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Total synthesis of pulverolide: revision of its structure

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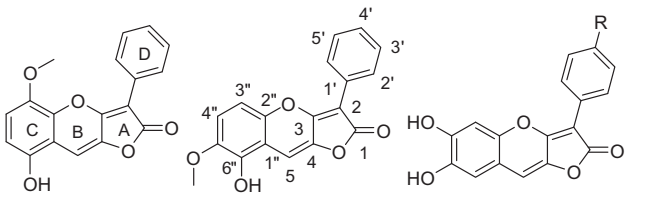
ABSTRACT

A flexible and practical strategy toward the synthesis of rare 2*H*-furo[3,2-*b*]benzopyran-2-one skeleton has been developed. With a microwave-assisted cyclization–dehydration as the key transformation, the first total synthesis of pulverolide has been completed in 10 steps with 9% overall yield, leading to the revision of its proposed structure.

Pulveroboletus ravenelii is a genus in the Boletaceae. The fruiting bodies are known as edibles and are used in traditional Chinese medicine to cure lumbago and painful legs, numbed limbs, and to stop bleeding.[1] The chemical study of *P. ravenelii* resulted in a new butenolide-type fungal pigment pulverolide (**1**, Fig. 1).[2] The structure of pulverolide, with a rare 2*H*-furo[3,2-*b*]benzopyran-2-one skeleton, was assigned on the basis of spectroscopic analysis. To date, there are only two analogs (aurantricholides A and B) found in nature.[3] These compounds are scarce components and could be isolated in only small amounts from higher fungi. Our previous biological assay indicated that pulverolide potentiated the glutamatergic transmission which is mediated by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor.[4] Therefore pulverolide could possibly serve as a starting point toward the discovery of drug candidates for treating Alzheimer's disease. Because of its unique structure and interesting bioactivity, we were prompted to undertake the synthesis of pulverolide (**1**). Herein we report the first total synthesis of pulverolide and the revision of its structure.

Although a synthetic route leading to aurantricholides A and B has been reported, which also served as a means for the confirmation of its structures,[3a] the key irradiation-mediated cyclization step in this synthesis gave only 1% yield of the desired cyclization products. In seeking a more efficient and flexible synthesis of **1** and its analogs, we designed a new synthetic plan as outlined in Scheme 1. We envisioned that the 2*H*-furo[3,2-*b*]benzopyran-2-one ring of pulverolide (**1**) could be assembled directly from intermediate **4** by a Lewis acid-mediated cyclization–dehydration. The key compound **4** could be accessed by a vinylogous aldol reaction. Starting from commercially available isovanillin, we expected that the highly rigid pulverolide-type skeleton could be obtained in an efficient fashion.

We began our research by the reaction of isovanillin with allyl bromide in the presence of potassium carbonate. The resulting allyl ether (**7**) was then subjected to a solvent-free Claisen rearrangement assisted by microwave irradiation[5] to afford phenol **8** in 90% yield. By treatment of phenol **8** with chloromethoxymethane in the presence of sodium hydride in THF, aldehyde **9** was obtained in 68% yield. Baeyer–Villiger oxidation of aldehyde **9** followed by hydrolysis of the resulting phenol ester gave phenol **10** (83% yield). After protection of the phenol group with benzyl bromide, isomerization of the double bond in the presence of *t*-BuOK[6] gave com-



1: Pulverolide (proposed structure) **2: Pulverolide** (revised structure) **3a: R = H, Aurantricholide A** **3b: R = OH, Aurantricholide B**

Figure 1. Natural products with 2*H*-furo[3,2-*b*]benzopyran-2-one.

