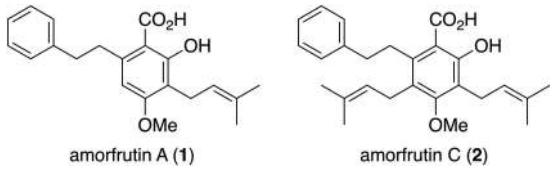
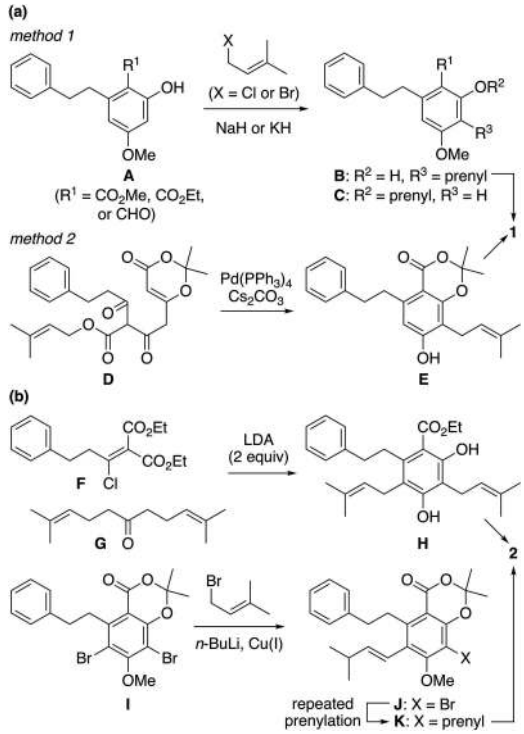
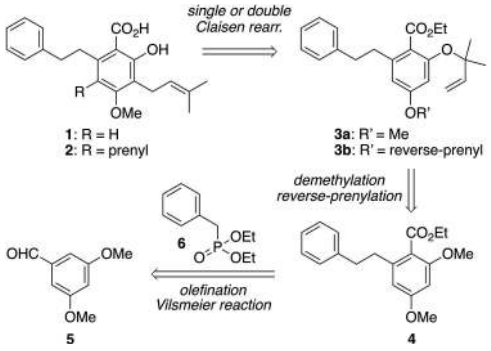


Figure 1. Structures of amorfrutins A (**1**) and C (**2**).



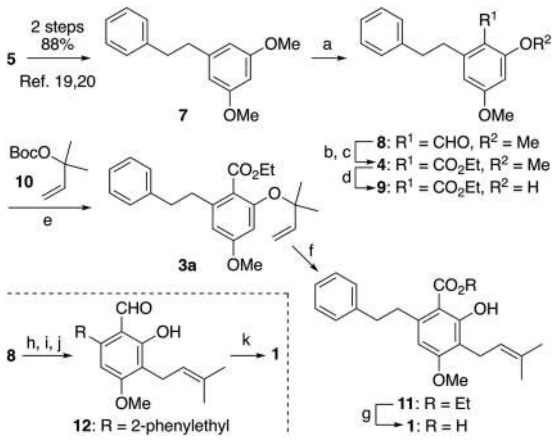
Scheme 1. Previous methods to install the C3-prenyl substituent of **1** (a) and C3- and C5-prenyl groups of **2** (b).



Scheme 2. Retrosynthetic analysis of amorfrutins A (**1**) and C (**2**).

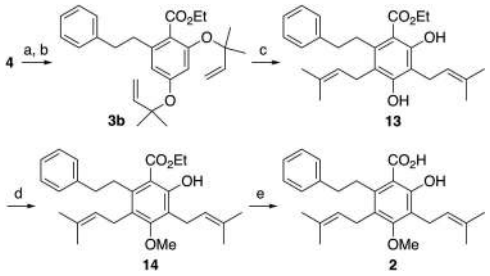
rearrangement of 2,4-di-*O*-(reverse-prenyl) ether **3b**. The aryl ethers, **3a** and **3b**, would be prepared from *m*-dimethoxybenzene derivative **4** as a common precursor by selective demethylation of the methyl ether moiety *ortho* to the ester group followed by reverse-prenylation and demethylation of the two methyl ether moieties at the C2 and C4 positions followed by double reverse-prenylation, respectively. The dimethoxy benzoate **4** should be prepared from known aromatic aldehyde **5** via its olefination with phosphonate **6** followed by hydrogenation to install the 2-phenylethyl side chain and the Vilsmeier-Haack reaction to introduce a carbonyl functionality at the C1 position.

