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Total synthesis of the proposed structure of a polyketide from *Phialomyces macrosporus*

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**Total synthesis of the proposed structure of a polyketide isolated from *Phialomyces macrosporus* are described. The synthesis involved chemoselective epoxidation, regioselective epoxide ring opening, and chemo- and diastereoselective dihydroxylation, followed by vinylation of the lactone accompanying formation of a furan ring.**

Polyketides are natural products constructed from simple unit such as acetylcoenzyme-A (acetylCoA) and malonylcoenzyme-A (malonylCoA) by the enzyme polyketide synthase. Polyketides have been recognized as important drug candidates because they often possess biological activity. In addition, many types of structures, such as macrolides, polyethers, and aromatic moieties, can be found in polyketides. Surprisingly, few reports exist describing a polyketide with a tethered aromatic furan ring, although other aromatic polyketides have been reported. In 1997, the polyketide 1 containing a dihydroisobenzofuranone skeleton and an aromatic furan ring was isolated from *Phialomyces macrosporus* MCI3226 along with standard polyketides 2–6 (Figure 1). Polyketides 1–6 inhibit intercellular adhesion molecule–1 (ICAM–1) expression. Therefore, the polyketides from *Phialomyces macrosporus* MCI3226 possess potential anti-inflammatory and immunosuppressive properties. A structurally closed compound with polyketide 1, asperfuranone (7), was isolated from *Aspergillus nidulans*. This polyketide 7 containing a furan ring exhibited anti-proliferative activity against human non-small cell lung cancer A549 cells. The Fas/FasL apoptotic system plays an important role in the anti-proliferative activity of asperfuranone. No synthetic study of these polyketides consisting of a dihydroisobenzofuranone skeleton and side chain, has been reported. The structural features and biological activities of polyketides 1 and 7 prompted synthetic studies based on divergent synthetic methodology using a key intermediate. The present report describes the stereoselective synthesis of polyketide 1, including the stereoselective construction of the dihydroisobenzofuranone skeleton.

The retrosynthetic analysis of polyketide 1 is outlined in Scheme 1. The target polyketide could be obtained by addition of n-propyl group side chain to the Weinreb amide 8 followed by several transformation steps. The Weinreb amide 8 would be derived from vinyl furan derivative 9, produced by vinylation of bicyclic lactone 10 accompanied by furan ring formation. The functionalized bicyclic lactone 10 would be constructed from allyl alcohol 11 in three steps involving protection of the secondary hydroxyl group of 11, chemo- and diastereoselective dihydroxylation, and protection of the resulting dihydroxy groups. The allyl alcohol 11 would be derived from epoxide 12 by regioselective epoxide ring opening of the epoxide obtained by chemoselective epoxidation of 13. The bicyclic compound 13 would be synthesized via Diels–Alder reaction of isoprene with the alkylene 14 prepared from commercially available propargyl alcohol.
The investigation began by constructing of the bicyclic framework through a Diels-Alder reaction as shown in Scheme 2. Alkyne 14, which acted as the dienophile of the Diels-Alder reaction, was prepared from propargyl alcohol (15) in two steps, protection of the hydroxyl group of 15 followed by installation of the methyl ester portion for the terminal alkyne. The Diels-Alder reaction of alkyne 14 and isoprene proceeded smoothly in the presence of ethyl aluminum dichloride as a Lewis acid, followed by treatment with 20% aqueous sulfonic acid to give 5-methyl-dihydroisobenzofuran-1-one derivative 13 in high yield (89%) and complete regioselectivity. Chemoselective epoxidation of 13 with mCPBA gave epoxide 12, which was oxidized of the carbon-carbon double bond at C5-C6, not at C3a-C7a, of 13. Regioselective epoxide ring opening of epoxide 12 was achieved after many attempts. The use of DBU as a base at low temperatures (4 °C) gave the best result to afford the desired secondary allyl alcohol 11, along with a trace amount of the tertiary allyl alcohol. The resulting secondary allyl alcohol 11 was used immediately in the next step because of its instability. Protection of the resulting hydroxyl group with TBS group provided the desired conjugated dienone 16 in 75% yield in two steps.

