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A facile total synthesis of amorfrutin A

Yao Yao Song, Hong Guang He, Yan Li, Yong Deng *

Key Laboratory of Drug Targeting and Drug Delivery System of the Education Ministry, Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu 610041, China

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ABSTRACT

A facile and efficient route for the synthesis of biological activity natural product amorfrutin A was described. The key steps including tandem Michael addition–intramolecular Claisen condensation and followed by oxidative aromatization. The overall yield was about 27.2%.

Introduction

Amorfrutin A (**1**) was isolated from *Amorpha fruticosa* and *Glycyrrhiza foetida*, whose dried stems and roots are used in traditional Indian medicine or as a condiment, respectively. It has been reported that amorfrutin A (**1**) exhibits narrow spectrum antimicrobial activity against Gram-positive and acid-fast microorganisms.[1] Furthermore it showed significant inhibitory activities on nuclear transcription factor-κ (NF-κB), which was known to play a crucial role in the regulation of genes controlling the immune system, apoptosis, tumor cell growth, and tissue differentiation.[2] In addition, amorfrutin A (**1**) has also been shown to exhibit antidiabetics with unprecedented effects for a dietary molecule. It binds to and activates peroxisome proliferator-activated receptor γ (PPARγ) and physiological profiles markedly different from activation by current marketed synthetic PPARγ drugs.[3] So this compound has currently caused the extensive concern for its biological activity. Due to its widely biological activity and predictable application prospects, further research focused on amorfrutin A (**1**) pharmacodynamics and structure–activity relationships. Quantities of amorfrutin A (**1**) and its derivatives were needed. A survey of the literature revealed there have three reports on the total synthesis of amorfrutin.[3–5] However, these methods were proved to be troublesome with expensive materials, longer reaction steps, harsh reaction conditions and low yield. So an efficient and practical process for the preparation of amorfrutin A (**1**) is still in demand. Herein we report our efforts on the development of a facial total synthesis of amorfrutin A (**1**) utilizing the tandem Michael addition–Claisen condensation reaction,[6] followed by oxidative aromatization as the key steps. This concise strategy opens a pathway for the syntheses of other compounds related to prenyl bibenzyl derivatives, as well as their derivatives and analogues.

The outline of our retrosynthetic analysis is shown in Figure 1. Retrofunctional group disconnection of **1** leads to two fragments, 2-hydroxy-4-methoxyl-6-phenethylbenzoic acid ester **2** and prenyl side chain. Compound **1** could be constructed by regioselective C-prenylation of **2**. The benzoic acid ester derivative **2** would in turn be constructed by oxidative aromatization and methylation of precursor 1,3-cyclohexanediketone **3**, which was derived from 5-phenyl-2-pentenoic acid ester **4** and acetoacetate **5**.

Results and discussion

The synthesis of the target molecule **1** commenced with commercially obtained phenylpropyl aldehyde **6** as shown in Figure 2.

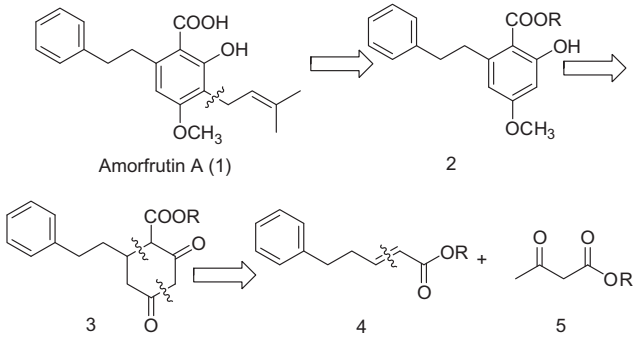

Figure 1. Retrosynthetic analysis of amorfrutin A.

* Corresponding author. Tel.:+86 28 85503790.
E-mail address: dengyong@scu.edu.cn (Y. Deng).