We first undertook the synthesis of amorfrutin A (**1**) (Scheme 3). Known bibenzyl compound **7**, obtained by the Horner–Wadsworth–Emmons olefination of **5** with **6** and subsequent catalytic hydrogenation of the resulting stilbene intermediate according to the literature [20,21], was subjected to the Vilsmeier–Haack reaction to give **8** as a single formylation product in 81% yield [22]. The Pinnick oxidation of the aromatic aldehyde **8** followed by esterification of the carboxylic acid thus produced afforded **4** in an excellent yield of 93% for the 2 steps. Selective mono-demethylation of the methyl ether moiety at the C2 position of **4** with BBr_3 (1.1 equiv) provided phenol **9** in 77% yield [23]. Treatment of **9** with carbonate **10** in the presence of a catalytic amount of $Pd(PPh_3)_4$ and 4Å molecular sieves in THF effected a Tsuji–Trost-type etherification [24], furnishing the aryl reverse-prenyl ether **3a** almost quantitatively. It is worth mentioning that the addition of pulverized activated 4Å molecular sieves was necessary to obtain reproducibly high yields of **3a**. The Claisen rearrangement of **3a** to **11** was performed in 77% yield by heating a solution of **3a** in xylene under microwave irradiation conditions. Finally, saponification of the ester **11** furnished amorfrutin A (**1**) in 94% yield. It should be noted that we first attempted the oxidation of *o*-hydroxy aldehyde **12** prepared from **8** in 3 steps, but all attempted conditions including the Jones and the Pinnick oxidation conditions, 1-Me-AZADO/$PhI(OAc)_2$, and $AgNO_3$/KOH resulted in low yields of up to 32%.



Scheme 3. Synthesis of amorfrutin A (**1**).

Reagents and conditions: (a) $POCl_3$, DMF, −4°C to rt, 21 h, 81%; (b) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF/H_2O (6:1), rt, 12 h; (c) K_2CO_3, EtI, MeCN, 46°C, 40 min, 93% from **8**; (d) BBr_3, CH_2Cl_2, −78°C, 4 h, 77%; (e) $Pd(PPh_3)_4$, 4Å MS, THF, −20°C, 19.5 h, 98%; (f) microwave irradiation, *o*-xylene, reflux, 70 min, 77%; (g) KOH, EtOH/H_2O (1:1), 80°C, 6 h, 94%; (h) BBr_3, CH_2Cl_2, −78°C to rt, 2.5 h, 90%; (i) **10**, $Pd(PPh_3)_4$, 4Å MS, THF, 0°C, 16.5 h, quant; (j) *o*-xylene, reflux, 2 h, 77%; (k) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF/H_2O (12:1), rt, 6 h, 32%.



Scheme 4. Synthesis of amorfrutin C (**2**).

Reagents and conditions: (a) BBr_3, CH_2Cl_2, 0ºC, 36 h, 75%; (b) $Pd(PPh_3)_4$, **10**, 4Å MS, THF, –20ºC, 18 h, quant; (c) microwave irradiation, *o*-xylene, reflux, 3 h, 52%; (d) MeI, K_2CO_3, acetone, rt, 19 h, 50%; (e) KOH, EtOH/H_2O (5:1), 70ºC, 70 h, 75%.

The synthesis of amorfrutin C (**2**) was implemented by a five-step sequence from the common intermediate **4** as shown in Scheme 4. Demethylation of both the C2 and C4 methoxy groups of **4** by treatment with an excess amount of BBr_3 afforded a resorcinol intermediate in 75% yield, although it required a higher temperature (0°C) and a longer reaction time (36 h) as compared to those employed for mono-demethylation of **4** to afford **9** (–78°C, 4 h; see Scheme 3). Reverse-prenylation of the two phenolic hydroxyls of the intermediate proceeded uneventfully to furnish a quantitative yield of **3b**, which was then heated under microwave irradiation conditions to perform its double Claisen rearrangement to **13**. This reaction gave a mixture of several products after complete consumption of the starting material **3b**, from which the desired product **13** was successfully isolated in a moderate yield of 52%. Finally, selective *O*-methylation of the C4-OH group of **13** with MeI and K_2CO_3 in acetone [17] followed by saponification of the resulting ester **14** completed the total synthesis of amorfrutin C (**2**). The spectroscopic data of the synthetic amorfrutin C (**2**) were in good agreement with those of natural product [5,18].

