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An efficient and robust synthesis of amorfrutin A

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ABSTRACT

Amorfrutin A was synthesized via a short sequence in an overall yield of 41% using a green, aerobic oxidation/re-arrangement process as the key-step.

Natural products possess a high chemical diversity, and their structural diversity continuously inspires the search for new drugs [1,2]. Thus, they remain one of the best sources of drugs. Recent statistical data have shown that the number of type 2 diabetes mellitus patients has increased worldwide during the last decade. Thus, this metabolic disease has evolved into a global epidemic. It is assumed that this metabolic syndrome already affects more than a quarter of the world's population [3,4].

One of the hallmarks of diabetes mellitus is characterized by insulin resistance. The nuclear peroxisome proliferator-activated receptor gamma, PPARγ, is activated after food intake by binding: for example, unsaturated fatty acids and several anti-diabetic drugs (such as rosiglitazone) are strong activators of PPARγ. However, these activators show some undesired side effects, and the search for more selective PPARγ activators is still of high scientific and economic interest [3,5].

Recently, the amorfrutins were identified as selective PPARγ modulators, which selectively modulate PPARγ gene expression networks in adipocytes. They have successfully been evaluated as anti-diabetics in mouse models for type 2 diabetes [6–10].

The access to amorfrutin A from natural sources is limited, although it has been isolated from the fruits of *Amorpha fruticose* [11] and from *Glycyrrhiza foetida* [4,12–14]. The content of amorfrutin A is low in these plants, and – as a consequence – several syntheses have been developed to overcome this shortage of material [15–19].

All of these syntheses allow the preparation of amorfrutin A, albeit their scaling up remains difficult. Hence, we became interested in an efficient synthesis from readily accessible and inexpensive starting materials with as few chromatography-based purification steps as possible. Furthermore, in order to take account of economic considerations, we attempted to avoid the use sensitive and/or expensive organometallic catalysts and reagents. Several years ago, a synthesis was proposed taking account of these requirements [20] but this approach was unsuccessful in our hands.

Knoevenagel condensation of 3,5-dimethoxy-benzaldehyde (**1**) with benzyl cyanide (**2**) [21] in the presence of sodium hydroxide gave stilbene derivative **3** in 92% isolated yield. The ratio of starting materials **1** and **2** as well as their concentration and the reaction temperature is essential to avoid the formation of bis-adduct **4** [20].

Reduction of **3** with sodium borohydride at room temperature for 1 day furnished **5** [21] in quantitative yield. Treatment of **5** with sodium hydroxide in propane-1,2-diol (microwave irradiation) for 4 min gave **6** (85%) [22] together with de-methylated **7** (10%) [23–25]. This de-methylation was somewhat unexpected since aromatic methyl ethers are usually cleaved under acid conditions (Scheme 1).

Reaction of **6** with boron trichloride in CH_2Cl_2 resulted in an intramolecular Friedel-Crafts acylation with concomitant selective mono-de-methylation, and **8** [26,27] was obtained in almost quantitative yield. This compound is characterized in its ^{13}C NMR spectrum by a signal at $\delta = 207.7$ ppm that was assigned to the carbonyl group. When **8** was treated with sodium methoxide at 40 °C with continuous bubbling of dry air through the reaction mixture, the cyclic ketone was transformed into lactone **9**. This compound is characterized in its ^{1}H NMR spectrum by the presence of an olefinic proton at $\delta = 6.87$ ppm, and in the ^{13}C NMR spectrum by two olefinic carbons at $\delta = 153.3$ and 102.8 ppm, respectively.

