This article is dedicated to Professor Satoshi Ōmura in celebration of his 2015 Nobel Prize.

Regular Article

Enantioselective Total Synthesis of the Proposed Structure of Furan-Containing Polyketide

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Enantioselective total synthesis of the proposed structure of furan-containing polyketide was accomplished. The key features include a chemo- and enantioselective epoxidation of 1,4-cyclohexadiene by Shi asymmetric epoxidation, a regioselective epoxide ring opening, chemo- and diastereoselective dihydroxylation of the conjugated dienone derivative, and vinylation of the lactone accompanied by formation of the furan ring.

Key words enantioselective synthesis; polyketide; Shi asymmetric epoxidation; regioselective epoxide ring opening

Fungi produce many kinds of metabolites such as terpenes, alkaloids, and polyketides, which are rich sources for new drug candidates.^{1–3)} Fungal polyketides possess various biological activities and their attractive structures, such as macrolides, polyethers, and aromatic compounds, are classified as polyketides.^{4–6)} In 1997, a novel polyketide **1**, possessing inhibitory activity of intercellular adhesion molecule-1 (ICAM-1) expression, was isolated from *Phialomyces macrosporus* MCI3226.⁷⁾ From this report, the structure of polyketide **1** was proposed, having a dihydroisobenzofuranone skeleton involving an aromatic furan ring as depicted in Fig. 1. Recently, a polyketide **2** exhibiting anti-proliferative activity against human non-small cell lung cancer A549 cells was isolated from *Aspergillus nidulans*, and named asperfuranone.^{8–11)} Its structure also was proposed to contain a dihydroisobenzofuranone skeleton involving an aromatic furan ring as in polyketide **1**. In the anti-proliferative activity of asperfuranone (**2**), the Fas/FasL apoptotic system plays an important role.⁹⁾ To our knowledge, there have been no synthetic studies of these polyketides consisting of the dihydroisobenzofuranone skeleton and side chain to date. The structural features and biological activities of these two polyketides **1** and **2** attracted our attention, and synthetic studies of these dihydroisobenzofuranone polyketides based on a divergent synthetic methodology using a key intermediate were started. Very recently, we reported the total synthesis of the proposed structure of polyketide **1** in racemic form, and suggested that the proposed structure of natural polyketide from *Phialomyces macrosporus* required revision.¹²⁾ This report describes the stereo- and enantioselective synthesis of the proposed structure of polyketide **1** using a key intermediate having a dihydroisobenzofuranone skeleton.

The synthetic strategy for this dihydroisobenzofuranone polyketide **1** is outlined in Chart 1. Target polyketide could be synthesized by the installation of the corresponding side

chain to the Weinreb amide **3**,^{13,14)} which is the key intermediate, followed by several transformation steps. The Weinreb amide **3** would be derived from the vinyl furan derivative **4**, produced by vinylation of bicyclic lactone **5**, accompanied by furan ring formation. The functionalized bicyclic lactone **5** would be constructed from the allyl alcohol **6** in three steps involving protection of the secondary hydroxyl group of **6**, chemo- and diastereoselective dihydroxylation, and protection of the resulting dihydroxyl groups. The allyl alcohol **6** would be derived from regioselective epoxide ring opening reaction of epoxide **7**, which in turn would be obtained by the chemo- and enantioselective epoxidation of **8** by the Shi asymmetric epoxidation protocol.^{15–17)} The bicyclic compound **8** can be easily prepared by the procedure in our previous report.¹²⁾

This synthetic project was started from the introduction of an asymmetric carbon to bicyclic lactone by Shi asymmetric epoxidation as shown in Chart 2. Chemo- and enantioselective epoxidation of **8** with Oxone[®] and Shi catalyst **9** prepared from D-fructose gave the epoxide **7**, which was oxidized selectively at the C5–C6 carbon–carbon double bond in quantitative yield. Enantiomeric excess of the obtained epoxide **7** was measured by chiral HPLC methodology as 87%.¹⁸⁾ After purified by recrystallization, enantiomerically pure **7** (99% enantiomeric excess (ee)) was obtained. Regioselective epoxide ring opening reaction of epoxide **7** was achieved after many trials. The use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base at low temperature (4°C) gave the best result to afford the desired secondary allyl alcohol **6** along with a trace amount of the tertiary allyl alcohol. The resulting secondary allyl alcohol **6** was immediately used in the next step, since it was an unstable compound. Protection of the resulting hydroxyl group with a *tert*-butyldimethylsilyl (TBS) group gave the desired conjugated dienone **10** in 80% yield for two steps. The absolute stereochemistry of the newly formed asymmetric carbon at C6 of **6** was confirmed by the

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Fig. 1. Structures of Polyketide 1 and Asperfuranone 2

Chart 1. Synthetic Strategy for the Proposed Structure of Polyketide 1

modified Mosher's method.^{19,20} Thus, the crude product of allyl alcohol **6** was transformed with (*R*)- and (*S*)- α -methoxy- α -trifluoromethylphenylacetyl (MTPA) chlorides to (*S*)- and (*R*)-MTPA esters **11** and **12**, respectively. From ¹H-NMR spectral analysis, the absolute configuration at the C6 asymmetric carbon was determined as *R*.