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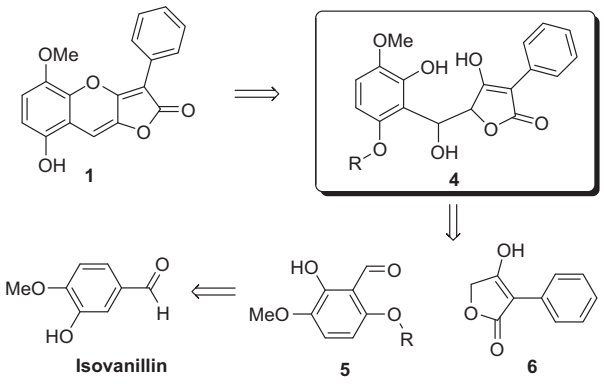
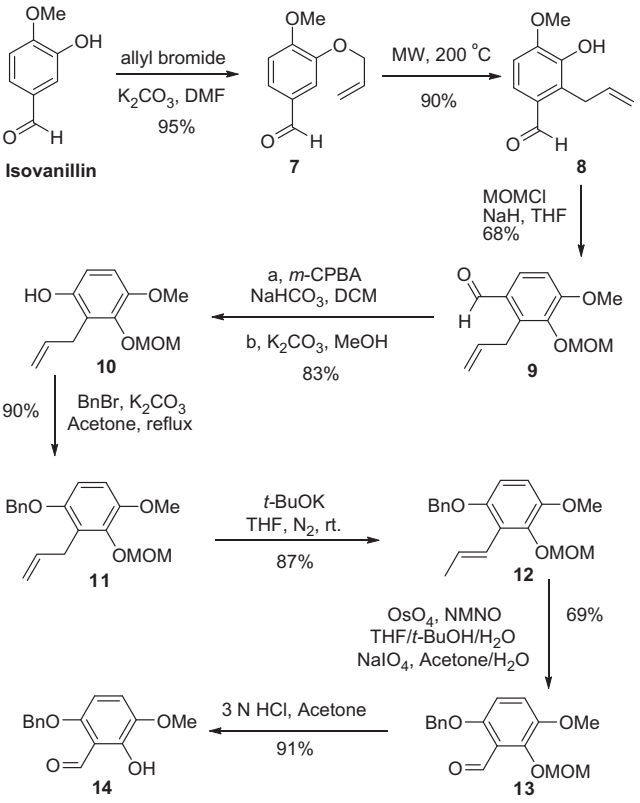


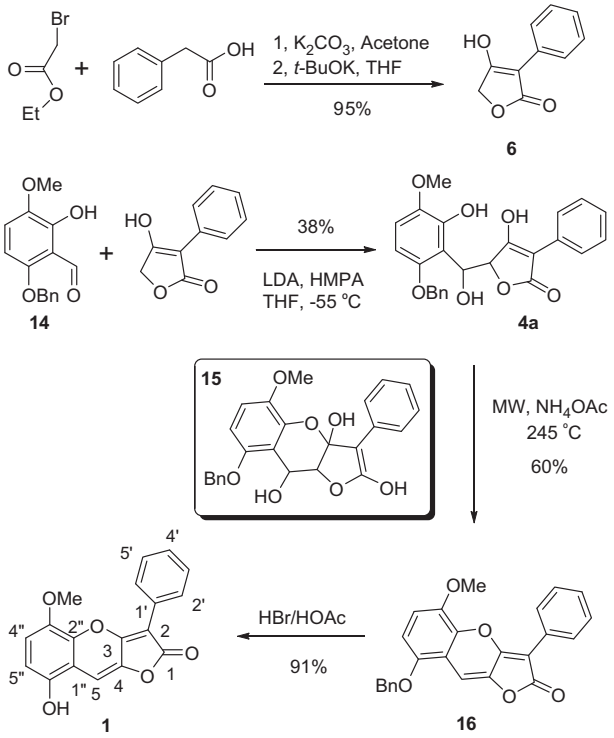
Scheme 1. Retrosynthetic analysis of pulverolide.

pound **12** (see Scheme 2, 78% over two steps). An oxidative cleavage of the double-bond in olefin **12** followed by hydrolysis in the presence of aqueous hydrochloric acid (3 N) in acetone resulted in aldehyde **14** (63%, two steps).

