Synlett H. Zeng et al. Letter

Biomimetic Total Synthesis of 6a,7,8,9,10,10a-Hexahydro-3,6,9-trimethyl-6-(4-methylpent-3-en-1-yl)-1,9-epoxy-6*H*-dibenzo-[*b*,*d*]pyran and Its Diastereoisomer

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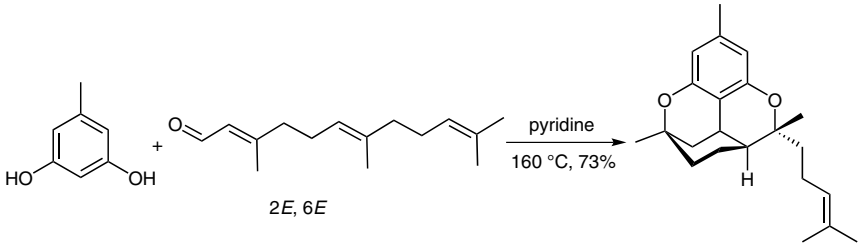


Received: 30.11.2014
Accepted after revision: 27.12.2014
Published online: 10.02.2015
DOI: 10.1055/s-0034-1380122; Art ID: st-2014-w0988-l

Abstract The first total synthesis of 6a,7,8,9,10,10a-hexahydro-3,6,9-trimethyl-6-(4-methylpent-3-en-1-yl)-1,9-epoxy-6*H*-dibenzo[*b*,*d*]pyran and its diastereoisomer via tandem pericyclic reactions were achieved in one step. Our biomimetic strategy features a sequential Aldol-type addition, 6π electrocyclization, and hetero-Diels–Alder cycloaddition, where three rings, two C–C bonds, and two C–O bonds were spontaneously constructed in a highly efficient way.

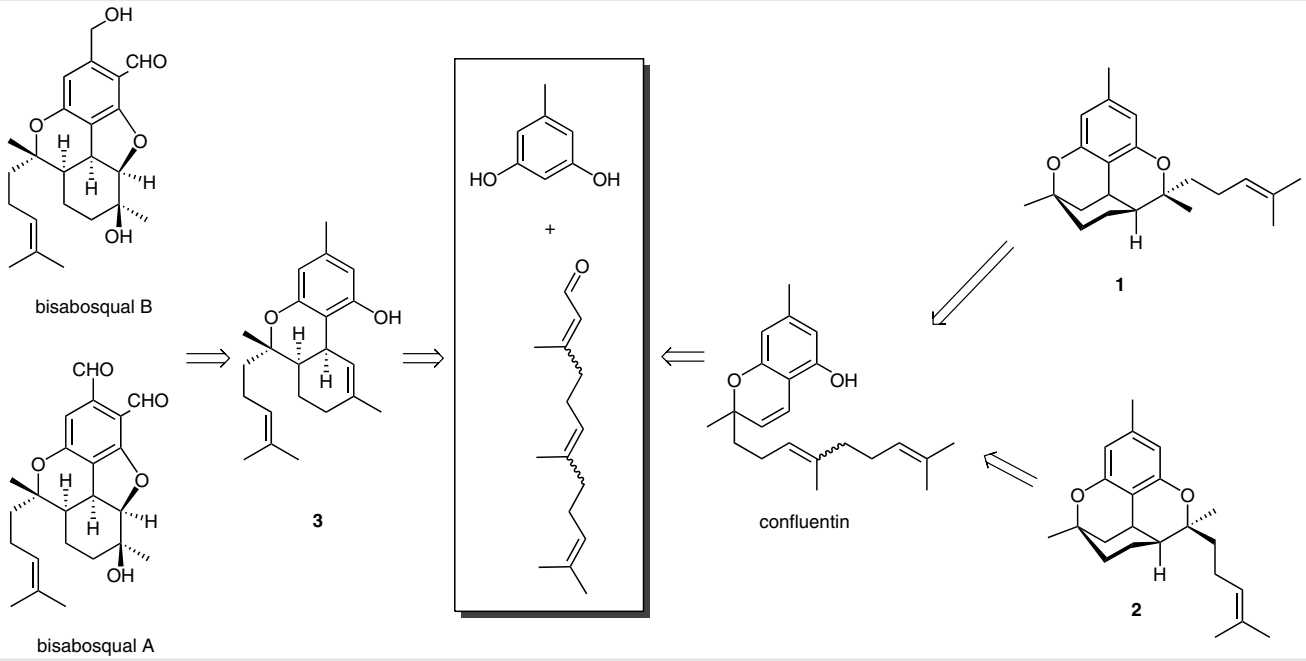
Key words biomimetic, total synthesis, tandem pericyclic reactions, 6π electrocyclization, hetero-Diels–Alder cycloaddition