Having the desired compound **10** in hand, our aim in this project was the asymmetric synthesis of the key intermediate Weinreb amide **3** as shown in Chart 3. Transformation of **10** to the key compound **3** was carried out using the same protocol as in our previous report on the synthesis of the proposed structure of racemic polyketide **1**.¹² Diastereoselective dihydroxylation of **10** with osmium tetroxide gave a mixture of the desired diol **13** and its diastereoisomer in a 10:1 ratio in 87% yield. Separation of these diastereomers was accomplished by protection of the resulting dihydroxyl group as an acetonide to afford the desired product **5** and its diastereoisomer **14** in 71 and 8% yields, respectively. Formation of the furan ring having a vinyl group was achieved by treatment of the desired lactone **5** with the vinyl lithium species prepared from tetravinyltin and methyl lithium to give the vinyl furan derivative **4** in 93% yield. Transformation of the vinyl group of **4** to the Weinreb amide group was carried out in three steps: oxidative cleavage of the vinyl group of **4**, oxidative esterification²¹ of the resulting aldehyde **15**, and amidation of the ester **16** with *N,O*-dimethylhydroxylamine hydrochloride and trimethylaluminum,²² to afford the Weinreb amide intermediate **3** in 71% yield over three steps.

Chart 2. Enantioselective Synthesis of the Desired Conjugated Dienone 10

Chart 3. Stereoselective Synthesis of the Key Intermediate 3

With the key intermediate **3** synthesized, we focused our efforts on the synthesis of polyketide having the dihydroisobenzofuranone skeleton. Asymmetric synthesis of the proposed structure of polyketide **1**, isolated from *Phialomyces macrorhizus*, was carried out as shown in Chart 4. The synthetic route of polyketide **1** from the Weinreb amide **3** employed approximately the same procedure as in our previous report.¹² Alkylation of the Weinreb amide **3** with *n*-propylmagnesium bromide gave **17** in 82% yield. Treatment of **17** with trifluoroacetic acid (TFA) in CH₂Cl₂-H₂O for 6 h selectively cleaved the acetonide group to afford **18** in 72% yield. After Ley

Chart 4. Asymmetric Synthesis of the Proposed Structure of Polyketide 1

oxidation^{23,24)} of the diol **18** to **19**, treatment of the resulting ketone **19** with tetra-*n*-butylammonium fluoride (TBAF) provided the target compound **1** in 90% yield. Both ¹H- and ¹³C-NMR spectral data were identical with those of the previously synthesized racemic **1**.¹²⁾

In summary, enantioselective total synthesis of the proposed structure of polyketide **1**, isolated from *Phialomyces macrosporus*, was achieved. The key features include a chemo- and enantioselective epoxidation of 1,4-cyclohexadiene by Shi asymmetric epoxidation, a regioselective epoxide ring opening, chemo- and diastereoselective dihydroxylation of the conjugated dienone derivative, and vinylation of the lactone accompanied by formation of a furan ring. This synthetic methodology will be useful for the synthesis of related polyketide asperguranone (**2**) isolated from *Aspergillus nidulans*, which is currently underway in our laboratory.

Experimental

All reactions involving air- and moisture-sensitive reagents were carried out using standard syringe-septumcap techniques. Unless otherwise noted, all solvents and reagents were obtained from commercial suppliers and used without further purification. Routine monitoring of reactions were carried out Merck silica gel 60 F254 TLC plates. Column chromatography was performed on Kanto Chemical Silica Gel 60N (spherical, neutral 60–230 μm) with the solvents indicated. Melting points were taken on a Yanako MP-S3 micro melting point apparatus and are uncorrected. ¹H- and ¹³C-NMR spectra were measured with a Burkert AV-300 (300 MHz) or a Burkert DPX-400 (400 MHz) spectrometer. Chemical shifts were expressed in ppm using CHCl₃ (7.26 ppm for ¹H-NMR, 77.0 ppm for ¹³C-NMR) in CDCl₃, CH₃CN (1.94 ppm for ¹H-NMR, 118.3 ppm for ¹³C-NMR) in CD₃CN as internal standard. Infrared spectral measurements were carried out with a Perkin-Elmer Paragon 1000 FT-IR and only noteworthy absorptions were listed. HR-MS spectra was measured on a Micromass LCT spectrometer. X-ray crystallographic analysis was taken with Burkert APEX2 Ultra TXS.

