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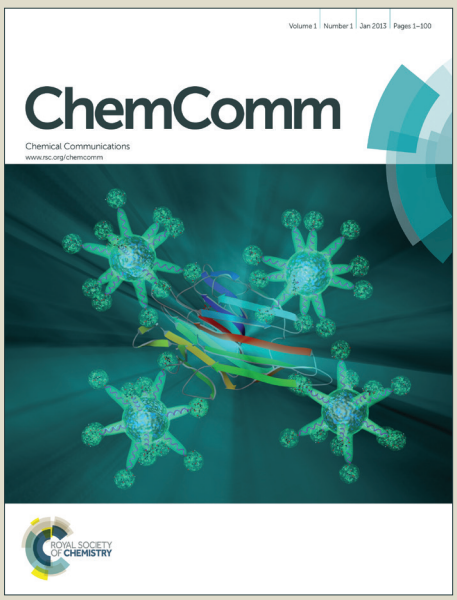

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Total synthesis of the proposed structure of a polyketide from *Phialomyces macrosporus*

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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 (manolylCoA) by the enzyme polyketide synthase.[1] 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).[2] 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*.[3] 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.[3b] 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.

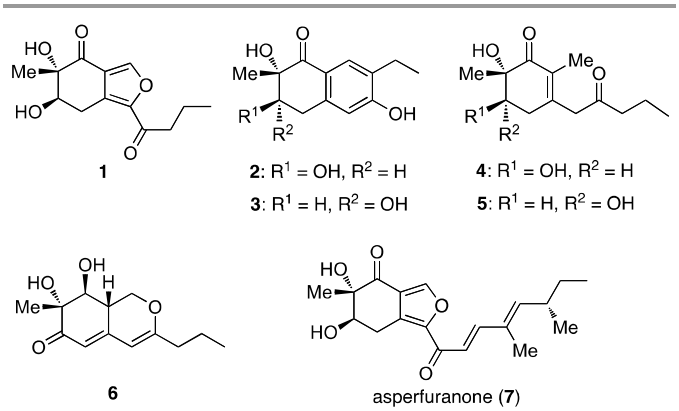
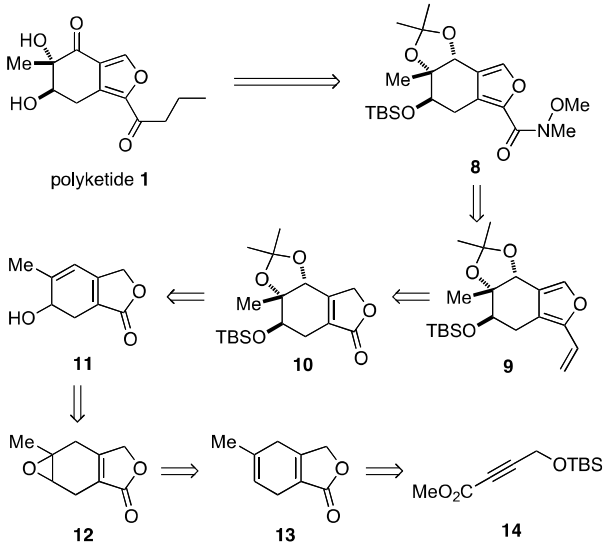


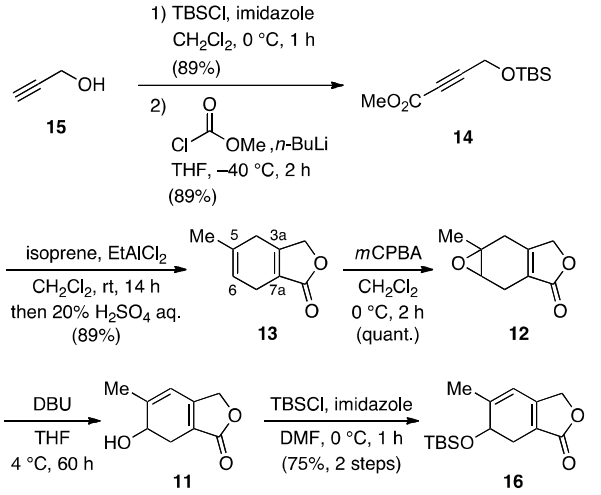
Fig 1. Structures of polyketides **1–6** isolated from *Phyalomyces macrosporus* and the related compound asperfuranone (**7**).