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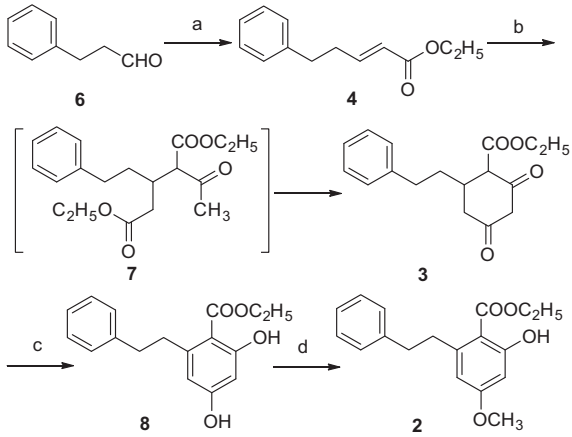

Figure 2. Reagents and conditions: (a) triethyl phosphonoacetate, K_2CO_3, PEG-400 (cat.), CH_2Cl_2, rt, 15 h, 96%; (b) ethyl acetoacetate, EtONa, EtOH, reflux; (c) $Hg(OAc)_2$, NaOAc, AcOH, reflux, 40% (three steps); (d) dimethyl sulfate, K_2CO_3, PEG-400 (cat.), acetone, 50 °C, overnight, 90%.

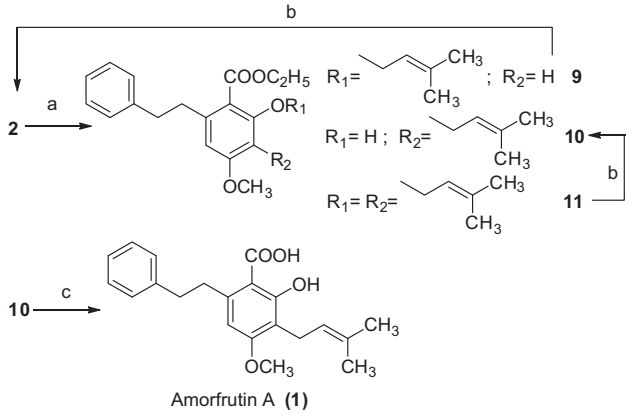

Figure 3. Reagents and conditions: (a) prenyl bromide, NaH, toluene, 75 °C ; (b) 2 mol/L HCl/EtOH (v/v, 1:1), 50 °C, 2 h, 84.5% (two steps, after recovering of compound **2**); (c) KOH, EtOH, H_2O, reflux, 93%.

(*E*)-Ethyl pentenoic acid **4** was obtained in 96% yield from **6** and triethyl phosphonoacetate using Wittig–Horner reaction under mild condition.[6d,7] To avoid the self condensation of compound **6** under strong basic conditions, we used anhydrous K_2CO_3 as base and PEG-400 as phase transfer catalyst. Next step was the key one of our synthetic route, compound **7** was expected to form from acrylic ester **4** and ethyl acetoacetate in NaOEt by Michael addition, followed by intramolecular Claisen condensation to afford the substituted 1,3-cyclohexanediketone **3** in a one pot reaction.[6] Because of the presence of keto-enol tautomerism and unstability in the separation process, intermediate **3** was used directly in the next step without further purification. Oxidative aromatization of the substituted 1,3-cyclohexanediketone **3** was the most important task in our synthetic route. We first tried Br_2/AcOH as oxidant, followed by debromination through catalytic hydrogenolysis under Pd/C and H_2 as reported by Gramatica.[8] Under these reaction conditions, a complex mixture of products was afforded from which it was not possible to isolate the corresponding 2,4-dihydroxy-6-phenethylbenzoic acid ester **8**. We then tried other oxidants, such as $CuCl_2$/LiCl,[9] Pd/C,[10] I_2/MeOH[11] and $BrCCl_3$,[12] but only a trace desired compound was obtained or a complex mixture of products. Finally aromatization of compound **3** was achieved using mercuric acetate and sodium acetate in acetic acid[13] and the corresponding **8** was obtained in 40% yield for the three steps.[14] When the intermediate **8** was subjected to reaction with dimethyl sulfate and potassium carbonate, the corresponding methyl ether **2** was regioselectively obtained in 90% yield.

With key intermediate **2** in hand, we then set out to convert compound **2** into the desired amorfrutin A (**1**) by regioselective C-prenylation and hydrolysis of the ester (Fig. 3). We initially examined the reaction according to Weidner's procedure,[3] in which the C-prenylation of **2** proceeded regioselectively.