(1*aR*,6*aS*)-6*a*-Methyl-1*a*,2,6,6*a*-tetrahydrooxireno[2,3-

f]isobenzofuran-3(5*H*)-one (**7**) To a stirred solution of **8** (500 mg, 3.33 mmol), tetra-*n*-butylammonium hydrosulfate (45.2 mg, 0.133 mmol) and ketone **9** (258 mg, 0.999 mmol) in CH₃CN–DMM [formaldehyde dimethylacetal]–0.05 M sodium tetraborate in 0.4 M disodium ethylenediaminetetraacetate (Na₂EDTA) aqueous solution (1:2:2, 83 mL) were added dropwise simultaneously, a solution of Oxone® (2.83 g, 4.66 mmol) in 0.4 M Na₂EDTA aqueous solution (23 mL) and a solution of K₂CO₃ (2.67 g, 19.3 mmol) in 0.4 M Na₂EDTA aqueous solution (23 mL) by using the syringe pump (0.24 mL/min) at 0°C under Ar. After stirred for 2 h at 0°C, the reaction was quenched with H₂O, and extracted with AcOEt. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (hexane–AcOEt, 1:1) to afford **7** (545 mg, 98, 87% ee) as white crystals. Recrystallization from CHCl₃–hexane gave the optically pure **7** (99% ee) as colorless needles. [α]_D²⁰ +32.5 (*c*=1.0, CHCl₃). mp: 90–93°C (CHCl₃–hexane). IR (KBr) cm^{−1}: 2982, 2925, 2908, 1766, 1758, 1755, 1746, 1692, 1445, 1433, 1413, 1352, 1342, 1276, 1202, 1151, 1087. ¹H-NMR (400 MHz, CDCl₃) δ: 1.48 (3H, d, *J*=2.8 Hz), 2.57–2.71 (2H, m), 2.75–2.92 (2H, m), 3.25–3.28 (1H, s), 4.57–4.73 (2H, m). ¹³C-NMR (100 MHz, CDCl₃) δ: 21.9, 22.6, 29.5, 56.6, 57.9, 71.4, 121.8, 156.1, 173.3. High resolution (HR)-MS (electrospray ionization-time-of flight (ESI-TOF)) Calcd for C₉H₁₀O₃Na [M+Na]⁺ 189.0528. Found 189.0526.

(*R*)-6-(*tert*-Butyldimethylsilyloxy)-5-methyl-6,7-dihydroisobenzofuran-1(3*H*)-one (**10**) To a stirred solution of **7** (420 mg, 2.53 mmol) in THF (25 mL) was added dropwise DBU (0.385 mL, 380 mg, 2.53 mmol) at 4°C, and the reaction mixture was stirred for 68 h at 4°C. The reaction mixture was quenched with H₂O, and extracted with AcOEt. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The resulting residue was dissolved in *N,N*-dimethylformamide (DMF) (2.3 mL), and imidazole (413 mg, 6.07 mmol) and *tert*-butyldimethylsilyl chloride (TBSCl) (458 mg, 3.04 mmol) were added in sequence to this reaction mixture at 0°C. After stirred for 1 h at 0°C, H₂O was added to this reaction mixture at 0°C, and the mixture was extracted with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (hexane–AcOEt, 1:1) to afford **10** (570 mg, 80% for 2 steps) as a colorless oil. [α]_D²⁰ +141.5 (*c*=1.1, CHCl₃). mp: 67–68°C (CHCl₃–hexane). IR (KBr) cm^{−1}: 2953, 2929, 2886, 2857, 1754, 1746, 1661, 1606, 1472, 1445, 1346, 1253, 1110, 1020, 1006. ¹H-NMR (400 MHz, CDCl₃) δ: 0.09 (3H, s), 0.10 (3H, s), 0.88 (9H, s), 1.98 (3H, s), 2.47–2.57 (1H, m), 2.60–2.70 (1H, m), 4.45–4.51 (1H, m), 4.70–4.82 (2H, m), 5.94 (1H, s). ¹³C-NMR (100 MHz, CDCl₃) δ: −4.9, −4.4, 18.0, 20.9, 25.7 (3C), 28.0, 69.6, 69.7, 114.5, 119.9, 150.1, 155.9, 173.4. HR-MS (ESI-TOF) Calcd for C₁₅H₂₄O₃SiNa [M+Na]⁺ 303.1392. Found 303.1391.