Conclusion

The concise total synthesis of amorfrutin A (**1**) has been accomplished from commercially available 3,5-dimethoxybenzaldehyde **5** in 38% overall yield by a nine-step sequence (or from the known compound **7** in 48% overall yield through 7 steps) that involves the Claisen rearrangement of the mono-reverse-prenylated intermediate **3a** as the key step. Amorfrutin C (**2**), 5-prenylated congener of **1**, has also been synthesized in ten steps from **5** in 10% overall yield by exploiting the double Claisen rearrangement of 2,4-di-*O*-reverse-prenylated intermediate **3b**, which was derived from the*m*-dimethoxybenzene derivertive **4**, a common synthetic precursor of the two amorfrutins. Synthetic efforts toward other members of this class of natural products are now in progress and will be reported in due course.

Experimental

General procedure

IR spectra were recorded by a Jasco FT/IR-4100 spectrometer using an ATR (ZnSe) attachment. NMR spectra were recorded with TMS as an internal standard in $CDCl_3$ by a Varian 400-MRTT spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C) or a Varian 600TT spectrometer (600 MHz for ^1H and 150 MHz for ^{13}C) unless otherwise stated. Optical rotation values were measured with a Jasco P-2200 polarimeter. Mass spectra were obtained with Jeol JMS-700 spectrometer operated in the FAB mode. Merck silica gel 60 (63–200 μm) was used for column chromatography unless otherwise stated. Analytical thin-layer chromatography was performed using Merck silica gel 60 F_{254} plates (0.25 mm thick). Solvents for reactions were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2 and DMF from CaH_2. All air- or moisture-sensitive reactions were conducted under a nitrogen atmosphere unless otherwise stated.

2,4-dimethoxy-6-(2-phenylethyl)benzaldehyde (8)

A stock solution of the Vilsmeier reagent (ca. 2.0 M in DMF) was prepared in advance from DMF (31.5 mL) and $POCl_3$ (7.20 mL, 77.3 mmol). The solution (18 mL, 36 mmol) was added dropwise to a stirred solution of 1,3-dimethoxy-5-(2-phenylethyl) benzene (3.53 g, 14.6 mmol) in DMF (24.0 mL) at – 4°C. The reaction mixture was warmed to room temperature and stirred for 21 h. The reaction mixture was quenched with satd aq NH_4Cl while cooling with an ice bath and extracted three times with EtOAc. The extract was successively washed with 5% aq LiCl and brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc = 9:1) to give aldehyde **8** (3.17 g, 81%) as a white solid, whose spectral data were identical to those reported in the literature [22].

Ethyl 2,4-dimethoxy-6-(2-phenylethyl)benzoate (4)

To a stirred solution of **8** (202 mg, 0.747 mmol) in THF/H_2O (6:1, 7 mL) was successively added NaH_2PO_4 (258 mg, 2.15 mmol), 2-methyl-2-butene (800 μL, 7.55 mmol) and $NaClO_2$ (75% dispersion in H_2O, 270 mg, 2.24 mmol) at room temperature. After stirring for 12 h, the reaction mixture was diluted with brine and extracted three times with CH_2Cl_2. The extract was dried (Na_2SO_4), filtered and concentrated in vacuo and the residue was taken up in MeCN (2.20 mL). To the solution was successively added K_2CO_3 (310 mg, 2.24 mmol) and EtI (300 μL, 3.75 mmol) at room temperature. The mixture was

warmed to 46°C and stirred for 40 min. The mixture was diluted with brine at room temperature and extracted three times with EtOAc. The extract was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc = 4:1) to give **4** (219 mg, 93% from **8**) as a colorless oil. IR: υ_{max} 1723 (s), 1602 (s), 1587 (m), 1496 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.1 Hz), 2.83–2.93 (4H, m), 3.75 (3H, s), 3.81 (3H, s), 4.38 (2H, q, J = 7.2 Hz), 6.24 (1H, d, J = 2.2 Hz), 6.33 (1H, d, J = 2.2 Hz), 7.16–7.22 (3H, m), 7.26–7.31 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 36.1, 37.6, 55.3, 55.9, 61.1, 96.6, 105.9, 116.6, 126.0, 128.36 (2C), 128.42 (2C), 141.5, 141.7, 158.0, 161.2, 168.3; HRMS (FAB): m/z calcd for $C_{19}H_{23}O_4$, 315.1591; found, 315.1599 ([M + H]$^+$).