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**,[4] 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 dihydroxyl 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 alkyne **14** prepared from commercially available propargyl alcohol.



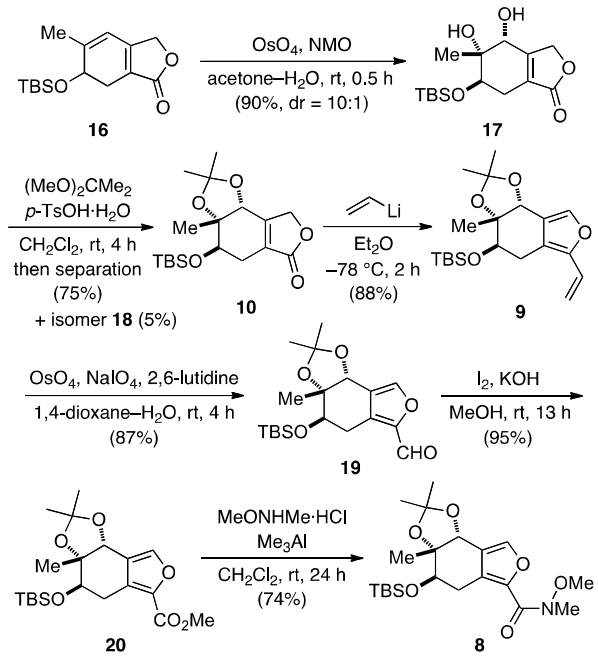
Scheme 1. Retrosynthesis of polyketide **1**.

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**[5] 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.[6] Chemoselective epoxidation of **13** with *m*CPBA 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.



Scheme 2. Synthesis of bicyclic compound **16**.

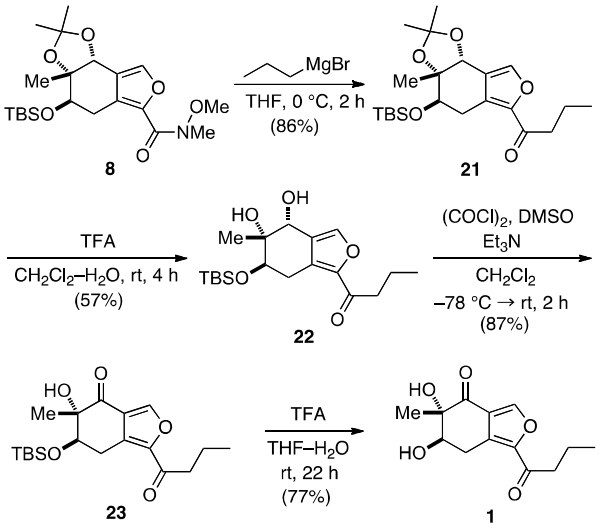
After obtaining **16**, the stereoselective construction of perhydroisobenzofurane moiety was examined, as shown in Scheme 3. Diastereoselective dihydroxylation of **16** with osmium tetraoxide gave the desired diol **17** and its diastereoisomer in 90% yield in a 10:1 ratio. The stereochemistry of the newly generated asymmetric carbons was confirmed by the X-ray crystallographic analysis of **17**,[7] which was a separable major isomer obtained with difficulty. This result proves that dihydroxylation with osmium tetraoxide occurred on the side opposite of the TBS-protected hydroxyl group at C6 of **16**. After protection of the resulting dihydroxyl group as an acetonide followed by complete separation, the desired product **10** and its diastereoisomer **18** were obtained in 75% and 5% yield respectively. Treatment of the desired lactone **10** with vinyl lithium species, prepared from tetravinyltin and methyl lithium, was accomplished the introduction of vinyl group along with formation of a furan ring from the lactone to give the vinyl furan derivative **9** in 88% yield. Transformation of the vinyl group of **9** to the Weinreb amide group was conducted in three steps: oxidative cleavage of the vinyl group of **9**, oxidative esterification of the resulting aldehyde **19** with iodine and potassium hydroxide in methanol,[8] and amidation of ester **20** with *N*,*O*-dimethylhydroxylamine hydrochoride using trimethylaluminum as a Lewis acid,[9] to afford the Weinreb amide intermediate **8** in 61% overall yield.