With the desired Weinreb amide 8 synthesized, the final stage of the synthetic study was performed. Addition of a side chain to the Weinreb amide derivative 8 using the corresponding n-propylmagnesium bromide gave 21 in 86% yield, as shown in Scheme 4. Many attempts to selectively cleave the acetonide group in the presence of a TBS group were done. Treatment of 21 with TFA in CH₂Cl₂/H₂O for 4 h gave the diol 22 in 57% yield. Finally, Swern oxidation of diol 22, followed by cleavage of the TBS group of the resulted diketone 23, afforded the target molecule 1 in 68% overall yield for 2 steps. Surprisingly, both the ¹H and ¹³C NMR spectral data of the synthetic polyketide 1 were not identical to those of the natural product. However, the structure of synthesized 1 was identified by X-ray crystallography. These results suggest that the
To resolve this discrepancy, the synthesis of 27, a diastereomer of 1, was conducted as shown in Scheme 5. The synthesis of 27 containing a cis-oriented vicinal diol, was started from lactone 18, which was the minor product obtained from the stereoselective dihydroxylation of 16. Using a procedure similar to that used for the synthesis of 21 (Schemes 3 and 4), compound 25 was produced in 41% overall yield for 5 steps from 18 via the Weinreb amide intermediate 24. The stereochemistry of 25 was confirmed using X-ray crystallographic analysis. Selective removal of the acetone group did not occur under the same conditions used for the synthesis of 22 from 21, and the triol 26 was obtained in 91% yield as the sole product (the corresponding diol was not obtained). Therefore, chemoselective oxidation of the hydroxy group at the allylic position in triol 26 was attempted. The Ley oxidation procedure using tetra-n-propylammonium perruthenate as the oxidant afforded compound 27 in 22% yield. However, the spectral data of 27 also did not identical with those of the natural product. The results of this study indicated that the originally proposed structure of natural polyketide isolated from Phialomyces macrosporus requires revision.

**Conclusions**

In summary, total synthesis of polyketide 1, isolated from the culture of *Phialomyces macrosporus*, was achieved. This synthesis featured the chemoselective epoxidation of 1,4-cyclohexadiene portion of 13, regioselective epoxide ring opening of 12, chemo- and diastereoselective dihydroxylation of the conjugated dienone derivative 16, and vinylation of lactone 10 accompanied by furan ring formation. Unfortunately, the NMR spectra of synthetic samples 1 and 27 were not identical to those reported for the natural product. This synthetic methodology contributes to the synthetic research of related polyketide asperfuranone (7) isolated from *Aspergillus nidulans*. This should lead to the actual structure of the natural product isolated from *Phialomyces macrosporus*.

**Notes and references**

6. This Diels-Alder reaction of the alkyne and isoprene proceeded with complete regioselectivity, and the 6-methyl-dihydroisobenzofuran-1-one derivative that was a regioisomer of the desired bicyclic compound 13 was not detected.
7. CCDC 1039794 contains the supplemental crystallographic data of 17 for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.


10. Data for 1. Colorless needles; mp 91–92°C; IR (KBr) 3446, 2966, 2935, 1704, 1695, 1682, 1593, 1532, 1446, 1404, 1372, 1293 cm⁻¹; ¹H NMR (400 MHz, CD₃CN) δ 0.96 (3H, t, J = 7.4 Hz), 1.28 (3H, s), 1.63–1.72 (2H, m), 2.81 (2H, t, J = 7.3 Hz), 2.88 (1H, dd, J = 17.8, 8.1 Hz), 3.25–3.50 (2H, m, including 1H, dd, J = 17.8, 4.8 Hz, at δ 3.37), 3.60–3.90 (1H, br s), 4.05 (1H, dd, J = 8.1, 4.8 Hz), 8.16 (1H, s); ¹³C NMR (100 MHz, CD₃CN) δ 13.9, 17.6, 17.6, 18.4, 28.2, 41.7, 74.1, 78.2, 124.9, 129.5, 147.6, 149.4, 191.5, 195.7; HRMS (ESI–TOF) calcd for C₁₃H₁₇O₅ ([M + H]⁺) 253.1076, found 253.1070.

11. The detailed comparison for ¹H and ¹³C NMR spectra data of synthetic 1 and 27 with those of natural polyketide is described in the supporting information. In addition, comparison for ¹³C NMR spectra of dihydroisobenzofuranone skeleton of synthetic 1 with that of asperfuranone (7) is described.

12. CCDC 1039795 contains the supplemental crystallographic data of 1 for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

13. CCDC 1039796 contains the supplemental crystallographic data of 25 for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


15. Data for 27. Colorless oil; IR (neat) 3463, 3132, 2962, 2926, 2874, 1701, 1674, 1592, 1531, 1458, 1404, 1376, 1334, 1242, 1128, 1062, 913, 882, 804, 738 cm⁻¹; ¹H NMR (400 MHz, CD₃CN) δ 0.96 (3H, t, J = 7.4 Hz), 1.27 (3H, s), 1.68 (2H, qt, J = 7.4, 7.4 Hz), 2.81 (2H, t, J = 7.4 Hz), 3.10–3.17 (1H, m), 3.29 (1H, dd, J = 18.6, 2.6 Hz), 3.43–3.46 (1H, br s), 3.91 (1H, s), 4.11–4.15 (1H, m), 8.17 (1H, s); ¹³C NMR (100 MHz, CD₃CN) δ 14.0, 17.6, 22.4, 28.3, 41.6, 76.3, 79.4, 124.7, 130.0, 147.1, 149.8, 191.5, 197.3; HRMS (ESI–TOF) calcd for C₁₃H₁₆O₅Na ([M + Na]⁺) 275.0895, found 275.0892.