Ethyl 2-hydroxy-4-methoxy-6-(2-phenylethyl)-benzoate (9)

To a stirred solution of **4** (128 mg, 0.407 mmol) in CH_2Cl_2 (4.10 mL) was added dropwise a solution of BBr_3 (1.0 M in CH_2Cl_2, 440 µL, 0.44 mmol) at – 78°C. After stirring for 4 h at the same temperature, the reaction mixture was quenched with satd aq $NaHCO_3$ and extracted three times with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc = 10:1) to give **9** (94.0 mg, 77%) as a white solid. Mp 51–52 °C; IR: υ_{max} 1651 (vs), 1616 (s), 1322 (m), 1257 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (3H, t, J = 7.1 Hz), 2.84–2.90 (2H, m), 3.18–3.24 (2H, m), 3.77 (3H, s), 4.44 (2H, q, J = 7.2 Hz), 6.25 (1H, d, J = 2.7 Hz), 6.36 (1H, d, J = 2.7 Hz), 7.15–7.23 (3H, m), 7.27–7.32 (2H, m), 11.9 (1H, s, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 38.0, 38.4, 55.3, 61.4, 99.2, 104.8, 110.9, 126.0, 128.2 (2C), 128.3 (2C), 141.8, 146.7, 163.9, 165.6, 171.4; HRMS (FAB): m/z calcd for $C_{18}H_{21}O_4$, 301.1434; found, 301.1438 ([M + H]$^+$).

Ethyl 4-methoxy-2-[(2-methylbut-3-en-2-yl)oxy]-6-(2-phenylethyl)benzoate (3a)

To a stirred solution of **9** (83.0 mg, 0.276 mmol) and *tert*-butyl (2-methylbut-3-en-2-yl) carbonate (**10**) (180 mg, 0.966 mmol) in degassed THF (550 µL) was added pulverized 4Å molecular sieves (276 mg) at room temperature. After cooling to – 20°C, $Pd(PPh_3)_4$ (16.0 mg, 0.0138 mmol) was added portionwise and the resulting suspension was stirred for 19.5 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The residue was purified by SiO_2 column chromatography (pentane/Et_2O = 8:1) to give **3a** (100 mg, 98%) as a colorless oil. IR: υ_{max} 3025 (m), 1725 (s), 1602 (s), 1579 (m), 1199 (m), 1158 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.1 Hz), 1.46 (6H, s), 2.80–2.91 (4H, m), 3.68 (3H, s), 4.35 (2H, q, J = 7.2 Hz), 5.16 (1H, dd, J = 0.9, 10.9 Hz), 5.23 (1H, dd, J = 0.9, 17.6 Hz), 6.19 (1H, dd, J = 10.9, 17.7 Hz), 6.29 (1H, d, J = 2.3 Hz), 6.58 (1H, d, J = 2.3 Hz), 7.15–7.21 (3H, m), 7.24–7.30 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 26.9 (2C), 36.1, 37.6, 55.2, 60.9, 80.6, 103.7, 107.6, 113.4, 120.6, 125.9, 128.3 (2C), 128.4 (2C), 140.9, 141.6, 144.8, 154.9, 160.1, 168.7; HRMS (FAB): m/z calcd for $C_{23}H_{29}O_4$, 369.2060; found, 369.2067 ([M + H]$^+$).