Pericyclic cascade reactions have been recognized to play essential roles in the biosynthesis of natural products. They are crucial and efficient in building up structural complexity from simple precursors. Many canonical syntheses have been achieved by ingenious combinations of electrocyclizations, sigmatropic rearrangements, and cycloadditions, such as 8π–6π electrocyclization cascades,[1] electrocyclizations followed by cycloadditions,[2] oxa 6π electrocyclization followed by [4+2] cycloadditions.[3] As the most powerful catalyst in nature, enzymes have miraculous abilities to control reaction pathways by converting the same simple starting materials into diverse products. Inspired by abilities of enzymes, synthetic organic chemists have designed tremendous amount of biomimetic strategies to control reaction pathways.[4]

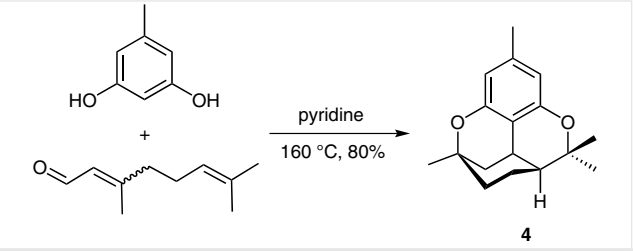
5-Methylbenzene-1,3-diol and farnesal are ubiquitous and fundamental natural products. They are important precursors for constructing various complex natural products via divergent biogenerative ways (Scheme 1). For instance, it can produce Bisabosqual's family core **3** via an Aldol-type reaction and a subsequent intramolecular [4+2] cycloaddition, which was achieved by Snider.[5] It can also be converted into confluentin via an Aldol-type reaction followed by an oxa 6π-electrocyclization, which was reported by Lee.[6] We envisioned that it is possible to form 6a,7,8,9,10,10a-hexahydro-3,6,9-trimethyl-6-(4-methylpent-3-en-1-yl)-1,9-epoxy-6*H*-dibenzo[*b*,*d*]pyran (**1**) and its diastereoisomer **2** via a sequential Aldol-type reaction, oxa-6π electrocyclization, and [4+2] cycloaddition. Those natural products were isolated by Kitanaka in 2002,[7] they were also isolated by Liu in 2013.[8] These biosynthetic considerations add attractiveness of those compounds as synthetic targets.

Apart from the structural features, their biological activities offer the impetus for them as the synthetic targets. They have good bioactivities, such as compound **1** and its diastereoisomer **2** have been tested as antiallergy, with IC_{50} values of 5.8 and 18.1 μg/mL against enzymatic activity of histidine decarboxylase, respectively.[7] This activity suggests that those molecules might be valuable leading compounds for treatment of histamine liberators. Combined the structure features and biological activities, herein we would like to report our endeavors which resulted in the first total synthesis of 6a,7,8,9,10,10a-hexahydro-3,6,9-trimethyl-6-(4-methylpent-3-en-1-yl)-1,9-epoxy-6*H*-dibenzo[*b*,*d*]pyran (**1**) and its diastereoisomer **2** in one step via biomimetic-controlling reaction pathway.

5-Methylbenzene-1,3-diol and *Z*/*E*-citral were used as starting materials for investigating the tandem-cyclization conditions (Scheme 2). In this model reaction, to our delight, the desired fused ring product **4** was obtained in 80% yield when the mixture was refluxed in pyridine at 160 °C under argon for 16 hours. Encouraged by this reaction, 5-methylbenzene-1,3-diol with *Z*/*E* mixture of farnesal was refluxed under the identical conditions, 6a,7,8,9,10,10a-hexahydro-3,6,9-trimethyl-6-(4-methylpent-3-en-1-yl)-1,9-epoxy-6*H*-dibenzo[*b*,*d*]pyran (**1**) and its diastereoisomer **2** were obtained in 38% and 29% yields, respectively



Scheme 1 Biogenerative relationship of complex natural products from 5-methylbenzene-1,3-diol and 3,7,11-trimethyldodeca-2,6,10-trienal