(*S*)-[(*R*)-6-Methyl-3-oxo-1,3,4,5-tetrahydroisobenzofuran-5-yl]-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**11**) To a stirred solution of **6** (20.0 mg, 0.120 mmol) in CH₂Cl₂ (1.2 mL) was added pyridine (0.120 mL, 1.20 mmol) and 4-dimethylaminopyridine (1.47 mg, 12.0 μmol), and (*R*)-(-)-MTPA chloride (45.0 μL, 60.6 μg, 0.240 mmol) in 0°C. After stirred for 3 h at room temperature, the reaction was quenched with 1 M HCl aqueous solution, and extracted with

CHCl_3 . The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The resulting residue was purified by column chromatography (hexane–AcOEt, 3:1) to afford **11** (30.3 mg, 66%) as a colorless oil. $[\alpha]_D^{20} +137.6$ ($c=0.34$, CHCl_3). IR (neat) cm^{-1} : 2948, 2850, 1755, 1610, 1450, 1351, 1270, 1250, 1169, 1122, 1013. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.86 (3H, s), 2.79–2.91 (2H, m), 3.49 (3H, s), 4.74–4.84 (2H, m), 5.78 (1H, dd, $J=6.5$, 6.5 Hz), 6.14 (1H, s), 7.31–7.61 (5H, m). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 20.8, 24.8, 55.4, 69.7, 71.7, 84.5 (q, $J=27.9$ Hz), 118.6, 119.4, 123.1 (q, $J=289.0$ Hz), 127.0 (2C), 128.5 (2C), 129.7, 131.8, 142.1, 155.4, 166.0, 172.4. HR-MS (ESI-TOF) Calcd for $\text{C}_{19}\text{H}_{17}\text{F}_3\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 405.0926. Found 405.0932.

(R)-[(R)-6-Methyl-3-oxo-1,3,4,5-tetrahydroisobenzofuran-5-yl]-3,3,3-trifluoro-2-methoxy-2-phenyl-propanoate (12) To a stirred solution of **6** (20.0 mg, 0.120 mmol) in CH_2Cl_2 (1.2 mL) was added pyridine (0.120 mL, 1.20 mmol) and 4-dimethylaminopyridine (1.47 mg, 12.0 μmol), and (S)-(+)-MTPA chloride (45.0 μL , 60.6 μg , 0.240 mmol) in 0°C . After stirred for 3 h at room temperature, the reaction was quenched with 1 M HCl aqueous solution, and extracted with CHCl_3 . The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The resulting residue was purified by column chromatography (hexane–AcOEt, 3:1) to afford **12** (21.1 mg, 46%) as a colorless oil. $[\alpha]_D^{20} +158.3$ ($c=0.04$, CHCl_3). IR (neat) cm^{-1} : 2949, 2849, 1753, 1745, 1611, 1450, 1350, 1270, 1250, 1168, 1121, 1015. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 2.02 (3H, s), 2.70–2.88 (2H, m), 3.49 (3H, s), 4.76–4.79 (2H, m), 5.79 (1H, dd, $J=7.3$, 5.5 Hz), 6.19 (1H, s), 7.27–7.50 (5H, m). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 21.2, 24.6, 55.4, 69.7, 71.7, 84.7 (q, $J=27.9$ Hz), 118.6, 119.7, 123.1 (q, $J=288.0$ Hz), 127.1 (2C), 128.5 (2C), 129.8, 131.7, 141.7, 154.9, 166.0, 172.4. HR-MS (ESI-TOF) Calcd for $\text{C}_{19}\text{H}_{17}\text{F}_3\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 405.0926. Found 405.0933.

(4R,5R,6R)-6-(tert-Butyldimethylsilyloxy)-4,5-dihydroxy-5-methyl-4,5,6,7-tetrahydroisobenzofuran-1(3H)-one (13) To a stirred solution of **10** (1.02 g, 3.63 mmol) and 4-methylmorpholine *N*-oxide (469 mg, 4.00 mmol) in acetone– H_2O (4:1, 36 mL) was added dropwise osmium tetroxide (4% in H_2O , 0.462 mL, 0.0727 mmol) at 0°C , and the mixture was stirred for 1 h at 0°C . The reaction was quenched with sat. $\text{Na}_2\text{S}_2\text{O}_3$ aqueous solution, and extracted with AcOEt. The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The resulting residue was purified by column chromatography (hexane–AcOEt, 1:1) to afford **13** and its diastereomer (0.996 g, 87%) as a separable mixture in ratio of 10:1 as white crystals. Recrystallization of the **13**, obtained with difficulty, from CHCl_3 –hexane gave **13** as colorless needles.

