

Syntheses of Amorfrutins and Derivatives via Tandem Diels–Alder and Anionic Cascade Approaches

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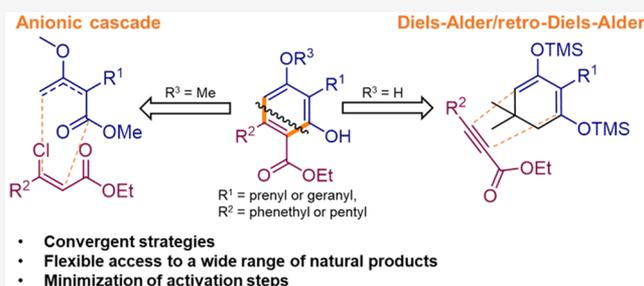
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ABSTRACT: We describe two complementary approaches based on a convergent [4+2] logic toward the synthesis of amorfrutins, cannabinoids, and related plant metabolites. An anionic cascade cyclization employing β -methoxycrotonates and β -chloro- α,β -unsaturated esters yielded amorfrutins in four linear steps and demonstrated utility of β -alkoxycrotonate-derived nucleophiles as functional equivalents of β -ketoester-derived dianions. Analogously, tandem Diels–Alder/retro-Diels–Alder cycloaddition of dimedone-derived bis(trimethylsiloxy)-dienes and α,β -alkynyl ester dienophiles provided facile access to resorcinol precursors of amorfrutins and cannabinoids, avoiding late-stage installation of prenyl or geranyl moieties as in previous approaches.



Amorfrutins are plant-derived natural products based on an isoprenoid-substituted β -resorcylic acid core, with a wide range of biological activities.^{1,2} Amorfrutin A (1) and B (2) (Figure 1a), isolated from *Amorpha fruticosa* and *Glycyrrhiza foetida*, increase insulin production in mice by targeting the peroxisome proliferator-activated receptor gamma (PPAR γ), a key regulator of fat and glucose metabolism, and further decrease inflammation.^{3–5} A structural variant, amorfrutin 2 (3), also demonstrates high affinity to PPAR γ despite bearing a pentyl group instead of the phenethyl moiety. Amorfrutin C (4), isolated from the plant *Glycyrrhiza foetida*, reduces colon cancer progression by disrupting mitochondrial function via an unknown mechanism.^{6,7} Corresponding resorcinol derivatives of amorfrutin A and B have been isolated from *R. complanata* and *H. umbraculigerum*,^{8–11} and similar resorcinol-based natural products have been described, such as grifolic acid (5) first identified from the fungus *Albatrellus confluens*.¹² Amorfrutins are closely related to cannabinoids, such as CBGA (6), with identical substitution positions of geranyl and pentyl groups about the resorcinol.¹¹

Given their potential pharmaceutical significance, numerous approaches to amorfrutins and related derivatives have been reported over the past decade.^{3,4,13–22} Earlier syntheses were based on extensive derivatization of phloroglucinol carboxylic acid (7) via Mitsunobu, Sonogashira coupling, and ortho-alkylation steps (Figure 1b, approach A).^{3,4} In application to amorfrutin A (1), an elegant tandem Michael–Claisen condensation approach using ethyl acetoacetate (8) and Michael acceptor (9) provided a 1,3-cyclohexadione adduct, which was converted to the corresponding resorcinol by oxidative aromatization using mercury(II) acetate (approach

B).¹³ Notably, the majority of previous amorfrutin syntheses include a problematic late-stage installation of prenyl or geranyl (R^1) substituents, requiring potassium phenolates/hydrophobic solvents to favor C- vs O-alkylation.^{3,4,13,14} Subsequent iterations of this approach employed a Claisen rearrangement of dimethylallyl ether precursors¹⁵ or a decarboxylative prenyl migration–aromatization sequence.¹⁶

We envisioned developing shorter and more broadly applicable routes that would minimize the use of activation steps and avoid late-stage installation of the R^1 moiety, while increasing the scope to include cannabinoid derivatives such as CBGA (6). Whereas most previous approaches employ aromatic precursors and proceed in a linear fashion, we here describe two routes to amorfrutins and related cannabinoids that both utilize a convergent [4+2] assembly strategy for the aromatic core. Approach C is based on a novel tandem anionic cascade addition sequence using enolates of β -methoxycrotonate methyl esters (10) and β -chloro- α,β -unsaturated Michael acceptors (11). Approach D is based on a Diels–Alder/retro-Diels–Alder step employing dimedone-derived 1,3-bis(trimethylsiloxy)-dienes (12) and α,β -alkynyl esters (13).^{23–25}

Approach C was inspired by a tandem Michael–Aldol sequence recently described for the synthesis of amorfrutin C

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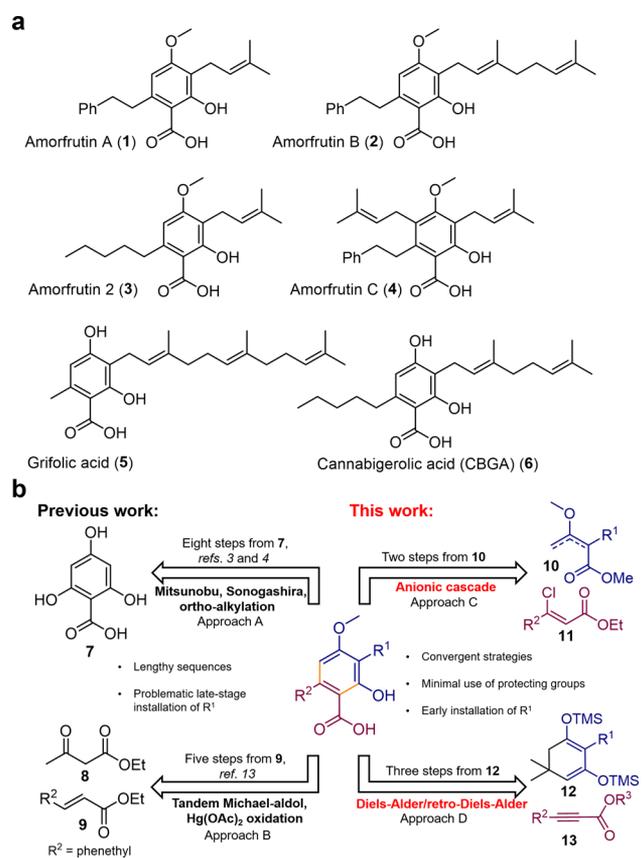
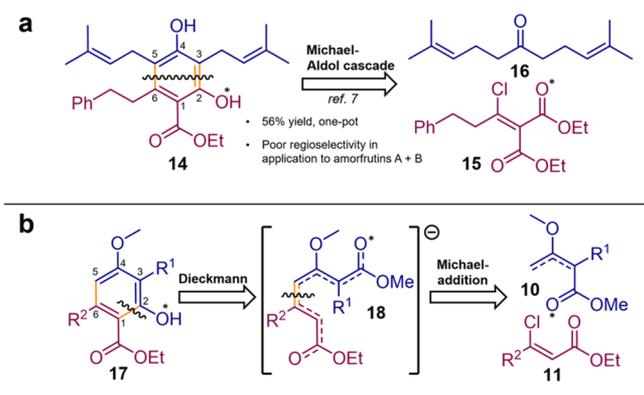


Figure 1. (a) Examples of amorfrutin and cannabinoid derivatives. (b) Representative previous approaches to amorfrutins (left) and this work (right).