Having obtained intermediate **14**, we then synthesized 3-phenyltetronic acid **6** via a Dieckmann condensation between phenylacetic acid and ethyl bromoacetate in the presence of bases (see Scheme 3, two steps, 95%).[7] Next, we came to the key stage of our research, a vinylogous aldol reaction and a ring-closing etherification. Aldol reaction between a sterically hindered aldehyde such as compound **14** and tetronic acid **6** has not been reported; therefore we decided to attempt the reaction by following a similar procedure documented in the literature.[7] The dianion form of tetronic acid **6** was generated by treatment of compound **6** with lithium diisopropylamide (LDA) in THF at -78 °C. To the dianion solution, salicylaldehyde **14** in THF was added. To our disappointment, low yield of alcohol **4a** (2%) was obtained. No desired product was detected when the reaction was conducted with LDA (3.0 equiv) in the presence of zinc chloride (1.0 equiv) or copper iodide (1.0 equiv). Finally we found that the yield could be increased by using lithium diisopropylamide (3.0 equiv) in the presence of hexamethylphosphoramide (HMPA). Under the optimal reaction condition, we were able to obtain alcohol **4a** as a mixture of two diastereoisomers (38% yield, see Scheme 3).



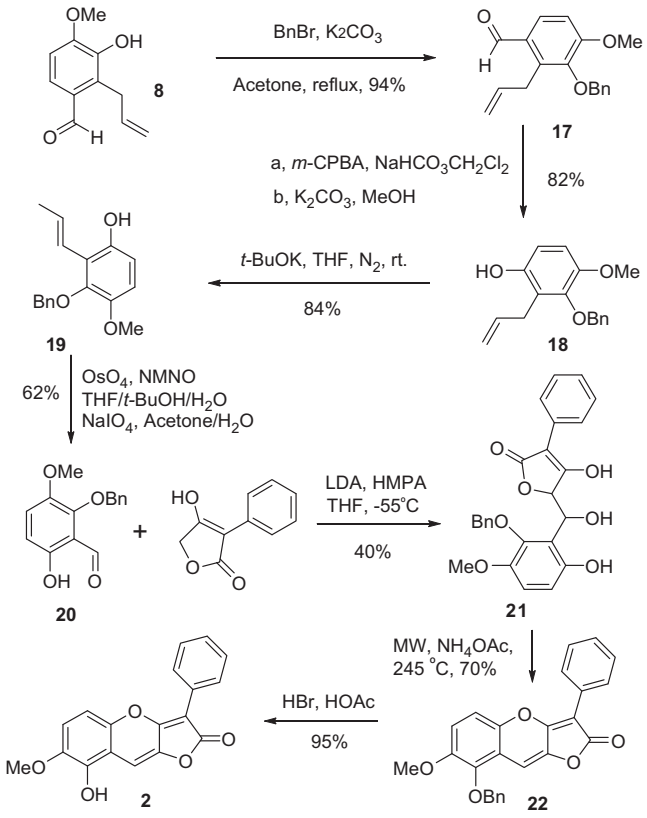
Scheme 2. Synthesis of aldehyde **14**.



Scheme 3. Studies on the synthesis of pulverolide (originally proposed structure).

With compound **4a** in hand, we came to the final stage toward the synthesis of pulverolide. Direct dehydration under high temperature (150 °C in DMF) in the presence of a Lewis acid (e.g., BF_3-Et_2O, TsOH) proved to be fruitless, giving a complex mixture. We then decided to attempt the ring-closing etherification under microwave heating in the presence of a Lewis acid. After a few screenings, we finally found that compound **16** could be obtained in 60% yield under the irradiation of microwave at 245 °C in *o*-xylene (see Scheme 3). Although amino acids such as glycine and proline could mediate this transformation, ammonium acetate, might serve as acid–base catalyst as well as dehydration agent, proved to be the best additive in this microwave-assisted reaction. This dehydration–cyclization might go through an intermediate (**15**) as highlighted in Scheme 3. The target molecule was finally obtained after the removal of benzyl-protecting group by hydrolysis in the presence of a strong acid (33 wt % HBr in acetic acid, 91% yield).[8]