Ethyl 2-hydroxy-4-methoxy-3-(3-methylbut-2-en-1-yl)-6-(2-phenylethyl)benzoate (11)

A solution of **3a** (99.0 mg, 0.269 mmol) in *o*-xylene (2.00 mL) in a microwave reaction vessel was heated to reflux under irradiation of microwave (300 W, CEM Discover Microwave System) for 70 min. The reaction mixture was concentrated in vacuo and the residue was purified by SiO_2 column chromatography (hexane/EtOAc = 20:1) to give **11** (76 mg, 77%) as a white solid. Mp 64°C; IR: υ_{max} 3027 (m), 1727 (s), 1650 (w), 1602 (s), 1459 (m), 1158 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (3H, t, J = 7.2 Hz), 1.66–1.69 (3H, m), 1.78 (3H, br s), 2.85–2.91 (2H, m), 3.19–3.25 (2H, m), 3.33 (2H, d, J = 7.0 Hz), 3.77 (3H, s), 4.44 (2H, q, J = 7.1 Hz), 5.17–5.23 (1H, m), 6.16 (1H, s), 7.15–7.23 (3H, m), 7.24–7.32 (2H, m), 11.8 (1H, s, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 17.8, 22.0, 25.8, 38.2, 38.8, 55.4, 61.3, 105.3, 106.0, 115.2, 122.4, 125.9, 128.31 (2C), 128.34 (2C), 131.6, 141.9, 143.9, 161.0, 161.9, 171.7; HRMS (FAB): m/z calcd for $C_{23}H_{28}O_4Na$, 391.1880; found, 391.1882 ([M+ Na]$^+$).

2-hydroxy-4-methoxy-3-(3-methylbut-2-en-1-yl)-6-(2-phenylethyl)benzoic acid: amorfrutin a (1)

To a stirred solution of **11** (53.0 mg, 0.144 mmol) in a mixed solvent of EtOH and H_2O (1:1, 1.40 mL) was added KOH (343 mg, 6.11 mmol) at room temperature. The reaction mixture was warmed to 80°C, stirred for 5 h, and then concentrated in vacuo. The residue was acidified with 2 M HCl (pH 3) and extracted five times with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc = 10:1) to give **1** (46 mg, 94%) as a white solid. An analytical sample was recrystallized from hexane/EtOAc to give NMR spectroscopically pure **1** as colorless prisms. Mp 151–152°C; IR: υ_{max} 3025 (m), 2926 (br), 1627 (s), 1610 (s), 1455 (m), 1267 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68 (3H, d, J = 0.9 Hz), 1.79 (3H, br s), 2.88–2.97 (2H, m), 3.22–3.31 (2H, m), 3.35 (2H, d, J = 7.0 Hz), 3.79 (3H, s), 5.17–5.24 (1H, m), 6.22 (1H, s), 7.17–7.23 (3H, m), 7.27–7.33 (2H, m), 11.6 (1H, br s, OH);^{13}C NMR (100 MHz, $CDCl_3$): δ 17.8, 22.0, 25.8,

38.1, 39.2, 55.5, 103.6, 106.5, 115.3, 122.1, 125.9, 128.4 (2C), 128.5 (2C), 131.8, 141.9, 145.8, 162.1, 162.9, 176.0; HRMS (FAB): *m/z* calcd for $C_{21}H_{24}O_4Na$, 363.1567; found, 363.1570 ([M+ Na]$^+$).

Ethyl 2,4-bis[(2-methylbut-3-en-2-yl)oxy]-6-(2-phenylethyl)benzoate (3b)