(4), which furnished the resorcinol precursor (14) in 56% yield from treatment of the β -chloro- α,β -unsaturated malonate derivative (15) with approximately two equivalents of lithiated 1,3-diprenylacetone (16) (Scheme 1a).⁷ However, when

Scheme 1. Retrosynthetic Analyses for Tandem Anionic Cascade Addition Approaches

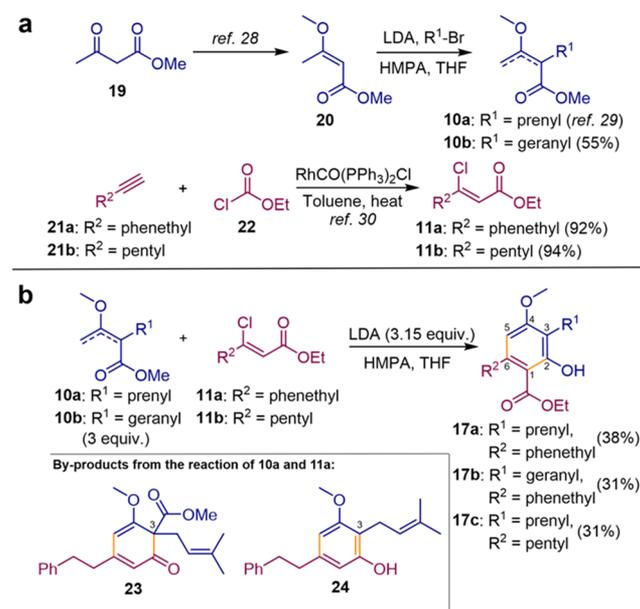


applied to unsymmetrically substituted ketones, this reaction produced mixtures of difficult-to-separate regioisomers. Next, we considered applicability of a tandem Michael-addition–Dieckmann condensation/annulation sequence as previously employed for the synthesis of mycophenolic acid,²⁶ suggesting a retrosynthetic cut in the ring formation step between C1–C2 (Scheme 1b) as opposed to C2–C3 for the Michael–Aldol approach (Scheme 1a). We envisioned that ring formation to

provide amorfrutin esters and derivatives (17) could result from a Dieckmann cyclization of an intermediate (18) derived from Michael addition of deprotonated β -methoxy- α -alkylcrotonate derivatives (10) to (*Z*)- β -chloro- α,β -unsaturated ester Michael acceptors (11) (Scheme 1b), analogous to a previously described method for the preparation of *p*-hydroxybenzoates.²⁷

α -Alkylation of methyl β -methoxycrotonate (20)²⁸ derived from commercially available methyl acetoacetate (19) provided facile access to mixtures of α,β - and β,γ -unsaturated enol ethers 10a and 10b (Scheme 2a).²⁹ (*Z*)- β -Chloro- α,β -

Scheme 2. Synthesis of Amorfrutin Derivatives via the Anionic Cascade Approach



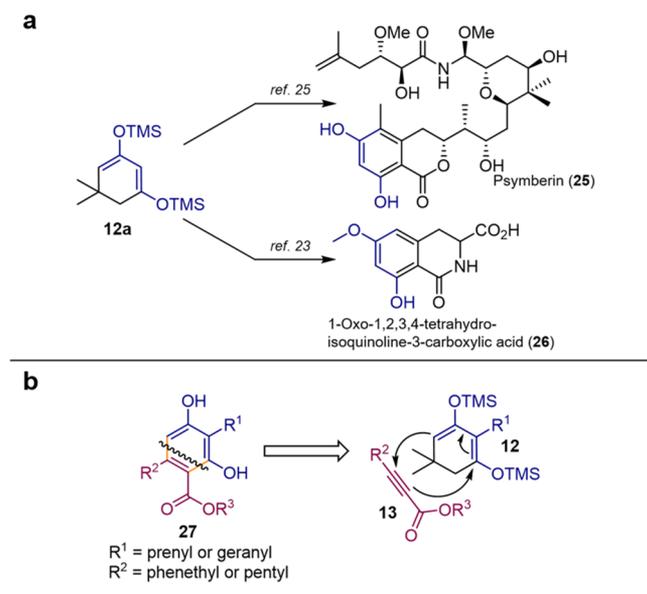
unsaturated esters 11a and 11b were prepared in a high yield in one step from terminal alkynes, e.g., 21a and 21b, using a rhodium-catalyzed chloroesterification approach using ethyl chloroformate (22).³⁰

Provided that initial Michael addition to β -chloroester Michael acceptors consumes one equivalent of base, it appeared that at least two equivalents of base were required to allow further deprotonation of the Michael adduct for subsequent Dieckmann cyclization, such as for the Michael–Aldol annulation (Scheme 1a). Varying equivalents of LDA and enol ether 10a/b, we found that use of three equivalents of base and enol ether was necessary for complete consumption of β -chloroesters 11, affording the desired amorfrutin ethyl esters 17a–c as well as byproducts (i.e., 23 and 24) derived from alternative cyclization via C3 and the ethyl ester moiety (see Figure S1), which could be easily separated. Byproduct formation could be partially suppressed by addition of a stoichiometric amount of HMPA. The excess of enol ethers 10a/b was recoverable and recyclable. Although modest yielding, this annulation sequence provided two carbon–carbon bonds in one pot, furnishing esters of amorfrutins A, B, and 2 (17a–c) in three linear steps starting from methyl acetoacetate (19).

Next, we examined a related retrosynthetic approach based on the formation of the same carbon–carbon bonds as in the Michael–Dieckmann cascade approach, but instead using a

Diels–Alder reaction. Tandem Diels–Alder/retro-Diels–Alder approaches using 1,3-bis(trimethylsilyloxy)-dienes derived from dimedone (i.e., **12a**) have been reported as highly regioselective for ene-yne²⁴ as well as α,β -alkynyl esters (**13**), e.g., in application to the syntheses of psymberin (**25**)²⁵ and 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**26**) (Scheme 3a).²³ We reasoned that the application of

Scheme 3. Utility of Tandem Diels–Alder/Retro-Diels–Alder Approaches to Resorcinol Derivatives

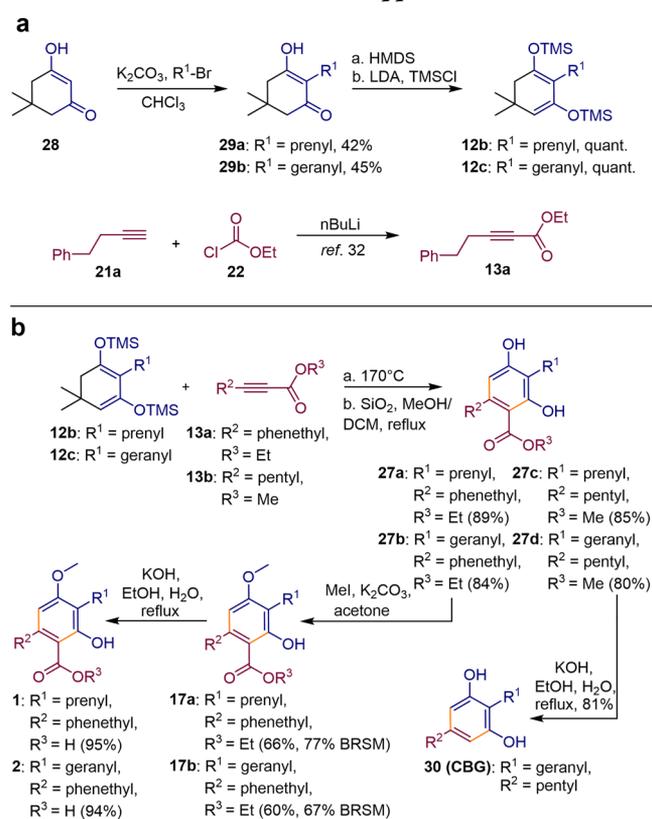


this methodology to 2-alkyldimedone derivatives should provide access to diverse amorfrutin and cannabinoid derivatives through their resorcinol precursors (**27**) (Scheme 3b).