The NMR spectral data of compound **1** unfortunately did not match that of natural pulverolide (see Supplementary data). The chemical shifts (^{1}H NMR) of protons attaching to the polysubstituted phenolic C-ring of natural pulverolide are found at 7.12 and 7.17 ppm, and are significantly downfield in comparison with the corresponding proton signals of synthetic compound **1**, which appear at 6.85 and 7.09 ppm. Differences of chemical shifts in the ^{13}C NMR were also noticed (see Supplementary data). The NMR data indicated that synthetic compound **1** and natural pulverolide are not the same. The methoxyl group in natural pulverolide, previously assigned at C-2 position, should be relocated to C-5 position as showed in Figure 1.



Scheme 4. Synthesis of pulverolide (revised structure).

To confirm the structure, compound **8** was then converted to benzyl ether **17** by treating with benzyl bromide in the presence of potassium carbonate. Baeyer–Villiger oxidation followed by hydrolysis of the resulting ester provided **18** (82%). After isomerization of the double bond, oxidative cleavage of the double-bond in compound **19** gave salicylaldehyde **20** (52% over two steps). A vinylogous Aldol reaction with tetronic acid **6** followed by dehydration under microwave condition afforded the tricyclic compound **22**. Deprotection of benzyl group with HBr (33% wt.) in acetic acid finally provided pulverolide **2** (95%, Scheme 4). ^{1}H and ^{13}C NMR spectra as well as IR spectroscopic data of synthetic compound **2** were identical to those reported for natural pulverolide. Therefore the revised structure for pulverolide **2** was confirmed.

In conclusion, we have developed the first practical and flexible method for the synthesis of 2*H*-furo[3,2-*b*]benzopyran-2-one skeletons. Based on a vinylogous aldol reaction and a microwave-assisted cyclization–dehydration, we successfully synthesized pulverolide. This synthetic work leads to the revision of its originally proposed structure. Further pulverolide analogs are now being prepared for bioassay, and the results will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.044.

References and notes

1. Duncan, C. J. G.; Cuendet, M.; Fronczek, F. R.; Pezzuto, J. M.; Mehta, R. G.; Hammann, M. T.; Ross, S. A. *J. Nat. Prod.* **2003**, *66*, 103.
2. Zhang, L.; Wang, F.; Dong, Z. J.; Steglich, W.; Liu, J. K. *Heterocycles* **2006**, *68*, 1455.
3. (a) Klostermeyer, D.; Knops, L.; Sindlinger, T.; Polborn, K.; Steglich, W. *Eur. J. Org. Chem.* **2000**, 603; (b) Knops, L.; Nieger, M.; Steffan, B.; Steglich, W. *Liebigs Ann.* **1995**, 77.
4. Yang, W. Ph.D. Thesis. Graduate School of Chinese Academy of Sciences, 2010, p 3.
5. Kumar, H. M. S.; Anjaneyulu, S.; Reddy, B. V. S.; Yadav, J. S. *Synlett* **2000**, 1129.
6. (a) Van, T. N.; Debenedetti, S.; Kimpe, N. D. *Tetrahedron Lett.* **2003**, *44*, 4199; (b) Kesteleyn, B.; Kimpe, N. D. *J. Org. Chem.* **2000**, *65*, 640.
7. (a) Mallinger, A.; Gall, T. L.; Mioskowski, C. *J. Org. Chem.* **2009**, *74*, 1124; (b) Pelter, A.; Al-Bayati, R. I. H.; Ayoub, M. T.; Lewis, W.; Pardasani, P.; Hansel, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 717.
8. Cherney, R. J.; Brogan, J. B.; Mo, R.; Lo, Y. C.; Yang, G.; Miller, P. B.; Scherle, P. A.; Molino, B. F.; Carter, P. H.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 597.