When **2** was treated with prenyl bromide (1.16 equiv) and NaH (1.04 equiv) in toluene at 70–75 °C, the O-prenylated product **9** was the major product in 60% conversion and the yield of the desired C-3 prenylated product **10** was very low (Table 1, entry 1). Further examination revealed that the use of EtONa and anhydrous K_2CO_3 afforded the only O-prenylated product **9** (entries 2 and 3). In future researches, we found the ratio of **9**–**10** was altered depending on the amount of NaH and prenyl bromide (entries 4–6). It was found that the desired product **10** was generated in 45% conversion along with the compound **9** (45%) and the unreacted intermediate **2** (10%) when the reaction was carried out in the presence of NaH and prenyl bromide in 1.2 equiv (entry 4). When the intermediate **2** was

Table 1
Optimization reaction conditions of C-prenylation of **2**[a]

Entry	Base	Mol Ratio[b]	Time (h)	Conversion[c] (%)			
				9	**10**	**11**	**2**
1	NaH	1:1.04:1.16	3.0	60	15	—	25
2	EtONa	1:1.5:1.5	5.0	90[d]	—	—	—
3	K_2CO_3	1:1.5:1.5	8.0	76[d]	—	—	—
4	NaH	1:1.2:1.2	4.0	45	45	—	10
5	NaH	1:1.5:1.5	4.0	45	40	15	—
6	NaH	1:2.0:2.0	4.0	53	—	47	—

[a] Reaction temperature 70–75 °C, toluene as solvent.
[b] Compound **2**: base: prenyl bromide.
[c] Determined by ^1H NMR.
[d] Isolated yield.

subjected to the reaction with 1.5 equiv NaH and prenyl bromide in toluene, **2** could be converted completely, and mono-prenylated compounds **9** and **10** were the major products along with the bis-prenylated compound **11** in 15% conversion (entry 5). On further increase in the amount of NaH and prenyl bromide to 2.0 equiv, compounds **9** and **11** were obtained as the only products (entry 6). The mechanism of this prenylation step is that after deprotonation of phenol under strong base condition to afford phenoxide and then resemble an enolate. This phenoxide reacted at the adjacent carbon with prenyl bromide to yield the corresponding C-prenylated phenols. Because of competing side reactions such as O-prenylation and bis-prenylation, compounds **9** and **11** were also generated in these reaction conditions.

In the isolation of **10** from mixed products, we found it was difficult by using silica gel flash column chromatography due to the very similar polarity of the compounds **9**, **10,** and **11**. In an effort to circumvent this problem, we found the prenyl ethers of O-prenylated product **9** and bis-prenylated compound **11** could be deprenylation under a solution mixture of HCl and EtOH (v/v, 1:1). This mild and chemoselective cleavage of prenyl aryl ethers method was not previously reported in the literature. Concerning the reaction mechanism, our experience suggests that H^+ can protonate the ethereal oxygen, thus weakening the carbon–oxygen bond of the prenyl ethers, which can undergo a nucleophilic attack by the chloride anion or eliminated one molecule of isoprene to give the corresponding phenols. Finally, we used the reaction conditions of entry 5 for the synthesis of C-3 prenylated compound **10** and after completion of the reaction, 2 mol/L HCl/EtOH (v/v, 1:1) was added and the mixture was stirred at 50 °C for 2 h. Then the desired product **10** and starting material **2** were easily seperated

by silica gel column chromatography in 50% and 40% isolated yield, respectively. Hydrolysis of the ester moiety in aqueous KOH solution produced the amorfrutin A (**1**) in 93% yield, whose spectral data[15] were in good agreement with the literature reported.[3,5]

Conclusion

In conclusion, we developed a concise and efficient route for the synthesis of biologically interesting natural amorfrutin A (**1**) from commercially available phenylpropyl aldehyde. The key steps in the synthetic strategy involve the Michael addition and intramolecular Claisen condensation in a one pot reaction and oxidative aromatization. The overall yield was about 27.2%. This method would be useful for the synthesis of amorfrutin A and its derivatives for further pharmacodynamic mechanism of action and structure–activity relationships studies.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.042.