The requisite 1,3-bis(trimethylsilyloxy)-dienes were prepared in two steps from dimedone (**28**) (Scheme 4a). Alkylation of dimedone (**28**) with prenyl and geranyl bromides furnished 2-substituted derivatives **29a** and **29b**, in addition to *O*-alkylation and bis-alkylation byproducts,³¹ which could be removed easily by crystallization of the product from the reaction mixture. The corresponding bis(trimethylsilyloxy)-dienes **12b** and **12c** were prepared analogous to known procedures.²³ Silylation proceeds quantitatively, and products require no purification for use in the subsequent Diels–Alder reaction. Dienophile (**13a**), targeting amorfrutin A and B, was prepared via acylation of 4-phenyl-1-butyne (**21a**) using *n*BuLi and ethyl chloroformate (**22**),³² whereas methyl-2-octynoate (**13b**), used for the preparation of amorfrutin 2 and cannabinoids, was commercially available.

The Diels–Alder/retro-cycloaddition step was performed neat using dienes **12b** or **12c** and alkynoates **13a** or **13b** (Scheme 4b). Complete consumption of dienophiles required high temperatures (~170 °C) and use of up to 4.3 equivalents of dienes **12b** and **12c**. Gratifyingly, ¹H NMR spectra of the crude reaction mixtures revealed formation of a single aromatic product, indicating near 100% regioselectivity (Figure S2). Following desilylation of the reaction crudes using SiO₂/MeOH,²⁵ pure resorcinols were obtained in excellent yields, including amorfrutin A and B precursors, **27a** (89%, based on dienophile) and **27b** (84%), respectively, from dienophile **13a** as well as amorfrutin 2 precursor **27c** (85%), and cannabinoid precursor **27d** (80%) from methyl-2-octynoate (**13b**). Excess

Scheme 4. Synthesis of Amorfrutin Derivatives via the Diels–Alder/Retro-Diels–Alder Approach



dienes **29a** and **29b** could be recovered almost quantitatively by crystallization and/or chromatography from the mixture following desilylation.

Methylation of resorcinols **27a** and **27b** afforded amorfrutin ethyl esters **17a** (66%, 77% BRSM) and **17b** (60%, 67% BRSM) (Scheme 4b). Although regioselective, we did observe formation of up to 20% of bis-methylated derivatives, even when methylation was terminated prior to complete consumption of starting material. Subsequent alkaline hydrolysis^{14,15} afforded amorfrutins A (**1**) and B (**2**) in four linear steps from methyl acetoacetate (**19**) and five linear steps from dimedone (**28**). Further, resorcinol **27d** was hydrolyzed and decarboxylated to afford pure cannabigerol (CBG, **30**) in 81% yield. Alternatively, careful treatment of **27d** with concentrated aqueous sodium sulfide has been reported to allow hydrolysis to CBGA (**5**), providing access to CBG and CBGA in four steps from dimedone.³³ While short synthetic approaches to CBG have been described from the condensation of geraniol and olivetol, additional undesired regioisomers and bis-geranylated products have been reported.^{34,35}

In summary, we here present two complementary convergent approaches to amorfrutins and related resorcinol derivatives, starting from simple, acyclic precursors. The tandem anionic cascade cyclization approach provides access to amorfrutins in only four linear steps from inexpensive precursors. Although yields of the anionic cyclization step are modest, the approach is scalable and products can be isolated easily in high purity. Further, this cyclization reaction demonstrates novel reactivity for a carbonyl-conjugated enol ether, which following deprotonation serves as a functional equivalent to a β -keto ester-derived dianion. In the context of amorfrutin synthesis, the use of the enol ether in this step

removed the need for late-stage monomethylation of a resorcinol intermediate; however, substitution of β -alkoxycrotonate-derived nucleophiles for β -keto ester-derived dianions may have more widespread utility. The tandem Diels–Alder/retro-Diels–Alder cycloaddition provided resorcinol derivatives with complete regioselectivity and higher yields than the anionic cascade cyclization approach; however, the preparation of the diene from dimedone is somewhat inefficient. Both routes presented here avoid the use of protection/deprotection steps, accommodate a wide range of substituents R^1 and R^2 , and are shorter than previous approaches to amorfrutins A, B, and 2, demonstrating the advantages of convergent [4+2] strategies for this class of natural products. The methods are applicable to a wide range of amorfrutins and cannabinoids as well as non-natural derivatives and probes, which will facilitate exploration of their biological activities and modes of action.

EXPERIMENTAL SECTION

General Procedures, Materials, and Instrumentation.

All oxygen- and moisture-sensitive reactions were carried out under an argon (Ar) atmosphere in flame-dried glassware. Solutions and solvents sensitive to moisture and oxygen were transferred via standard syringe and cannula techniques. Reaction mixtures were cooled using dry ice–acetone or ice–water baths and heated using a mineral oil bath. Unless stated otherwise, all chemicals and reagents used for synthetic compound preparation were purchased from Sigma-Aldrich and used without further purification. Tetrahydrofuran (THF), toluene, dichloromethane (DCM), and hexamethylphosphoramide (HMPA) were dried and stored over 3 or 4 Å molecular sieves prior to use. Diisopropylamine (DIPA) was passed through a plug of silica and dried over 4 Å molecular sieves. 4-Phenyl-1-butyne and bis(triphenylphosphine)rhodium(I) carbonyl chloride were purchased from BeanTown Chemical. Ethyl chloroformate was purchased from Alfa Aesar. Chloroform (CHCl_3), DCM, diethyl ether (Et_2O), ethyl acetate (EtOAc), ethanol (EtOH), hexanes, and toluene were purchased from Fisher Scientific. Thin-layer chromatography (TLC) was performed using J. T. Baker Silica Gel IB2F plates. Flash chromatography was performed using Teledyne Isco CombiFlash systems with Teledyne Isco RediSep Rf silica or manually using aluminum oxide, activated, neutral, Brockmann grade 1, 58 Å (Alfa Aesar). All deuterated solvents were purchased from Cambridge Isotopes. Nuclear magnetic resonance (NMR) spectra were recorded on Varian INOVA 600 (600 MHz), Varian INOVA 400 (400 MHz), and Bruker AV500 spectrometers at Cornell University's NMR facility. ^1H NMR chemical shifts are reported in ppm (δ) relative to residual solvent peaks (7.26 ppm for chloroform- d , 7.16 ppm for benzene- d_6 , 2.05 for acetone- d_6). NMR spectroscopic data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (Hz), and integrals. ^{13}C NMR chemical shifts are reported in ppm (δ) relative to residual solvent peaks (77.16 ppm for chloroform- d , 128.06 ppm for benzene- d_6 , and 29.84 for acetone- d_6). All NMR data processing was done using MNOVA 12.0.1 (<https://mestrelab.com/>). All high-resolution mass spectrometry data were acquired using a Thermo Scientific Q Exactive HF hybrid quadrupole-orbitrap mass spectrometer and reported to four decimal places.