To a stirred solution of **4** (3.05 g, 9.70 mmol) in CH_2Cl_2 (60.0 mL) was added dropwise a solution of BBr_3 (1.0 M in CH_2Cl_2, 50.0 mL, 48.5 mmol) at 0 °C. After stirring for 36 h, the reaction mixture was quenched with satd aq $NaHCO_3$ and extracted four times with $CHCl_3$. The extract was successively washed with water and brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc = 8:1) to give ethyl 2,4-dihydroxy-6-(2-phenylethyl)benzoate (2.08 g, 75%) as a pale yellow solid. Mp 89–90°C; IR: υ_{max} 3381 (br), 1652 (s), 1618 (s), 1495 (m), 1314 (s), 1262 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (3H, t, J = 7.2 Hz), 2.84–2.90 (2H, m), 3.17–3.23 (2H, m), 4.44 (2H, q, J = 7.2 Hz), 5.10–5.13 (1H, m), 6.18 (1H, d, J = 2.6 Hz), 6.30 (1H, d, J = 2.6 Hz), 7.15–7.23 (3H, m), 7.25–7.33 (2H, m) 11.8 (1H, s, OH);^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 37.8, 38.1, 61.6, 101.6, 104.9, 111.3, 125.9, 128.1 (2C), 128.3 (2C), 141.6, 147.6, 160.6, 164.9, 171.5; HRMS (FAB): *m/z* calcd for $C_{17}H_{19}O_4$, 287.1278; found, 287.1288 ([M + H]$^+$). To a stirred solution of the dihydroxy benzoate obtained above (517 mg, 1.81 mmol) and *tert*-butyl (2-methylbut-3-en-2-yl) carbonate (2.06 g, 11.1 mmol) in THF (3.60 mL) was added pulverized 4Å molecular sieves (1.38 g) at room temperature. After cooling to – 20°C, $Pd(PPh_3)_4$ (209 mg, 0.181 mmol) was added portionwise and the resulting suspension was stirred for 18 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The residue was purified by SiO_2 column chromatography (pentane/Et_2O = 9:1, containing 1% Et_3N) to give **3b** (770 mg, quant) as a pale yellow oil. IR: υ_{max} 3025 (w), 1730 (s), 1602 (s), 1264 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34–1.39 (9H, m), 1.43 (6H, s), 2.76–2.89 (4H, m), 4.35 (2H, q, J = 7.2 Hz), 5.06–5.21 (4H, m), 6.03 (1H, dd, J = 10.7, 17.8 Hz), 6.13 (1H, dd, J = 10.9, 17.6 Hz), 6.41 (1H, d, J = 2.1 Hz), 6.65 (1H, d, J = 2.1 Hz), 7.13–7.19 (3H, m), 7.23–7.29 (2H, m);^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 26.86 (2C), 26.90 (2C), 35.7, 37.4, 60.8, 79.6, 80.4, 109.5, 113.1, 113.2, 115.4, 121.4, 125.8, 128.27 (2C), 128.34 (2C), 139.9, 141.6, 144.0, 144.5, 154.0, 156.7, 168.8; HRMS (FAB): *m/z* calcd for $C_{27}H_{35}O_4$, 423.2530; found, 423.2539 ([M + H]$^+$).

Ethyl 2,4-dihydroxy-3,5-bis(3-methylbut-2-en-1-yl)-6-(2-phenylethyl)benzoate (13)

A stirred solution of **3b** (808 mg, 1.91 mmol) in *o*-xylene (2.0 mL) in a microwave reaction vessel was heated to reflux under irradiation of microwave (300 W, CEM Discover Microwave System) for 3 h. The reaction mixture was concentrated in vacuo and the residue was purified two times by SiO_2 column chromatography (hexane/EtOAc = 9:1 and then CH_2Cl_2/benzene = 1:1) to give **13** (420 mg, 52%) as a pale yellow oil. IR: υ_{max} 3403 (br), 3020 (w), 1647 (s), 1605 (m), 1311(s), 1267(s), 1199(s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (3H, t, J = 7.1 Hz), 1.71 (3H, d, J = 1.2 Hz), 1.75 (6H, s), 1.83 (3H, br s), 2.81–2.88 (2H, m), 3.19–3.26 (2H, m), 3.36 (2H, br d, J = 6.4 Hz), 3.45 (2H, br d, J = 7.0 Hz), 4.44 (2H, q, J = 7.2 Hz), 5.03–5.09 (1H, m), 5.22–5.29 (1H, m), 6.02 (1H, s), 7.18–7.25 (3H, m), 7.28–7.34 (2H, m), 11.7 (1H, s, OH);^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 17.9, 18.0, 22.4, 25.1, 25.7, 25.8, 32.6, 37.1, 61.5, 105.8, 112.3, 119.3, 121.7, 122.9, 125.9, 128.0 (2C), 128.4 (2C), 133.3, 134.9, 141.1, 142.1, 158.3, 160.0, 172.0; HRMS (FAB): *m/z* calcd for $C_{27}H_{34}O_4Na$, 445.2349; found, 445.2355 ([M+ Na]$^+$).