Data for **13**

$[\alpha]_D^{20} -61.8$ ($c=1.0$, CHCl_3). mp: 142–144 $^\circ\text{C}$. IR (KBr) cm^{-1} : 3433, 2952, 2929, 2886, 2857, 1738, 1732, 1682, 1470, 1462, 1350, 1257, 1219, 1077, 1020. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 0.05 (3H, s), 0.08 (3H, s), 0.82 (9H, s), 1.32 (3H, s), 2.15 (1H, brd, $J=17.6$ Hz), 2.62 (1H, brd, $J=17.6$ Hz), 2.79 (1H, s), 3.35 (1H, d, $J=7.5$ Hz), 3.99–4.02 (1H, m), 4.34 (1H, d, $J=6.9$ Hz), 4.79 (1H, brd, $J=17.6$ Hz), 4.93 (1H, brd, $J=17.6$ Hz). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : -5.0, -4.4, 17.7, 21.5, 25.6 (3C), 26.9, 68.8, 71.0, 73.0, 73.4, 125.0, 160.0, 174.2. HR-MS (ESI-TOF) Calcd for $\text{C}_{15}\text{H}_{26}\text{O}_5\text{SiNa}$ $[\text{M}+\text{Na}]^+$ 337.1447. Found 337.1448.

(3aR,4R,8bR)-4-(tert-Butyldimethylsilyloxy)-2,2,3a-

trimethyl-4,5,8,8b-tetrahydro-[1,3]dioxolo[4,5-*e*]isobenzofuran-6(3aH)-one (5) and (3aS,4R,8bS)-4-(tert-Butyldimethylsilyloxy)-2,2,3a-trimethyl-4,5,8,8b-tetrahydro-[1,3]dioxolo[4,5-*e*]isobenzofuran-6(3aH)-one (14)

To a stirred solution of the diastereomeric mixture of **13** (339 mg, 1.08 mmol) in CH_2Cl_2 (5 mL) were added 2,2-dimethoxypropane (1.32 mL, 1.12 g, 10.8 mmol) and *p*-toluenesulfonic acid monohydrate (20.5 mg, 0.108 mmol) at room temperature, and the mixture was stirred for 3 h at the same temperature. The reaction was quenched with sat. NaHCO_3 aqueous solution, and extracted with CHCl_3 . The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The resulting residue was purified by column chromatography (hexane–AcOEt, 7:1) to afford **5** (271 mg, 71%) as colorless needles, and **14** (28.8 mg, 8%) as colorless needles.

Data for **5**

$[\alpha]_D^{20} -15.9$ ($c=1.0$, CHCl_3). mp: 97–99 $^\circ\text{C}$ (CHCl_3 –hexane). IR (KBr) cm^{-1} : 2987, 2953, 2933, 2886, 2857, 1769, 1689, 1472, 1463, 1380, 1256, 1217, 1196, 1122, 1046, 1015. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 0.08 (3H, s), 0.10 (3H, s), 0.87 (9H, s), 1.35 (3H, s), 1.37 (3H, s), 1.45 (3H, s), 2.14–2.23 (1H, m), 2.53–2.62 (1H, m), 3.96 (1H, dd, $J=7.6$, 4.7 Hz), 4.47 (1H, s), 4.74–4.81 (1H, m), 4.93 (1H, ddd, $J=17.3$, 2.7, 2.7 Hz). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : -4.73, -4.69, 17.9, 19.3, 25.7 (3C), 27.4, 27.6, 28.5, 70.7, 72.5, 75.7, 82.9, 110.8, 127.3, 155.7, 172.6. HR-MS (ESI-TOF) Calcd for $\text{C}_{18}\text{H}_{31}\text{O}_5\text{Si}$ $[\text{M}+\text{H}]^+$ 355.1941. Found 355.1942.

Data for **14**

$[\alpha]_D^{20} -31.0$ ($c=1.0$, CHCl_3). mp: 124–126 $^\circ\text{C}$ (CHCl_3 –hexane). IR (KBr) cm^{-1} : 2955, 2932, 2887, 2857, 1765, 1686, 1473, 1463, 1380, 1370, 1258, 1236, 1138, 1105, 1073, 1039, 1020. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 0.11 (3H, s), 0.13 (3H, s), 0.93 (9H, s), 1.22 (3H, s), 1.48 (3H, s), 1.50 (3H, s), 2.47–2.53 (2H, m), 3.75 (1H, dd, $J=8.1$, 6.6 Hz), 4.51–4.54 (1H, brs), 4.69–4.76 (1H, m), 4.87–4.94 (1H, m). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : -4.8, -4.3, 18.1, 23.4, 25.6, 25.8 (3C), 28.2, 29.0, 70.0, 73.6, 76.3, 82.9, 111.7, 126.5, 157.6, 172.5. HR-MS (ESI-TOF) Calcd for $\text{C}_{18}\text{H}_{30}\text{O}_5\text{SiNa}$ $[\text{M}+\text{Na}]^+$ 377.1760. Found 377.1754.