Methyl 2-Prenyl-3-methoxy-2- and 3-butenate (10a). This reagent was prepared according to a previously published procedure using enol ether **20**²⁸ and prenyl bromide.²⁹

Methyl 2-Geranyl-3-methoxy-2- and 3-butenate (10b). This reagent was prepared according to a previously published procedure.²⁹ To a freshly prepared solution of LDA from $n\text{BuLi}$ (4.30 mL, 10.75 mmol, 2.5 M in hexanes, 1.16 equiv) and DIPA (1.40 mL, 10.0 mmol, 1.08 equiv) in 10 mL of THF was added enol ether **20** (1.20 g, 9.23 mmol, 1.00 equiv)²⁸ in 2 mL of THF at -78°C dropwise under Ar. The resulting solution was stirred up to 0°C (formation of a white precipitate was observed). HMPA (1.70 mL, 9.78 mmol, 1.06 equiv) was added; then, the solution was cooled down to -78°C to which geranyl bromide (3.00 g, 13.8 mmol, 1.49 equiv) was added dropwise in 3 mL THF. The reaction mixture was stirred up to room temperature over a 1 h period and then stirred at that temperature for 42 h. The solution was poured into cold sat. aqueous NaHCO_3 and extracted with EtOAc (3 \times). Combined organics were washed with brine, dried with MgSO_4 , filtered, and concentrated *in vacuo*. Flash column chromatography on alumina using 3% EtOAc in hexanes afforded **10b** (1.40 g, 55%, primarily β,γ isomer) as a colorless oil, with up to ~9% (mol/mol) bis-alkyl impurity. ^1H NMR (500 MHz, benzene- d_6): δ 5.27 (t, $J = 7.1$ Hz, 1H), 5.19 (t, $J = 7.0$ Hz, 1H), 4.14 (d, $J = 2.4$ Hz, 1H), 3.92 (d, $J = 2.4$ Hz, 1H), 3.37 (s, 3H), 3.24 (t, $J = 7.7$ Hz, 1H), 3.14 (s, 3H), 2.82 (ddd, $J = 14.6, 7.4$ Hz, 1H), 2.66 (ddd, $J = 14.6, 7.4$ Hz, 1H), 2.12 (q, $J = 7.6$ Hz, 2H), 2.03 (t, $J = 7.3$ Hz, 2H), 1.67 (br s, 3H), 1.58 (s, 3H), 1.54 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, benzene- d_6): δ 172.3, 161.4, 137.3, 131.1, 124.8, 121.8, 83.0, 54.8, 51.9, 51.5, 40.2, 29.2, 27.1, 25.9, 17.8, 16.1. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{27}\text{O}_3$, 267.1955; found, 267.1951.

(Z)-Ethyl-3-chloro-5-phenylpent-2-enoate (11a). Chloroester **11a** was prepared according to a previously reported procedure.³⁰ Ethyl chloroformate (**22**, 5.74 mL, 60.3 mmol, 3.00 equiv), 4-phenyl-1-butyne (**21a**, 2.80 mL, 20.1 mmol, 1.00 equiv), and bis(triphenylphosphine)rhodium(I) carbonyl chloride (139 mg, 0.20 mmol, 0.01 equiv) were dissolved in 16 mL of dry toluene in a sealed container and heated to 110°C for 18 h. The reaction mixture was cooled to room temperature, quenched with the addition of sat. aqueous NaHCO_3 , and extracted 3 \times with EtOAc. Organics were dried with MgSO_4 , filtered, and concentrated *in vacuo*. Flash column chromatography on silica using a gradient of 0–20% EtOAc in hexanes was performed, affording **11a** (4.40 g, 92%) as a yellow oil. ^1H NMR (500 MHz, benzene- d_6): δ 7.13–7.05 (m, 2H), 7.06–6.99 (m, 1H), 6.90–6.84 (m, 2H), 5.71 (t, $J = 0.9$ Hz, 1H), 3.95 (q, $J = 7.1$ Hz, 2H), 2.59–2.51 (m, 2H), 2.28–2.20 (m, 2H), 0.94 (t, $J = 7.1$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, benzene- d_6): δ 163.3, 148.7, 140.0, 128.7, 128.6, 126.6, 117.5, 60.2, 43.0, 33.6, 14.2. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{16}\text{ClO}_2$, 239.0833; found, 239.0830.

(Z)-Ethyl-3-chlorooct-2-enoate (11b). Chloroester **11b** was prepared according to a previously reported procedure.³⁰ Ethyl chloroformate (**22**, 2.86 mL, 30.0 mmol, 3.00 equiv), 1-heptyne (**21b**, 1.31 mL, 10.0 mmol, 1.00 equiv, Sigma-Aldrich), and bis(triphenylphosphine)rhodium(I) carbonyl chloride (69.0 mg, 0.10 mmol, 0.01 equiv) were dissolved in 6 mL of dry toluene in a sealed container and heated to 110°C for 24 h. The reaction mixture was cooled to room temperature, quenched by the addition of sat. aqueous NaHCO_3 , and extracted 3 \times with EtOAc. Organics were dried with Na_2SO_4 , filtered, and concentrated *in vacuo*. Flash column chromatography on silica using a gradient of 0–20% EtOAc in hexanes afforded **11b** (1.93 g, 94%) as a light yellow

oil. ^1H NMR (500 MHz, benzene- d_6): δ 5.85 (t, J = 1.0 Hz, 1H), 4.01 (q, J = 7.1 Hz, 2H), 1.97 (t, J = 7.6 Hz, 2H), 1.29 (p, J = 7.6 Hz, 2H), 1.13–1.02 (m, 2H), 1.00–0.92 (m, 2H), 0.98 (t, J = 7.1 Hz, 3H), 0.76 (t, J = 7.3 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, benzene- d_6): δ 163.5, 150.2, 116.9, 60.2, 41.2, 30.8, 27.0, 22.6, 14.3, 14.0. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{18}\text{ClO}_2$, 205.0990; found, 205.0987.

General Procedure for the Anionic Cascade Approach. To a freshly prepared solution of LDA from $n\text{BuLi}$ (0.53 mL, 1.32 mmol, 2.5 M in hexanes, 3.15 equiv) and DIPA (0.18 mL, 1.32 mmol, 3.15 equiv) in 20 mL of THF was added enol ether **10a** or **10b** (1.26 mmol, 3.00 equiv) at -30°C dropwise under Ar. The resulting solution was stirred up to approximately 0 – 5°C (total time roughly 1 h) and then cooled to -20°C after which HMPA (0.22 mL, 1.26 mmol, 3.00 equiv) was added, followed by dropwise addition of chloroester **11a** or **11b** (0.42 mmol, 1.00 equiv) in 2 mL of THF up to approximately -10 to 0°C . The resulting solution was stirred up to room temperature over a 4 h period. The reaction was quenched at 0°C with the addition of cold sat. aqueous NaHCO_3 solution, and the organics were extracted three times with EtOAc (3 \times). Combined organics were washed with brine, dried with MgSO_4 , filtered, and concentrated *in vacuo*.

Amorfrutin A Ethyl Ester (17a). According to the general procedure, enol ether **10a** (250 mg, 1.26 mmol, 3.00 equiv), chloride **11a** (100 mg, 0.42 mmol, 1.00 equiv), and 22 mL of THF were used. Purification by flash column chromatography on silica using a gradient of 0 – 10% EtOAc in hexanes (w/0.3% TEA) was performed (to recover clean enol ether **10a**), followed by additional purification with 0 – 50% DCM in hexanes, affording **17a** (59 mg, 38%) as a colorless oil, and recovered **10a** (150 mg). ^1H NMR (500 MHz, benzene- d_6): δ 12.55 (s, 1H), 7.20–7.17 (m, 2H), 7.12–7.06 (m, 3H), 6.00 (s, 1H), 5.70 (t, J = 7.3 Hz, 1H), 3.97 (q, J = 7.1 Hz, 2H), 3.80 (d, J = 7.1 Hz, 2H), 3.26 (s, 3H), 3.22–3.17 (m, 2H), 2.86–2.81 (m, 2H), 1.90 (br s, 3H), 1.69 (br s, 3H), 0.89 (t, J = 7.1 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, benzene- d_6): δ 172.1, 163.1, 161.6, 144.3, 142.3, 131.2, 128.7, 126.3, 123.5, 116.0, 106.2, 105.9, 61.3, 55.0, 39.0, 38.5, 26.0, 22.8, 18.1, 14.0. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{29}\text{O}_4$, 369.2060; found, 369.2051. See Tables S1 and S2 for NMR spectroscopic data of byproducts **23** and **24**.