Ethyl 2-hydroxy-4-methoxy-3,5-bis(3-methylbut-2-en-1-yl)-6-(2-phenylethyl)benzoate (14)

To a stirred solution of **13** (82.0 mg, 0.194 mmol) in acetone (1.90 mL) was added portionwise K_2CO_3 (26.0 mg, 0.188 mmol) at room temperature. After stirring for 5 min, the reaction mixture was cooled to – 1°C. To the mixture was added MeI (12.0 μL, 0.193 mmol) and the mixture was warmed to room temperature and stirred for 19 h. The reaction mixture was concentrated in vacuo and the residue was diluted with a mixed solvent of H_2O, hexane and Et_2O (1:1:1). The mixture was neutralized with 1 M HCl and extracted three times with Et_2O. The extract was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc = 24:1) to give **14** (42 mg, 50%) as a colorless oil. IR: υ_{max} 3382 (br), 1651 (s), 1317 (s), 1264 (s), 1198 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (3H, t, J = 7.1 Hz), 1.66 (3H, d, J = 1.3 Hz), 1.70 (3H, d, J = 1.2 Hz), 1.71 (3H, d, J = 0.9 Hz), 1.79 (3H, d, J = 0.8 Hz), 2.78–2.85 (2H, m), 3.19–3.26 (2H, m), 3.34 (2H, d, J = 6.1 Hz), 3.39 (2H, d, J = 6.6 Hz), 3.71 (3H, s), 4.45 (2H, q, J = 7.2 Hz), 4.99–5.06 (1H, m), 5.22–5.28 (1H, m), 7.17–7.24 (3H, m), 7.27–7.33 (2H, m), 11.2 (1H, s, OH);^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 17.9,

18.0, 23.5, 25.3, 25.6, 25.7, 32.4, 37.3, 61.5, 61.7, 109.7, 121.2, 122.8, 124.2, 125.9, 126.1, 128.0 (2C), 128.3 (2C), 131.5, 131.7, 141.4, 142.1, 160.1, 161.4, 171.6; HRMS (FAB): *m/z* calcd for $C_{28}H_{36}O_4Na$, 459.2506; found, 459.2510 ([M+ Na]$^+$).

2-hydroxy-4-methoxy-3,5-bis(3-methylbut-2-en-1-yl)-6-(2-phenylethyl)benzoic acid: odfamorfrutin C (2)

To a stirred solution of **14** (51.0 mg, 0.117 mmol) in a mixed solvent of EtOH and H_2O (5:1, 1.2 mL) was added KOH (34.0 mg, 0.606 mmol) at room temperature. The mixture was warmed to 70°C and stirred for 70 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo and the residue was acidified with 1 M HCl (pH 3). The mixture was extracted four times with $CHCl_3$ and the extract was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc = 3:1) to give **2** (36 mg, 75%) as a white solid. An analytical sample was recrystallized from hexane/EtOAc to give NMR spectroscopically pure **2** as colorless needles. Mp 112–113°C; IR: υ_{max} 3025 (m), 2970 (br), 1634 (s), 1590 (m), 1452 (m), 1259 (s); ^{1}H NMR (600 MHz, CD_3OD): δ 1.67 (6H, br s), 1.72 (3H, s), 1.78 (3H, s), 2.75–2.81 (2H, m), 3.16–3.21 (2H, m), 3.33–3.36 (4H, m), 3.67 (3H, s), 4.99–5.04 (1H, m), 5.20–5.25 (1H, m), 7.13–7.21 (3H, m), 7.25 (2H, t, J = 7.4 Hz);^{13}C NMR (150 MHz, CD_3OD): δ 18.0, 18.2, 24.3, 25.8, 25.9, 26.2, 34.4, 38.7, 61.9, 110.8, 122.0, 124.3, 125.7, 126.87, 126.93, 129.27, 129.32, 131.9 (2C), 132.1 (2C), 143.5, 143.8, 161.9, 162.5, 175.0; HRMS (FAB): *m/z* calcd for $C_{26}H_{32}O_4Na$, 431.2193; found, 431.2198 ([M+ Na]$^+$).

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Author contribution

Y.O. and S.K. designed the synthetic route. Y.O. and S. K. wrote the manuscript. T.F. conducted the synthetic experiments with the aid of Y.O.

Disclosure statement

No potential conflict of interest was reported by the authors.

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