tert-Butyldimethyl[(3aR,4R,8bR)-2,2,3a-trimethyl-6-vinyl-3a,4,5,8b-tetrahydro-[1,3]dioxolo[4,5-*e*]isobenzofuran-4-yloxy]silane (4) To a stirred solution of **5** (1.24 g, 3.50 mmol) in Et_2O (36 mL) was added dropwise a solution of vinylolithium in Et_2O , prepared from tetravinyltin (0.236 mL, 294 mg, 1.29 mmol) and methylolithium (1.14 M in Et_2O , 4.60 mL, 5.25 mmol) in Et_2O (9.4 mL), at -78 $^\circ\text{C}$ under Ar, and the mixture was stirred for 2 h at -78 $^\circ\text{C}$. The reaction was quenched with sat. NH_4Cl aqueous solution, and extracted with AcOEt. The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The resulting residue was purified by column chromatography (hexane–AcOEt, 10:1) to afford **4** (1.19 g, 93%) as a colorless oil. $[\alpha]_D^{20} +15.1$ ($c=1.0$, CHCl_3). IR (neat) cm^{-1} : 3101, 2984, 2953, 2931, 2886, 2856, 1647, 1540, 1472, 1462, 1378, 1255, 1215, 1200, 1180, 1121, 1099, 1039. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.07 (3H, s), 0.11 (3H, s), 0.89 (9H, s), 1.31 (3H, s), 1.43 (3H, s), 1.47 (3H, s), 2.35 (1H, dd, $J=16.0$, 9.7 Hz), 2.78 (1H, dd, $J=16.0$, 5.1 Hz), 4.02 (1H, dd, $J=9.7$, 5.1 Hz), 4.86 (1H, s), 5.15 (1H, d, $J=11.4$ Hz), 5.56 (1H, dd, $J=17.5$, 0.9 Hz), 6.45 (1H, dd, $J=17.5$, 11.4 Hz), 7.46 (1H, s). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ : -4.7, -4.5, 17.95, 18.00, 25.7 (3C), 27.2, 27.5, 28.7, 72.7, 74.3,

82.9, 109.1, 111.7, 117.1, 120.9, 123.4, 140.3, 147.4. HR-MS (ESI-TOF) Calcd for $C_{20}H_{32}O_4SiNa$ $[M+Na]^+$ 387.1968. Found 387.1963.

(3aR,4R,8bR)-4-(tert-Butyldimethylsilyloxy)-2,2,3a-trimethyl-3a,4,5,8b-tetrahydro-[1,3]dioxolo[4,5-e]isobenzofuran-6-carbaldehyde (15) To a stirred solution of **4** (479 mg, 1.31 mmol) and 2,6-lutidine (0.307 mL, 282 mg, 2.63 mmol) in 1,4-dioxane–H₂O (4:1, 6.5 mL) were added dropwise osmium tetroxide (4% in H₂O, 0.250 mL, 0.0394 mmol) and sodium periodate (1.41 g, 6.57 mmol) at 0°C, and the mixture was stirred for 3 h at room temperature. The reaction was quenched with sat. Na₂S₂O₃ aqueous solution, and the mixture was extracted with AcOEt. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (hexane–AcOEt, 10:1) to afford **15** (411 mg, 85%) as a colorless oil. $[\alpha]_D^{20} +20.0$ ($c=1.2$, CHCl₃). IR (neat) cm^{-1} : 3142, 3113, 2986, 2952, 2932, 2885, 2855, 2824, 1686, 1681, 1607, 1537, 1472, 1462, 1421, 1371, 1253, 1236, 1216, 1200, 1178, 1126, 1096, 1048, 1029. ¹H-NMR (300 MHz, CDCl₃) δ : 0.07 (3H, s), 0.11 (3H, s), 0.84 (9H, s), 1.34 (3H, s), 1.38 (3H, s), 1.48 (3H, s), 2.77 (1H, dd, $J=17.2$, 7.9 Hz), 3.17 (1H, dd, $J=17.2$, 4.3 Hz), 4.07 (1H, dd, $J=7.9$, 4.3 Hz), 4.89 (1H, s), 7.71 (1H, s), 9.73 (1H, s). ¹³C-NMR (75 MHz, CDCl₃) δ : –4.7 (2C), 17.9, 19.6, 25.6 (3C), 27.2, 27.6, 28.5, 72.3, 73.5, 82.5, 109.9, 123.5, 131.2, 146.1, 147.6, 178.2. HR-MS (ESI-TOF) Calcd for $C_{19}H_{30}O_5SiNa$ $[M+Na]^+$ 389.1760. Found 389.1769.