Scheme 3. Stereoselective synthesis of the Weinreb amide **8**.

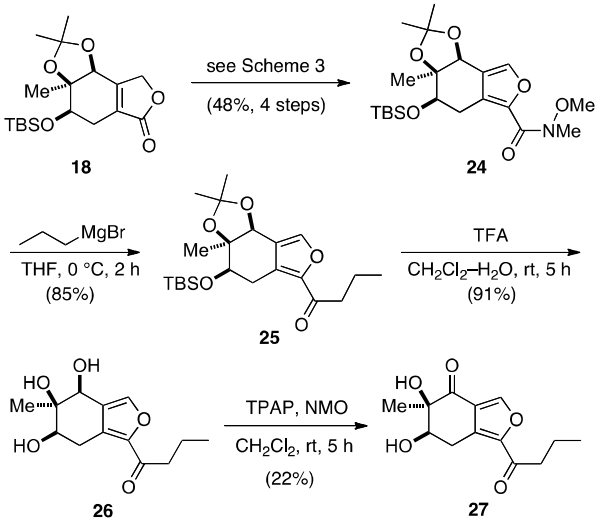
With the desired Weinreb amide **8** synthesized, the final stage of the synthetic study was performed. Addition of a side chain to the Weinreb amide derivative **8** using the corresponding *n*-propylmagnesium bromide gave **21** in 86% yield, as shown in Scheme 4. Many attempts to selectively cleave the acetonide group in the presence of a TBS group were done. Treatment of **21** with TFA in CH_2Cl_2/H_2O 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**[10] in 68% overall yield for 2 steps. Surprisingly, both the ^1H and ^{13}C NMR spectral data of the synthetic polyketide **1** were not identical to those of the natural product.[11] However, the structure of synthesized **1** was identified by X-ray crystallography.[12] These results suggest that the

structure of natural polyketide differ from the originally proposed structure.



Scheme 4. Synthesis of the proposed structure of polyketide **1**.

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.[13] Selective removal of the acetonide 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[14] using tetra-*n*-propylammonium perruthenate as the oxidant afforded compound **27** in 22% yield. However, the spectral data of **27**[15] also did not identical with those of the natural product.[11] The results of this study



Scheme 5. Synthesis of the *cis*-isomer **27**.

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

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Electronic Supplementary Information (ESI) available: Experimental procedure and spectroscopic data. See DOI: 10.1039/c000000x/

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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 *via* www.ccdc.cam.ac.uk/data_request/cif.

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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, CD_3CN) 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); ^{13}C NMR (100 MHz, CD_3CN) δ 13.9, 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 $C_{13}H_{17}O_5$ ($[M + H]^+$) 253.1076, found 253.1070.
11. The detailed comparison for ^1H and ^{13}C NMR spectra data of synthetic **1** and **27** with those of natural polyketide is described in the supporting information. In addition, comparison for ^{13}C 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.
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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, CD_3CN) 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); ^{13}C NMR (100 MHz, CD_3CN) 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 $C_{13}H_{16}O_5Na$ ($[M + Na]^+$) 275.0895, found 275.0892.