Amorfrutin B Ethyl Ester (17b). According to the general procedure, enol ether **10b** (335 mg, 1.26 mmol, 3.00 equiv), chloride **11a** (100 mg, 0.42 mmol, 1.00 equiv), and 22 mL of THF were used. Purification by flash column chromatography on silica using a gradient of 0 – 10% Et_2O in hexanes afforded **17b** (57.0 mg, 31%). ^1H NMR (400 MHz, benzene- d_6): δ 12.58 (s, 1H), 7.26–7.17 (m, 2H), 7.15–7.00 (m, 3H), 6.00 (s, 1H), 5.75 (t, J = 7.0 Hz, 1H), 5.20 (t, J = 7.1 Hz, 1H), 3.96 (q, J = 7.4 Hz, 2H), 3.84 (d, J = 7.3 Hz, 2H), 3.26 (s, 3H), 3.24–3.15 (m, 2H), 2.87–2.79 (m, 2H), 2.23–2.08 (m, 4H), 1.96 (br s, 3H), 1.61 (br s, 3H), 1.49 (br s, 3H), 0.87 (t, J = 7.2 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, benzene- d_6): δ 172.0, 163.1, 161.6, 144.3, 142.3, 135.0, 130.9, 128.7, 126.3, 125.1, 123.3, 116.0, 106.2, 105.9, 61.3, 55.0, 40.4, 39.0, 38.5, 27.3, 25.8, 22.7, 17.7, 16.5, 14.0. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{37}\text{O}_4$, 437.2686; found, 437.2679.

Amorfrutin 2 Ethyl Ester (17c). According to the general procedure, enol ether **10a** (250 mg, 1.26 mmol, 3.00 equiv), chloride **11b** (86.0 mg, 0.42 mmol, 1.00 equiv), and 22 mL of THF were used. Purification by flash column chromatography

on silica using a gradient of 0 – 50% DCM in hexanes afforded **17c** (44.0 mg, 31%). ^1H NMR (500 MHz, benzene- d_6): δ 12.57 (s, 1H), 6.16 (s, 1H), 5.71 (t, J = 7.0 Hz, 1H), 3.97 (q, J = 7.1 Hz, 2H), 3.82 (d, J = 7.2 Hz, 2H), 3.32 (s, 3H), 2.91–2.87 (m, 2H), 1.91 (s, 3H), 1.69 (s, 3H), 1.62–1.52 (m, 2H), 1.38–1.30 (m, 4H), 0.93 (m, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, benzene- d_6): δ 172.2, 163.1, 161.6, 145.6, 131.1, 123.5, 115.7, 105.9, 105.8, 61.1, 55.0, 38.0, 32.6, 32.5, 26.0, 23.1, 22.8, 18.1, 14.4, 14.0. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{31}\text{O}_4$, 335.2217; found, 335.2209.

2-Prenyldimedone (29a). To a mixture of dimedone (**28**, 6.00 g, 42.8 mmol, 1.00 equiv, Sigma-Aldrich) in 170 mL of CHCl_3 was added K_2CO_3 (11.00 g, 79.6 mmol, 1.86 equiv), followed by prenyl bromide (5.60 mL, 48.5 mmol, 1.13 equiv). The reaction mixture was stirred at room temperature for 60 h and was then diluted with 50 mL of CHCl_3 and 50 mL of H_2O followed by acidification to $\text{pH} \sim 5$ using aqueous 1 M HCl. The organic layer was separated, and the aqueous layer was extracted with three 100 mL portions of CHCl_3 . Combined organics were washed with brine, dried with MgSO_4 , filtered, and concentrated *in vacuo*. The residue was stirred with hexanes to remove *O*-alkyl and bis-alkyl products along with excess 3,3-dimethylallyl bromide resulting in the formation of a precipitate, which was collected via vacuum filtration, affording **29a** (3.77 g, 42%), as a white solid containing $\sim 1\%$ of unreacted dimedone as an impurity. ^1H NMR (400 MHz, chloroform- d , enol): δ 6.78 (br s, 1H), 5.20 (t, J = 7.3 Hz, 1H), 3.08 (d, J = 7.4 Hz, 2H), 2.27 (s, 4H), 1.79–1.71 (m, 6H), 1.06 (s, 6H). ^1H NMR (400 MHz, chloroform- d , keto): δ 5.06 (t, J = 7.2 Hz, 1H), 3.28 (t, J = 6.1 Hz, 1H), 2.63 (d, J = 13.7 Hz, 2H), 2.54–2.44 (m, 2H), 2.48 (d, J = 13.7 Hz, 2H), 1.66 (s, 3H), 1.64 (s, 3H), 1.14 (s, 3H), 0.87 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform- d , keto–enol): δ 204.7, 136.3, 133.9, 122.0, 121.1, 112.6, 67.0, 54.3, 31.9, 31.1, 30.1, 28.5, 28.4, 26.8, 25.9, 22.6, 21.3, 18.0, 17.9. HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{21}\text{O}_2$, 209.1536; found, 209.1538.

2-Geranyldimedone (29b). To a mixture of dimedone (**28**, 2.80 g, 20.0 mmol, 1.00 equiv) in 75 mL of CHCl_3 was added K_2CO_3 (5.50 g, 39.8 mmol, 1.99 equiv), followed by geranyl bromide (4.40 mL, 22.1 mmol, 1.10 equiv). The reaction mixture was stirred at room temperature for 70 h and was then diluted with 50 mL of CHCl_3 and 10 mL of H_2O , followed by acidification to $\text{pH} \sim 6$ using aqueous 1 M HCl. The organic layer was separated, and the aqueous layer was extracted with two 50 mL portions of CHCl_3 . Combined organics were washed with brine, dried with MgSO_4 , filtered, and concentrated *in vacuo*. The crude oil was stored at -20°C for 24 h, and the resulting solid was separated from the remaining yellow oil (*O*-alkyl and bis-alkyl products along with any excess geranyl bromide) by washing with hexanes via vacuum filtration, affording **29b** (2.52 g, 45%) as a white solid. NMR spectroscopic data were identical to those reported previously.³⁶

Diene (12b).²³ To a suspension of **29a** (2.00 g, 9.60 mmol, 1.00 equiv) in 14 mL of DCM was added hexamethyldisilazane (HMDS) (2.60 mL, 12.4 mmol, 1.29 equiv). The resulting solution was concentrated *in vacuo* after 12 h and added in 5 mL of THF to a freshly prepared solution of LDA from $n\text{BuLi}$ (4.21 mL, 10.5 mmol, 2.5 M in hexanes, 1.09 equiv) and DIPA (1.47 mL, 10.5 mmol, 1.09 equiv) in 25 mL of THF at -78°C over a 10 min period under Ar. After stirring up to -40°C over a 1 h period, the solution was cooled to -78°C , TMSCl (1.40 mL, 11.0 mmol, 1.14 equiv) was added dropwise, and

the resulting solution was stirred up to room temperature over a 2 h period. The reaction mixture was concentrated *in vacuo*, diluted in hexanes, filtered, and concentrated *in vacuo*, affording bis-TMS diene **12b** (3.37 g, 100%) as a yellow oil. ^1H NMR (400 MHz, benzene- d_6): δ 5.49 (t, $J = 6.9$ Hz, 1H), 4.60 (s, 1H), 3.22 (d, $J = 6.7$ Hz, 2H), 2.20 (s, 2H), 1.77 (br s, 3H), 1.69 (br s, 3H), 1.08 (s, 6H), 0.24 (s, 9H), 0.16 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, benzene- d_6): δ 149.6, 147.7, 129.9, 125.0, 115.0, 107.9, 45.0, 32.2, 29.2, 25.9, 23.7, 18.2, 1.06, 0.37.