(3aR,4R,8bR)-Methyl 4-(tert-butyldimethylsilyloxy)-2,2,3a-trimethyl-3a,4,5,8b-tetrahydro-[1,3]dioxolo[4,5-e]isobenzofuran-6-carboxylate (16) To a stirred solution of **15** (1.35 g, 3.69 mmol) and potassium hydroxide (625 mg, 9.58 mmol) in MeOH (22 mL) was added dropwise a solution of iodine (1.22 g, 4.79 mmol) in MeOH (15 mL) at 0°C, and the mixture was stirred for 16 h at room temperature. The reaction was quenched with 1.0 M HCl aqueous solution, and extracted with AcOEt. The combined organic layers were washed with sat. Na₂S₂O₃ aqueous solution and brine, dried over MgSO₄, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (hexane–AcOEt, 15:1) to afford **16** (1.36 g, 93%) as a colorless oil. $[\alpha]_D^{20} +14.5$ ($c=1.0$, CHCl₃). IR (neat) cm^{-1} : 3126, 2986, 2953, 2930, 2886, 2856, 1736, 1715, 1619, 1549, 1472, 1462, 1440, 1408, 1378, 1372, 1325, 1256, 1200, 1122, 1099. ¹H-NMR (400 MHz, CDCl₃) δ : 0.06 (3H, s), 0.09 (3H, s), 0.84 (9H, s), 1.33–1.35 (6H, brs), 1.46 (3H, s), 2.72 (1H, dd, $J=17.2$, 8.4 Hz), 3.14 (1H, dd, $J=17.2$, 4.5 Hz), 3.88 (3H, s), 4.04 (1H, dd, $J=8.4$, 4.5 Hz), 4.86 (1H, s), 7.62 (1H, s). ¹³C-NMR (100 MHz, CDCl₃) δ : –4.73, –4.66, 17.9, 19.3, 25.6 (3C), 27.5, 28.0, 28.5, 51.7, 72.4, 73.7, 82.5, 109.6, 122.5, 129.6, 138.9, 144.3, 159.4. HR-MS (ESI-TOF) Calcd for $C_{20}H_{32}O_6SiNa$ $[M+H]^+$ 419.1866. Found 419.1881.

(3aR,4R,8bR)-4-(tert-Butyldimethylsilyloxy)-N-methoxy-N,2,2,3a-tetramethyl-3a,4,5,8b-tetrahydro-[1,3]dioxolo[4,5-e]isobenzofuran-6-carboxamide (3) To a stirred solution of *N,O*-dimethylhydroxylamine hydrochloride (270 mg, 2.77 mmol) in CH₂Cl₂ (8 mL) was added dropwise trimethylaluminum (1.07 M in hexane, 2.59 mL, 2.77 mmol) at 0°C. To this mixture was added dropwise a solution of **16** (366 mg, 0.924 mmol) in CH₂Cl₂ (15 mL) at room temperature, and stirred for 40 h at room temperature. The reaction was quenched with sat. potassium sodium tartrate aqueous solu-

tion, and extracted with CHCl₃. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (hexane–AcOEt, 10:1) to afford **3** (354 mg, 90%) as a pale yellow oil. $[\alpha]_D^{20} +8.4$ ($c=1.0$, CHCl₃). IR (neat) cm^{-1} : 3119, 2955, 2933, 2890, 2856, 1650, 1644, 1634, 1547, 1470, 1462, 1422, 1378, 1255, 1215, 1198, 1181, 1123, 1039. ¹H-NMR (400 MHz, CDCl₃) δ : 0.06 (3H, s), 0.09 (3H, s), 0.86 (9H, s), 1.33 (3H, s), 1.39 (3H, s), 1.47 (3H, s), 2.68 (1H, dd, $J=17.4$, 9.2 Hz), 3.21 (1H, dd, $J=17.4$, 4.7 Hz), 3.31 (3H, s), 3.79 (3H, s), 4.02 (1H, dd, $J=9.2$, 4.7 Hz), 4.87 (1H, s), 7.56 (1H, s). ¹³C-NMR (100 MHz, CDCl₃) δ : –4.7, –4.6, 18.0, 18.5, 25.7 (3C), 27.4, 28.6, 28.8, 33.9, 62.0, 72.5, 73.9, 82.7, 109.4, 121.8, 129.5, 140.6, 142.4, 160.4. HR-MS (ESI-TOF) Calcd for $C_{21}H_{36}NO_6Si$ $[M+H]^+$ 426.2312. Found 426.2317.