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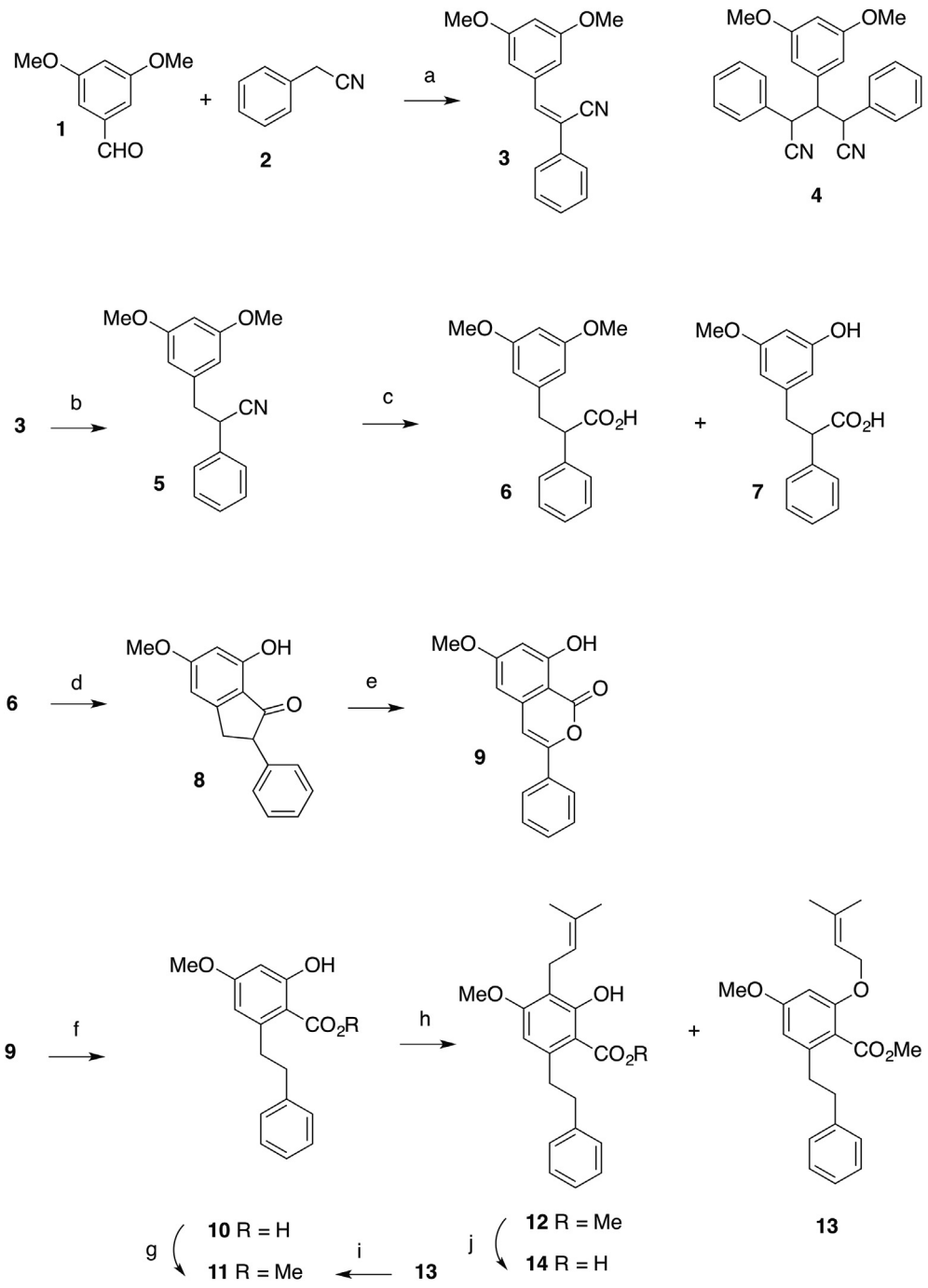

Scheme 1. Synthesis of amorfrutin A (**14**): Reagents and conditions: a) NaOH, EtOH, 12 h, 25 °C, 92%; b) $NaBH_4$, EtOH, 1 d, 50 °C, quant.; c) 1,2-propane-diol, NaOH, microwave irradiation (180 °C, 4 min, 160 W), 85% (**6**) + 10% (**7**); d) BCl_3, CH_2Cl_2, 0 °C → 25 °C, 98% (from **6**); e) NaOMe, MeOH, air, 2 d, 40 °C, 89%; f) H_2 (75 psi), Pd/C (10%), EtOAc/MeOH, 6 h, 25 °C, 93%; g) Cs_2CO_3, MeI, DMF, 12 h, 25 °C, 98%; h) KH, toluene, prenyl chloride, 20 min, 25 °C → 70 °C, **12** (72%) + **13** (25%); i) $CeCl_3$, ACN, NaI, 3 h, 25 °C, 95%; j) KOH, MeOH, 7 h, 25 °C, 92%.