Diene (12c).²³ To a suspension of **29b** (1.05 g, 3.80 mmol, 1.00 equiv) in 6 mL of DCM was added HMDS (1.00 mL, 4.78 mmol, 1.26 equiv). The resulting solution was concentrated *in vacuo* after 24 h and added in 3 mL of THF to a freshly prepared solution of LDA from *n*BuLi (1.74 mL, 4.35 mmol, 2.5 M in hexanes, 1.14 equiv) and DIPA (0.61 mL, 4.35 mmol, 1.14 equiv) in 10 mL of THF at -78 °C over a 10 min period under Ar. After stirring up to -10 °C over a 1 h period, the solution was cooled to -78 °C, TMSCl (0.70 mL, 5.51 mmol, 1.45 equiv) was added dropwise, and the resulting solution was stirred up to room temperature over a 1 h period. The reaction mixture was concentrated *in vacuo*, diluted in hexanes, filtered, and concentrated *in vacuo*, affording bis-TMS diene **12c** (1.60 g, 100%) as a yellow oil. ^1H NMR (400 MHz, benzene- d_6): δ 5.53 (t, $J = 6.9$ Hz, 1H), 5.24 (t, $J = 7.0$ Hz, 1H), 4.60 (s, 1H), 3.24 (d, $J = 6.7$ Hz, 2H), 2.24–2.09 (m, 4H), 2.21 (s, 2H), 1.81 (br s, 3H), 1.67 (br s, 3H), 1.55 (br s, 3H), 1.08 (s, 6H), 0.25 (s, 9H), 0.17 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, benzene- d_6): 149.6, 147.7, 133.8, 130.9, 125.1, 124.8, 115.0, 107.8, 45.0, 40.3, 32.3, 29.2, 27.3, 25.9, 23.6, 17.8, 16.6, 1.07, 0.40.

Ethyl 5-Phenylpent-2-ynoate (13a). This reagent was prepared according to a previously published procedure starting from 4-phenyl-1-butyne (**21a**) and ethyl chloroformate (**22**) using *n*BuLi.³²

General Procedure for Diels–Alder Approach. Excess diene (**12b** or **12c**) and alkyne (**13a** or **13b**) were combined and heated in a sealed tube at 170 °C for the indicated time period, allowing for complete consumption of alkyne. The reaction was then diluted with a mixture of MeOH/DCM, SiO₂ was added, and the resulting mixture was refluxed for several hours, until all TMS-ethers had been deprotected, as determined by TLC. The reaction mixture was then filtered and concentrated *in vacuo*.

Resorcinol (27a). According to the general procedure, diene (**12b**, 3.30 g, 9.35 mmol, 4.08 equiv) and alkyne (**13a**, 465 mg, 2.29 mmol, 1.00 equiv) were heated for 42 h. TMS deprotection was performed for 5 h with 60 mL of MeOH/6 mL of DCM and 5.6 g of SiO₂. The reaction mixture was filtered and concentrated *in vacuo*. To precipitate excess 2-prenyldimedone (**29a**), a 1:1 mixture of hexanes/DCM (100 mL) was added to the crude, and the mixture was then vacuum filtered. The collected solid was washed with hexanes, affording pure recovered 2-prenyldimedone (**29a**, 1.34 g, 6.44 mmol, 91% of expected recovery). The filtrate was concentrated *in vacuo*, and flash column chromatography on silica using a gradient of 0–20% EtOAc in hexanes afforded **27a** (721 mg, 89%) as an off-white solid. ^1H NMR (500 MHz, benzene- d_6): δ 12.81 (s, 1H), 7.22–7.17 (m, 2H), 7.14–7.07 (m, 3H), 5.93 (s, 1H), 5.45 (t of septets, $J = 7.1$, 1.4 Hz, 1H), 5.21 (s, 1H), 3.95 (q, $J = 7.1$ Hz, 2H), 3.64 (d, $J = 7.3$ Hz, 2H), 3.14–3.09 (m, 2H), 2.82–2.77 (m, 2H), 1.69 (br s, 3H), 1.57 (d, $J = 1.0$ Hz, 3H), 0.87 (t, $J = 7.1$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, benzene- d_6): δ 172.2, 163.9, 159.5, 144.5, 142.4, 133.7, 128.7,

128.6, 126.3, 122.5, 113.1, 111.2, 105.2, 61.3, 38.6, 38.5, 25.8, 22.7, 17.8, 14.0. HRMS (ESI) m/z : $[\text{M} - \text{H}]^-$ calcd for C₂₂H₂₅O₄, 353.1758; found, 353.1753.

Resorcinol (27b). According to the general procedure, diene (**12c**, 1.03 g, 2.45 mmol, 4.30 equiv) and alkyne (**13a**, 115 mg, 0.57 mmol, 1.00 equiv) were heated for 23 h. TMS deprotection was performed for 4.5 h with 15 mL of MeOH/2 mL of DCM and 1.7 g of SiO₂. The reaction mixture was filtered and concentrated *in vacuo*. Flash column chromatography on silica using a gradient of 0–30% EtOAc in hexanes afforded **27b** (203 mg, 84%) as a yellow solid, along with recovered 2-geranyldimedone (**29b**, 380 mg, 1.38 mmol, 73% of expected recovery). ^1H NMR (500 MHz, benzene- d_6): δ 12.84 (s, 1H), 7.22–7.18 (m, 2H), 7.13–7.08 (m, 3H), 5.99 (s, 1H), 5.49 (t of septets, $J = 7.3$, 1.4 Hz, 1H), 5.32 (s, 1H), 5.13 (t of septets, $J = 7.1$, 1.4 Hz, 1H), 3.95 (q, $J = 7.1$ Hz, 2H), 3.66 (d, $J = 7.2$ Hz, 2H), 3.16–3.08 (m, 2H), 2.83–2.76 (m, 2H), 2.09 (q, $J = 7.5$ Hz, 2H), 2.00 (t, $J = 7.5$ Hz, 2H), 1.72 (br s, 3H), 1.66 (br s, 3H), 1.50 (d, $J = 1.3$ Hz, 3H), 0.86 (t, $J = 7.1$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, benzene- d_6): δ 172.2, 163.9, 159.8, 144.6, 142.4, 137.8, 131.5, 128.7, 128.6, 126.3, 124.6, 122.4, 113.0, 111.3, 105.2, 61.3, 40.1, 38.6, 38.5, 26.9, 25.9, 22.7, 17.7, 16.2, 14.0. HRMS (ESI) m/z : $[\text{M} - \text{H}]^-$ calcd for C₂₇H₃₃O₄, 421.2384; found, 421.2376.

Resorcinol (27c). According to the general procedure, diene (**12b**, 1.70 g, 4.81 mmol, 4.15 equiv) and alkyne (**13b**, 176 mg, 1.16 mmol, 1.00 equiv) were heated for 36 h. TMS deprotection was performed for 4 h with 30 mL of MeOH/3 mL of DCM and 2.7 g of SiO₂. The reaction mixture was filtered and concentrated *in vacuo*. Flash column chromatography on silica using a gradient of 0–20% EtOAc in hexanes afforded **27c** (279 mg, 85%) as an off-white solid. ^1H NMR (500 MHz, benzene- d_6): δ 12.67 (s, 1H), 6.04 (s, 1H), 5.42 (t of septets, $J = 7.3$, 1.4 Hz, 1H), 5.27 (s, 1H), 3.62 (d, $J = 7.3$ Hz, 2H), 3.33 (s, 3H), 2.80–2.74 (m, 2H), 1.67 (br s, 3H), 1.55 (d, $J = 1.0$ Hz, 3H), 1.54–1.46 (m, 2H), 1.33–1.46 (m, 2H), 0.92–0.86 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, benzene- d_6): δ 172.7, 163.8, 159.7, 145.7, 133.7, 122.6, 112.7, 111.0, 105.0, 51.3, 37.1, 32.5, 32.0, 25.8, 22.9, 22.7, 17.8, 14.3. HRMS (ESI) m/z : $[\text{M} - \text{H}]^-$ calcd for C₁₈H₂₅O₄, 305.1758; found, 305.1750.