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15. Compound **2**: pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.86 (s, 1H), 7.32–7.27 (m, 2H), 7.22–7.17 (m, 3H), 6.36 (d, J = 2.8 Hz, 1H), 6.25 (d, J = 2.8 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 3.78 (s, 3H), 3.21 (t, J = 8.0 Hz, 2H), 2.87 (t, J = 8.0 Hz, 2H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.4, 165.6, 163.9, 146.6, 141.7, 128.3, 128.2, 125.9, 110.8, 104.7, 99.1, 61.4, 55.3, 38.4, 38.0, 14.3.
Compound **4**: colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31–7.26 (m, 2H), 7.22–7.17 (m, 3H), 7.00 (dt, J = 6.8 Hz, 16.0 Hz, 1H), 5.84 (d, J = 16.0 Hz, 1H), 4.18 (q, J = 6.8 Hz, 2H), 2.75 (t, J = 7.6 Hz, 2H), 2.55–2.52 (q, J = 7.6 Hz, 2H), 1.28 (t, J = 6.8 Hz, 3H).
Compound **8**: white solid, mp 85.5–86.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.81 (s, 1H), 7.32–7.27 (m, 2H), 7.23–7.18 (m, 3H), 6.31 (d, J = 2.4 Hz, 1H), 6.18 (d, J = 2.4 Hz, 1H), 5.22 (brs, 1H), 4.43 (q, J = 7.2 Hz, 2H), 3.20 (t, J = 7.6 Hz, 2H), 2.87 (t, J = 7.6 Hz, 2H), 1.39 (t, J = 7.2 Hz, 3H).
Compound **9**: colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31–7.27 (m, 2H), 7.22–7.18 (m, 3H), 6.34 (d, J = 2.0 Hz, 1H), 6.25 (d, J = 2.0 Hz, 1H), 5.46–5.42 (m, 1H), 4.52 (d, J = 6.4 Hz, 2H), 4.38 (q, J = 7.2 Hz, 2H), 3.75 (s, 3H), 2.91–2.85 (m, 4H), 1.77 (s, 3H), 1.72 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.2, 161.0, 157.3, 141.5, 137.3, 128.3, 128.2, 125.9, 119.6, 116.9, 105.8, 97.7, 65.6, 60.8, 55.2, 37.6, 36.0, 25.6, 18.2, 14.2; HR-ESI-MS: calcd. for $C_{23}H_{28}O_4$ $[M+K]^+$: 407.1625, found: 407.1624.
Compound **10**: colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.83 (s, 1H), 7.31–7.27 (m, 2H), 7.22–7.17 (m, 3H), 6.16 (s, 1H), 5.20 (t, J = 7.2 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 3.77 (s, 3H), 3.34 (d, J = 7.2 Hz, 2H), 3.22 (t, J = 7.6 Hz, 2H), 2.88 (t, J = 7.6 Hz, 2H), 1.78 (s, 3H), 1.70 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.7, 161.8, 161.0, 143.9, 141.8, 131.6, 128.3, 128.2, 125.9, 122.4, 115.1, 105.9, 105.2, 61.3, 55.4, 38.7, 38.1, 25.8, 21.9, 17.8, 14.3; HR-ESI-MS: calcd. for $C_{23}H_{28}O_4$ $[M+K]^+$: 407.1625, found: 407.1628.
Compound **11**: colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31–7.28 (m, 2H), 7.22–7.17 (m, 3H), 6.39 (s, 1H), 5.50 (t, J = 6.8 Hz, 1H), 5.15 (t, J = 6.4 Hz, 1H), 4.38 (d, J = 6.4 Hz, 2H), 4.36 (q, J = 6.8 Hz, 2H), 3.78 (s, 3H), 3.33 (d, J = 6.4 Hz, 2H), 2.91–2.86 (m, 4H), 1.77 (s, 3H), 1.74 (s, 3H), 1.67 (s, 6H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 168.7, 159.1, 155.2, 141.6, 138.5, 137.3, 131.4, 128.4, 128.3, 125.9, 122.9, 121.8, 121.5, 120.5, 107.5, 72.3, 61.1, 55.6, 37.8, 36.1, 25.8, 25.7, 23.0, 18.0, 17.9, 14.3; HR-ESI-MS: calcd. for $C_{28}H_{36}O_4$ $[M+K]^+$: 475.2251, found: 475.2257.
Compound **1**: off-white solid: mp 136–138 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ: 7.30–7.27 (m, 4H), 7.20–7.18 (m, 1H), 6.50 (s, 1H), 5.19 (t, J = 1.2 Hz, 1H), 3.85 (s, 3H), 3.31–3.27 (m, 4H), 2.93 (t, J = 8.0 Hz, 2H), 1.76 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ: 174.4, 163.4, 162.1, 145.9, 143.1, 131.2, 129.2, 129.0, 126.5, 123.5, 115.2, 106.7, 105.4, 55.9, 39.9, 39.1, 25.8, 22.5, 17.8. HR-ESI-MS: calcd. for $C_{21}H_{24}O_4$ $[M+Na]^+$: 363.1572, found: 363.1573.