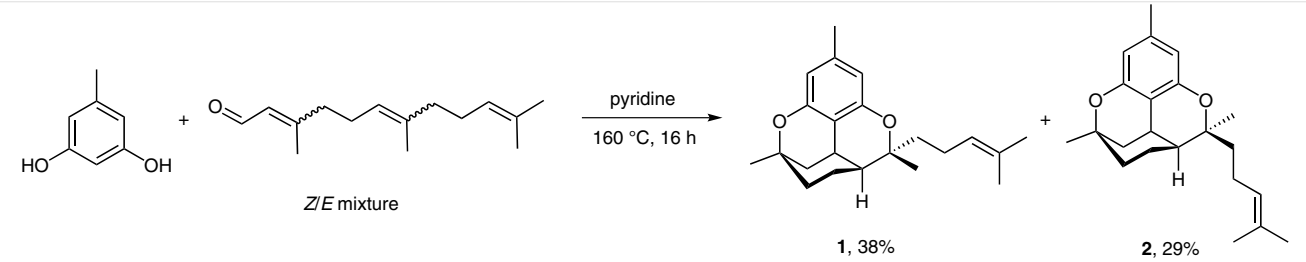
Scheme 2 Model reaction

(67% overall yield, Scheme 3). The spectroscopic data of our synthetic products are in agreement with those reported in the literature.[9] The plausible mechanism of those transformations has been outlined in Scheme 4. Initially, farnesal is treated with diphenol to generate intermediate **5** via an aldol-type or a Friedel–Crafts-type reaction, followed by dehydration to form vinyl-*ortho*-quinone methide **6**.

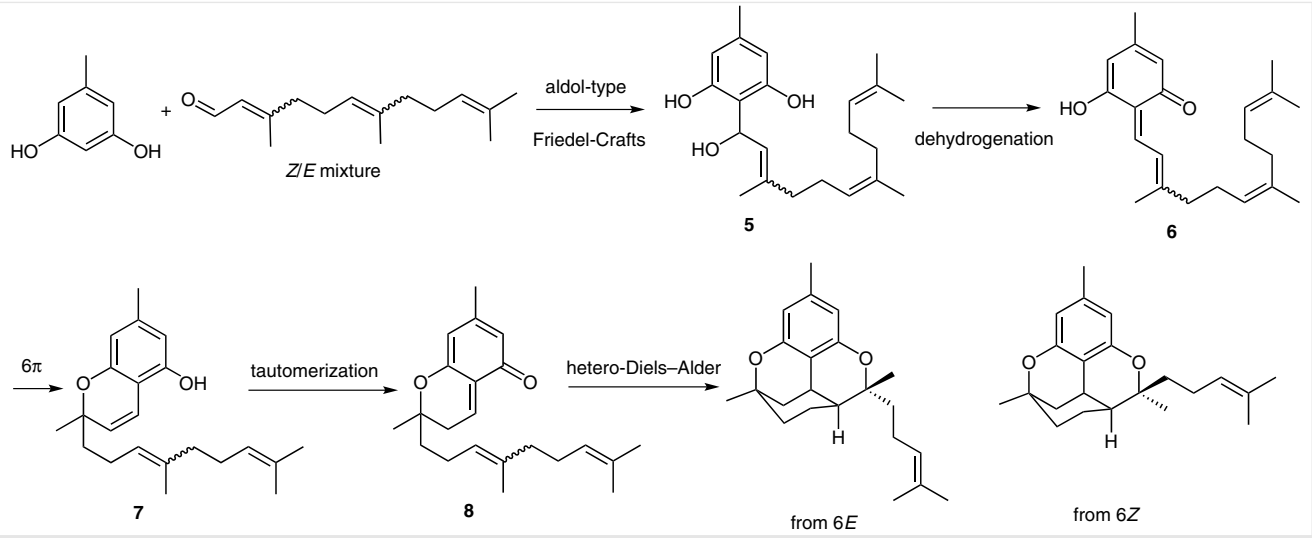
The intermediate **7**, derived from a 6π electrocyclization of **6**, tautomerized to *ortho*-quinone methide **8**, which undergoes an intramolecular hetero-Diels–Alder reaction to furnish the desired product **1** [only from (6*E*)-farnesal] and its diastereoisomer **2** [only from (6*Z*)-farnesal].

A pure (2*E*,6*E*)-farnesal[10] was also subjected to the identical conditions (Scheme 5), and we were pleased to find that compound **1** can be synthesized in a diastereoselective fashion in 73% yield.[11]