Resorcinol (27d). According to the general procedure, diene (**12c**, 0.93 g, 2.21 mmol, 4.25 equiv) and alkyne (**13b**, 79.0 mg, 0.52 mmol, 1.00 equiv) were heated for 36 h. TMS deprotection was performed for 4 h with 15 mL of MeOH/2 mL of DCM and 1.6 g of SiO₂. The reaction mixture was filtered and concentrated *in vacuo*. Flash column chromatography on silica using a gradient of 0–10% EtOAc in hexanes afforded **27d** (155 mg, 80%) as a yellow solid. ^1H NMR (500 MHz, benzene- d_6): δ 12.70 (s, 1H), 6.10 (s, 1H), 5.46 (t of septets, $J = 7.3$, 1.4 Hz, 1H), 5.39 (s, 1H), 5.12 (t of septets, $J = 7.0$, 1.4 Hz, 1H), 3.65 (d, $J = 7.2$ Hz, 2H), 3.33 (s, 3H), 2.80–2.74 (m, 2H), 2.08 (q, $J = 7.4$ Hz, 2H), 1.98 (t, $J = 7.5$ Hz, 2H), 1.70 (br s, 3H), 1.66 (br s, 3H), 1.54–1.47 (m, 2H), 1.49 (br s, 3H), 1.32–1.25 (m, 4H), 0.91–0.87 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, benzene- d_6): δ 172.7, 163.7, 159.9, 145.8, 137.9, 131.6, 124.6, 122.4, 112.6, 111.1, 105.0, 51.3, 40.1, 37.1, 32.5, 32.0, 26.8, 25.9, 22.9, 22.6, 17.7, 16.2, 14.3. HRMS (ESI) m/z : $[\text{M} - \text{H}]^-$ calcd for C₂₃H₃₃O₄, 373.2384; found, 373.2381.

Amorfrutin A Ethyl Ester (17a). To a solution of resorcinol **27a** (100 mg, 0.28 mmol, 1.00 equiv) in acetone (4.8 mL) was added K₂CO₃ (0.73 g, 5.29 mmol, 18.9 equiv) followed by MeI

(26.0 μL , 0.42 mmol, 1.50 equiv). The resulting mixture was vigorously stirred at room temperature for 3 h, neutralized with 1 M aqueous HCl, and extracted with EtOAc ($3 \times 15 \text{ mL}$). The combined organics were washed with brine, dried with MgSO_4 , filtered, and concentrated *in vacuo*. Flash column chromatography on silica using a gradient of 0–10% EtOAc in hexanes afforded **17a** (68.0 mg, 66%) as a colorless oil, along with recovered **27a** (11.0 mg, 11%). NMR spectroscopic data were identical to those reported previously.

Amorfrutin B Ethyl Ester (17b). To a solution of resorcinol **27b** (100 mg, 0.23 mmol, 1.00 equiv) in acetone (4 mL) was added K_2CO_3 (0.62 g, 4.49 mmol, 19.5 equiv) followed by MeI (20.0 μL , 0.35 mmol, 1.52 equiv). The resulting mixture was vigorously stirred at room temp for 3.5 h, acidified with 1 M aqueous HCl, and extracted with EtOAc ($3 \times$). The organics were washed with brine, dried with MgSO_4 , filtered, and concentrated *in vacuo*. Flash column chromatography on silica using a gradient of 0–10% EtOAc in hexanes was performed, affording **17b** (62.0 mg, 60%) as a colorless oil, along with recovered **27b** (7.0 mg, 7%). NMR spectroscopic data were identical to those reported previously.

Cannabigerol (CBG, 30). Resorcinol **27d** (57.0 mg, 0.15 mmol, 1.00 equiv) was combined with KOH (408 mg, 7.28 mmol, 48.5 equiv) in a 1:1 mixture of EtOH/ H_2O (5 mL) and was refluxed for 8 h. The resulting solution was concentrated *in vacuo*, acidified with 1 M aqueous HCl to pH ~ 5 , and then extracted with EtOAc ($3 \times$). The combined organic layers were dried with MgSO_4 , filtered, and concentrated *in vacuo*. Flash column chromatography on silica using a gradient of 0–30% EtOAc in hexanes afforded **30** (39.0 mg, 81%) as an off-white solid. NMR spectroscopic data were identical to those reported previously.³⁴

Amorfrutin A (1). A mixture of **17a** (71 mg, 0.19 mmol, 1.00 equiv) and KOH (101 mg, 1.80 mmol, 9.47 equiv) in 3 mL of EtOH and 2 mL of H_2O was refluxed for 2.5 h. The resulting solution was concentrated *in vacuo*, acidified with 1 M aqueous HCl to pH ~ 2 , and then extracted with EtOAc ($4 \times$). The combined organic extracts were dried with MgSO_4 , filtered, and concentrated *in vacuo*. Flash column chromatography on silica using a gradient of 0–60% EtOAc in hexanes afforded **1** (62 mg, 95%) as a white solid. NMR spectroscopic data were identical to those reported previously.³

Amorfrutin B (2). A mixture of **17b** (70 mg, 0.16 mmol, 1.00 equiv) and KOH (100 mg, 1.78 mmol, 11.12 equiv) in 3 mL of EtOH and 2 mL of H_2O was refluxed for 1.75 h. The resulting solution was concentrated *in vacuo*, acidified with 1 M aqueous HCl to pH ~ 1 , and then extracted with EtOAc ($4 \times$). The combined organic extracts were dried with MgSO_4 , filtered, and concentrated *in vacuo*. Flash column chromatography on silica using a gradient of 0–60% EtOAc in hexanes afforded **2** (61 mg, 94%) as a white solid. NMR spectroscopic data were identical to those reported previously.⁴

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.0c03043>.

Suppression of by-product formation in the anionic cascade reaction, regioselectivity of Diels–Alder/retro-Diels–Alder reaction, and NMR spectroscopic data (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare the following competing financial interest(s): F.C.S. is a founder of Ascribe Bioscience, a company that develops plant treatments based on natural small molecules.

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■ REFERENCES

- (1) Lefebvre, P.; Staels, B. Naturally improving insulin resistance with amorfrutins. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109* (19), 7136–7137.
- (2) Sauer, S. Amorfrutins: A Promising Class of Natural Products That Are Beneficial to Health. *ChemBioChem* **2014**, *15* (9), 1231–1238.
- (3) Weidner, C.; de Groot, J. C.; Prasad, A.; Freiwald, A.; Quedenau, C.; Kliem, M.; Witzke, A.; Kodelja, V.; Han, C.-T.; Giegold, S.; Baumann, M.; Klebl, B.; Siems, K.; Muller-Kuhrt, L.; Schurmann, A.; Schuler, R.; Pfeiffer, A. F. H.; Schroeder, F. C.; Bussow, K.; Sauer, S. Amorfrutins are potent antidiabetic dietary natural products. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109* (19), 7257–7262.
- (4) De Groot, J. C.; Weidner, C.; Krausz, J.; Kawamoto, K.; Schroeder, F. C.; Sauer, S.; Bussow, K. Structural Characterization of

Amorfrutins Bound to the Peroxisome Proliferator-Activated Receptor γ . *J. Med. Chem.* **2013**, *56* (4), 1535–1543.

(5) Fuhr, L.; Rousseau, M.; Plauth, A.; Schroeder, F. C.; Sauer, S. Amorfrutins Are Natural PPAR γ Agonists with Potent Anti-inflammatory Properties. *J. Nat. Prod.* **2015**, *78* (5), 1160–1164.

(6) Weidner, C.; Rousseau, M.; Micikas, R. J.; Fischer, C.; Plauth, A.; Wowro, S. J.; Siems, K.; Hetterling, G.; Kliem, M.; Schroeder, F. C.; Sauer, S. Amorfrutin C Induces Apoptosis and Inhibits Proliferation in Colon Cancer Cells through Targeting Mitochondria. *J. Nat. Prod.* **2016**, *79* (1), 2–12.