Because the reaction of ketone **8** to the lactone **9** is the key step in our synthesis, it should be discussed in more detail (see Scheme 2). Ketones possessing α-hydrogens are easily autoxidized under alkaline conditions to carboxylic or dicarboxylic acids and other oxidation products [28–30]. Thus, ketone **8** reacts initially with oxygen in the presence of methanolate to the unstable peroxide intermediate **A** which presumably cyclizes to 1,2-dioxetane derivative **B**. Decomposition of **B** under C—C—bond cleavage leads to the formation of ketocarboxylate **C**. The cyclization of **C** in a favored *6-exo-trig* process yields the hydroxylactone **D** (corresponding anion). This reaction appears to be relatively fast because no significant amounts of products from the competitive further oxidation of **C** were obtained. Finally, lactone **9** is formed after protonation and the elimination of water.

Hydrogenation of **9** with Pd/C (10%) in methanol/ethyl acetate led to the formation of **10** [22] in 93% yield; this compound was easily transformed into its methyl ester **11** [6,16,24]. Prenylation of **11** with prenyl chloride/potassium hydride in dry toluene gave the methyl ester of amorfrutin A (**12**, 72%) [16,24,27] together with prenyl ether **13** (25%). The latter compound could be used

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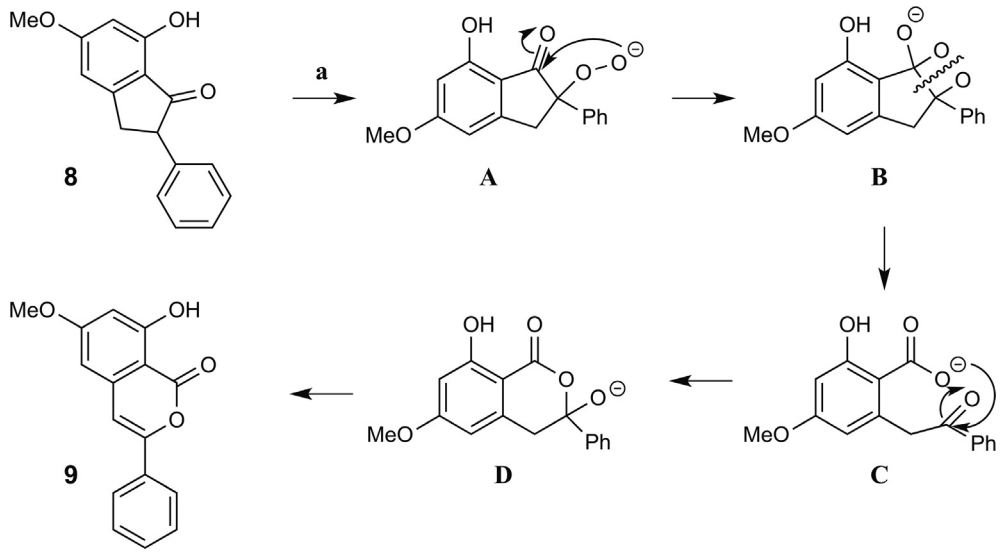

Scheme 2. Proposed reaction sequence for the conversion of ketone **8** to lactone **9**: Reagents and conditions: a) O_2, NaOMe, MeOH b) H^+, $-H_2O$.

to "recycle" valuable **11**. Thus, its reaction with $CeCl_3$ heptahydrate/sodium iodide in acetonitrile furnished 95% of parent **11**. Finally, when methyl ester **12** was treated with KOH in MeOH/H_2O amorfrutin A (**14**) [15,16,19,26] was obtained in 92% yield being identical in every respect to an authentic commercially available reference sample.

In summary, amorfrutin A was obtained from inexpensive, commercially available starting materials using a short reaction sequence. This sequence can easily be scaled up and provides amorfrutin A in an overall yield of 41%.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.04.028.