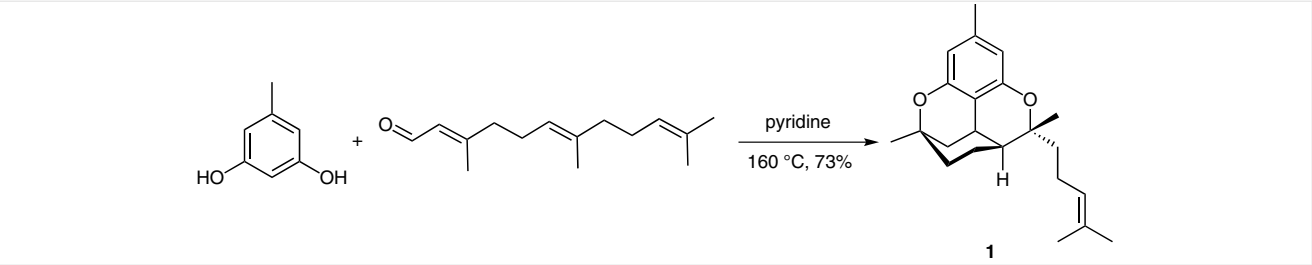
In conclusion, the first total synthesis of (±)-6a,7,8,9,10,10a-hexahydro-3,6,9-trimethyl-6-(4-methylpent-3-en-1-yl)-1,9-epoxy-6*H*-dibenzo[*b*,*d*]pyran (**1**) and its diastereoisomer **2** have been accomplished in one step with 38% and 29% yields, respectively (67% overall yield). When a pure (2*E*,6*E*)-farnesal was used as the starting material, diastereoselective total synthesis of (±)-6a,7,8,9,10,10a-hexahydro-3,6,9-trimethyl-6-(4-methylpent-3-en-1-yl)-1,9-epoxy-6*H*-dibenzo[*b*,*d*]pyran (**1**) was achieved in 73% yield. The transformation involves a 6π



Scheme 3 Total synthesis of 6a,7,8,9,10,10a-hexahydro-3,6,9-trimethyl-6-(4-methylpent-3-en-1-yl)-1,9-epoxy-6*H*-dibenzo[*b*,*d*]pyran (**1**) and its diastereoisomer **2** in one step



Scheme 4 Possible mechanism of the total synthesis of those natural products from 5-methylbenzene-1,3-diol and farnesal



Scheme 5 Diastereoselective total synthesis of 6a,7,8,9,10,10a-hexahydro-3,6,9-trimethyl-6-(4-methylpent-3-en-1-yl)-1,9-epoxy-6*H*-dibenzo[*b*,*d*]pyran (**1**)

electrocyclization, followed by [4+2] cycloaddition to simultaneously construct three rings. Two C–C bonds, two C–O bonds, and two quaternary carbon centers were generated. The simplicity of this biomimetic synthesis highly resembles the enzymatic process to generate natural products via pericyclic cascade reactions. Further expansion of this protocol to synthesize other natural products is in progress in our group.

Acknowledgment

We gratefully acknowledge the National Natural Science Foundation of China (NSFC) (No. 21302073), Natural Science Foundation of Jiangxi Province (No. 20122BAB213005, 2011-32-30), Jinggangshan University (No. JZB11033, No JZ11014) for financial support.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380122.

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(9) See ref. 7 and the Supporting Information for the comparison of the natural products and our synthesized compounds.
(10) (2*E*,6*E*)-Farnesal was oxidized from (2*E*,6*E*)-farnesol, see: (a) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616. (b) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647.
(11) **Diastereoselective Total Synthesis of 3,6,9-Trimethyl-6-(4-methylpent-3-en-1-yl)-1,9-epoxy-6*H*-dibenzo[*b*,*d*]pyran (1)**
(2*E*,6*E*)-Farnesal (440 mg, 2 mmol) and 5-methylbenzene-1,3-diol (372 mg, 3 mmol) were added to pyridine (15 mL) and the mixture was refluxed rigorously at 160 °C for 16 h under argon. The reaction mixture was cooled to r.t., and the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel with the appropriate mixture of hexane and EtOAc to give 6a,7,8,9,10,10a-hexahydro-3,6,9-trimethyl-6-(4-methylpent-3-en-1-yl)-1,9-epoxy-6*H*-dibenzo[*b*,*d*]pyran (**1**, 476 mg, 73%) as pale yellow liquid. IR (film): ν_{max} = 1621, 1067 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.31 (s, 1 H), 6.27 (s, 1 H), 5.17 (t, *J* = 7.0 Hz, 1 H), 2.85 (s, 1 H), 2.25 (s, 3 H), 2.21–2.19 (m, 1 H), 2.17 (dd, *J* = 4.5, 3.3 Hz, 1 H), 2.08 (ddd, *J* = 11.6, 5.3, 2.9 Hz, 2 H), 1.95–1.85 (m, 1 H), 1.82–1.73 (m, 3 H), 1.71 (s, 3 H), 1.65 (s, 3 H), 1.46–1.38 (m, 1 H), 1.37 (s, 3 H), 0.96 (s, 3 H), 0.87 (dt, *J* = 6.6, 5.1 Hz, 1 H), 0.63 (ddd, *J* = 25.0, 13.3, 6.1 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.7, 156.5, 137.2, 131.8, 124.3, 114.3, 110.7, 109.6, 85.8, 74.5, 45.3, 42.1, 37.5, 35.3, 29.1, 27.9, 25.7, 22.9, 22.2, 21.7, 20.9, 17.7. HRMS (APCI): *m/z* calcd for $C_{22}H_{31}O_2$: 327.2319; found: 327.2305 [M + H].