(7) Sauer, S.; Weidner, C.; Kliem, M.; Schroeder, F. C.; Micikas, R. J. Amorfrutin analogs as ppargamma-modulators. U.S. Patent WO2014177593, 2014.

(8) Asakawa, Y.; Kusube, E.; Takemoto, T.; Suire, C. New bibenzyls from *Radula complanata*. *Phytochemistry* **1978**, *17* (12), 2115–2117.

(9) Asakawa, Y.; Toyota, M.; Takemoto, T. Seven new bibenzyls and a dihydrochalcone from *Radula variabilis*. *Phytochemistry* **1978**, *17* (11), 2005–2010.

(10) Asakawa, Y.; Takikawa, K.; Toyota, M.; Takemoto, T. Novel bibenzyl derivatives and ent-cuparene-type sesquiterpenoids from *Radula* species. *Phytochemistry* **1982**, *21* (10), 2481–2490.

(11) Bohlmann, F.; Hoffmann, E. Cannabigerol-ähnliche Verbindungen aus *Helichrysum umbraculigerum*. *Phytochemistry* **1979**, *18* (8), 1371–1374.

(12) Zechlin, L.; Wolf, M.; Steglich, W.; Anke, T. Cristatsäure, ein modifiziertes Farnesylphenol aus Fruchtkörpern von *Albatrellus cristatus*. *Liebigs Ann. Chem.* **1981**, *1981*, 2099–2105.

(13) Song, Y. Y.; He, H. G.; Li, Y.; Deng, Y. A facile total synthesis of amorfrutin A. *Tetrahedron Lett.* **2013**, *54* (21), 2658–2660.

(14) Weber, B.; Brandes, B.; Powroznik, D.; Kluge, R.; Csuk, R. An efficient and robust synthesis of amorfrutin A. *Tetrahedron Lett.* **2019**, *60* (20), 1379–1381.

(15) Fujita, T.; Kuwahara, S.; Ogura, Y. Unified total synthesis of amorfrutins A and C via the Claisen rearrangement. *Biosci., Biotechnol., Biochem.* **2019**, *83* (9), 1635–1641.

(16) Laclef, S.; Anderson, K.; White, A. J. P.; Barrett, A. G. M. Total synthesis of amorfrutin A via a palladium-catalyzed migratory prenylation-aromatization sequence. *Tetrahedron Lett.* **2012**, *53* (2), 225–227.

(17) Fujita, T.; Kuwahara, S.; Ogura, Y. Synthesis of amorfrutins B and D from amorfrutin A ethyl ester. *Tetrahedron Lett.* **2020**, *61* (6), 151477.

(18) Aidhen, I. S.; Mukkamala, R.; Weidner, C.; Sauer, S. A Common Building Block for the Syntheses of Amorfrutin and Cajaninstilbene Acid Libraries toward Efficient Binding with Peroxisome Proliferator-Activated Receptors. *Org. Lett.* **2015**, *17* (2), 194–197.

(19) Grandhi, G. S.; Selvakumar, J.; Dana, S.; Baidya, M. Directed C-H Bond Functionalization: A Unified Approach to Formal Syntheses of Amorfrutin A, Cajaninstilbene Acid, Hydrangenol, and Macrophyllol. *J. Org. Chem.* **2018**, *83* (19), 12327–12333.

(20) Xu, X. J.; Zeng, T.; Huang, Z. X.; Xu, X. F.; Lin, J.; Chen, W. M. Synthesis and Biological Evaluation of Cajaninstilbene Acid and Amorfrutins A and B as Inhibitors of the *Pseudomonas aeruginosa* Quorum Sensing System. *J. Nat. Prod.* **2018**, *81* (12), 2621–2629.

(21) Miao, Q.; Li, Y.; Xu, J.; Lin, A.; Tanabe, G.; Muraoka, O.; Wu, X.; Xie, W. First Total Syntheses of Amorfrutin C and pseudo-Amorfrutin A. *Eur. J. Org. Chem.* **2018**, *2018* (12), 1443–1448.

(22) Patel, C.; Mies, T.; White, A. J. P.; Parsons, P. J.; Barrett, A. Biomimetic Syntheses of Amorfrutin C and C-5 Substituted Amorfrutin Analogues. *Eur. J. Org. Chem.* **2021**, *2021*, 1258.

(23) Quintiliano, S. A. P.; Silva, L. F. Practical synthesis of a functionalized 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid. *Tetrahedron Lett.* **2012**, *53* (29), 3808–3810.

(24) Dai, M.; Sarlah, D.; Yu, M.; Danishefsky, S. J.; Jones, G. O.; Houk, K. N. Highly Selective Diels-Alder Reactions of Directly Connected Enyne Dienophiles. *J. Am. Chem. Soc.* **2007**, *129* (3), 645–657.

(25) Yu, J.; Yang, M.; Guo, Y.; Ye, T. Total Synthesis of Psymberin (Irciniastatin A). *Org. Lett.* **2019**, *21* (10), 3670–3673.

(26) Covarrubias-Zúñiga, A.; González-Lucas, A. A total synthesis of mycophenolic acid. *Tetrahedron Lett.* **1998**, *39*, 2881–2882.

(27) Kileñyi, S. N.; Smith, A. B., III. Avermectin-milbemycin studies. 4. An expedient two-step preparation of p-hydroxybenzoate. *Tetrahedron Lett.* **1985**, *26* (37), 4419–4422.

(28) Essig, S.; Bretzke, S.; Müller, R.; Menche, D. Full Stereochemical Determination of Ajudazols A and B by Bioinformatics Gene Cluster Analysis and Total Synthesis of Ajudazol B by an Asymmetric Ortholithiation Strategy. *J. Am. Chem. Soc.* **2012**, *134* (47), 19362–19365.

(29) Caron, B.; Brassard, P. An integrated approach to the synthesis of contiguously substituted xanthopurpurins, pachybasins and purpurins. *Tetrahedron* **1993**, *49* (4), 771–784.

(30) Hua, R.; Shimada, S.; Tanaka, M. The First Example of Rhodium(I)-Catalyzed Regio- and Stereoselective Chloroesterification of Alkynes with Chloroformate Esters. *J. Am. Chem. Soc.* **1998**, *120* (47), 12365–12366.

(31) Grabovyi, G. A.; Mohr, J. T. Total Synthesis of Grifolin, Grifolic Acid, LL-Z1272 α , LL-Z1272 β , and Ilicicolinic Acid A. *Org. Lett.* **2016**, *18* (19), 5010–5013.

(32) Zhang, J.; Cheng, C.; Wang, D.; Miao, Z. Regio- and Diastereoselective Construction of Spirocyclopenteneoxindoles through Phosphine-Catalyzed [3 + 2] Annulation of Methyleneindolinone with Alkynoate Derivatives. *J. Org. Chem.* **2017**, *82* (19), 10121–10128.

(33) Reekie, T.; Scott, M.; Kassiou, M. Synthesis of phytocannabinoids including a demethylation step. AU Patent WO2019033164, 2019.

(34) Jentsch, N. G.; Zhang, X.; Magolan, J. Efficient Synthesis of Cannabigerol, Grifolin, and Piperogalin via Alumina-Promoted Allylation. *J. Nat. Prod.* **2020**, *83*, 2587–2591.

(35) Smeltzer, T.; David, R.; Colvin, S.; Black, J. C. Synthesis of Cannabigerol. US Patent WO2020115306, 2020.

(36) Takenaka, K.; Mohanta, S. C.; Patil, M. L.; Rao, C. V. L.; Takizawa, S.; Suzuki, T.; Sasai, H. Enantioselective Wacker-Vale Cyclization of 2-Alkenyl-1,3-diketones Promoted by Pd-SPRIX Catalyst. *Org. Lett.* **2010**, *12* (15), 3480–3483.