References

[1] B. Shen, Cell 163 (2015) 1297–1300.
[2] D.J. Newman, G.M. Cragg, J. Nat. Prod. 75 (2012) 311–335.
[3] L. Wang, B. Waltenberger, E.-M. Pferschy-Wenzig, M. Blunder, X. Liu, C. Malainer, T. Blazevic, S. Schwaiger, J.M. Rollinger, E.H. Heiss, D. Schuster, B. Kopp, R. Bauer, H. Stuppner, V.M. Dirsch, A.G. Atanasov, Biochem. Pharmacol. 92 (2014) 73–89.
[4] C. Weidner, G.J.C. de, A. Prasad, A. Freiwald, C. Quedenau, M. Kliem, A. Witzke, V. Kodelja, C.-T. Han, S. Giegold, M. Baumann, B. Klebl, K. Siems, L. Muller-Kuhrt, A. Schurmann, R. Schuler, A.F.H. Pfeiffer, F.C. Schroeder, K. Bussow, S. Sauer, Proc. Natl. Acad. Sci. USA 109 (2012) 7257–7262.
[5] P.S. Bairy, J. Asian, Pharm. Clin. Res. 10 (2017) 40–44.
[6] J.C. de Groot, C. Weidner, J. Krausze, K. Kawamoto, F.C. Schroeder, S. Sauer, K. Buessow, J. Med. Chem. 56 (2013) 1535–1543.
[7] S. Garcia-Vallve, L. Guasch, S. Tomas-Hernandez, J.M. del Bas, V. Ollendorff, L. Arola, G. Pujadas, M. Mulero, J. Med. Chem. 58 (2015) 5381–5394.
[8] P. Lefebvre, B. Staels, Proc. Natl. Acad. Sci. USA 109 (2012) 7136–7137.
[9] S. Sauer, Chembiochem 15 (2014) 1231–1238.
[10] C. Weidner, S.J. Wowro, A. Freiwald, K. Kawamoto, A. Witzke, M. Kliem, K. Siems, L. Mueller-Kuhrt, F.C. Schroeder, S. Sauer, Diabetologia 56 (2013) 1802–1812.
[11] C. Chen, Y. Wu, Y. Chen, L. Du, J. Sep. Sci. 38 (2015) 2924–2929.
[12] C. Chen, Y. Wu, L. Du, Pharm. Biol. 54 (2016) 488–493.
[13] L. Fuhr, M. Rousseau, A. Plauth, F.C. Schroeder, S. Sauer, J. Nat. Prod. 78 (2015) 1160–1164.
[14] C. Weidner, M. Rousseau, R.J. Micikas, C. Fischer, A. Plauth, S.J. Wowro, K. Siems, G. Hetterling, M. Kliem, F.C. Schroeder, S. Sauer, J. Nat. Prod. 79 (2016) 2–12.
[15] I.S. Aidhen, R. Mukkamala, C. Weidner, S. Sauer, Org. Lett. 17 (2015) 194–197.
[16] X.-Y. Ji, J.-H. Chen, G.-H. Zheng, M.-H. Huang, L. Zhang, H. Yi, J. Jin, J.-D. Jiang, Z.-G. Peng, Z.-R. Li, J. Med. Chem. 59 (2016) 10268–10284.
[17] S. Laclef, K. Anderson, A.J.P. White, A.G.M. Barrett, Tetrahedron Lett. 53 (2012) 225–227.
[18] Y.Y. Song, H.G. He, Y. Li, Y. Deng, Tetrahedron Lett. 54 (2013) 2658–2660.
[19] X.-J. Xu, T. Zeng, Z.-X. Huang, X.-F. Xu, J. Lin, W.-M. Chen, J. Nat. Prod. 81 (2018) 2621–2629.
[20] E.A.V. Chanis, PhD thesis, University of Kansas, USA, 1992.
[21] A. Akincioglu, E. Kocaman, H. Akincioglu, R.E. Salmas, S. Durdagi, I. Gulcin, C.T. Supuran, S. Goksu, Bioorg. Chem. 74 (2017) 238–250.
[22] J.L. Douglas, T. Money, Tetrahedron 23 (1967) 3545–3555.
[23] Y. Deng, Y. Song, H. He, Y. Li, Q. Liu, 2013, CN103102264A.
[24] G.S. Grandhi, J. Selvakumar, S. Dana, M. Baidya, J. Org. Chem. 83 (2018) 12327–12333.
[25] Z. Li, X. Ji, S. Xue, G. Zheng, Y. Li, P. Tao, J. Jiang, 2013, CN103172512A.
[26] I.S. Aidhen, R. Mukkamala, 2015, IN2013CH05457A.
[27] E.L. Ghisalberti, P.R. Jefferies, D. McAdam, Phytochemistry 20 (1981) 1959–1961.
[28] X. Wang, R.-X. Chen, Z.-F. Wei, C.-Y. Zhang, H.-Y. Tu, A.-D. Zhang, J. Org. Chem. 81 (2016) 238–249.
[29] T.J. Wallace, H. Pobiner, A. Schriesheim, J. Org. Chem. 30 (1965) 3768–3771.
[30] W.v.E. Doering, R.M. Haines, J. Am. Chem. Soc. 76 (1954) 482–486.