1-[(3aR,4R,8bR)-4-tert-Butyldimethylsilyloxy-2,2,3a-trimethyl-3a,4,5,8b-tetrahydro-[1,3]dioxolo[4,5-e]isobenzofuran-6-yl]butan-1-one (17) To a stirred solution of **3** (248 mg, 0.583 mmol) in THF (6 mL) was added *n*-propylmagnesium bromide (1.02 M in THF, 1.71 mL, 1.75 mmol) at 0°C under Ar. After stirred for 1 h at 0°C, the reaction was quenched with sat. NH₄Cl aqueous solution, and extracted with AcOEt. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (hexane–AcOEt, 10:1) to afford **17** (195 mg, 82%) as a colorless oil. $[\alpha]_D^{18} +4.8$ ($c=0.10$, CHCl₃). IR (neat) cm^{-1} : 3116, 2958, 2933, 2886, 2858, 1674, 1607, 1537, 1463, 1411, 1372, 1256. ¹H-NMR (300 MHz, CDCl₃) δ : 0.06 (3H, s), 0.10 (3H, s), 0.85 (9H, s), 0.98 (3H, t, $J=7.4$ Hz), 1.34 (3H, s), 1.37 (3H, s), 1.47 (3H, s), 1.72 (2H, qt, $J=7.4$, 7.4 Hz), 2.73 (1H, dd, $J=17.6$, 8.7 Hz), 2.79 (2H, td, $J=7.4$, 2.0 Hz), 3.22 (1H, dd, $J=17.6$, 4.7 Hz), 4.03 (1H, dd, $J=8.7$, 4.7 Hz), 4.87 (1H, s), 7.57 (1H, s). ¹³C-NMR (75 MHz, CDCl₃) δ : –4.7, –4.6, 13.8, 17.3, 17.9, 19.0, 25.7 (3C), 27.5, 28.6 (2C), 40.8, 72.4, 73.8, 82.5, 109.6, 123.0, 128.3, 143.2, 147.5, 191.2. HR-MS (ESI-TOF) Calcd for $C_{22}H_{36}O_5SiNa$ $[M+Na]^+$ 431.2230. Found 431.2222.

1-[(4R,5R,6R)-6-tert-(Butyldimethylsilyloxy)-4,5-dihydroxy-5-methyl-4,5,6,7-tetrahydroisobenzofuran-1-yl]butan-1-one (18) To a stirred solution of **17** (153 mg, 0.374 mmol) in CH₂Cl₂–H₂O (4:1, 3.75 mL) was added dropwise TFA (0.75 mL) at 0°C, and the mixture was stirred for 6 h at room temperature. The reaction was quenched with 28% ammonia aqueous solution at 0°C, and extracted with CHCl₃. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (hexane–AcOEt, 10:1) to afford **18** (99.7 mg, 72%) as a white powder. $[\alpha]_D^{20} -11.2$ ($c=0.44$, CHCl₃). mp 123–125°C. IR (KBr) cm^{-1} : 3436, 3144, 2957, 2932, 2885, 2858, 1652, 1604, 1532, 1472, 1463, 1408, 1258, 1087. ¹H-NMR (300 MHz, CDCl₃) δ : 0.127 (3H, s), 0.133 (3H, s), 0.90 (9H, s), 0.98 (3H, t, $J=7.4$ Hz), 1.20 (3H, s), 1.72 (2H, qt, $J=7.4$, 7.4 Hz), 2.47 (1H, s), 2.71 (1H, dd, $J=18.2$, 8.1 Hz), 2.79 (2H, t, $J=7.4$ Hz), 2.84 (1H, d, $J=3.2$ Hz), 3.31 (1H, dd, $J=18.2$, 5.4 Hz), 4.21 (1H, dd, $J=8.1$, 5.4 Hz), 4.64 (1H, d, $J=3.2$ Hz), 7.56 (1H, s). ¹³C-NMR (75 MHz, CDCl₃) δ : –4.9, –4.2, 13.9, 17.3, 17.9, 19.7, 25.7 (3C), 29.1, 40.7, 67.3, 71.3, 73.9, 126.0, 128.0, 143.1, 147.6, 191.2. HR-MS (ESI-TOF) Calcd for $C_{19}H_{33}O_5Si$ $[M+H]^+$ 369.2097. Found 369.2089.

(5S,6R)-6-(tert-Butyldimethylsilyloxy)-1-butyryl-5-hydroxy-5-methyl-6,7-dihydroisobenzofuran-4(5H)-one (19)

To a stirred suspension of **18** (50.6 mg, 0.137 mmol), 4-methylmorpholine *N*-oxide (48.3 mg, 0.412 mmol) and molecular sieves 4 Å (500 mg) in CH₂Cl₂ (7 mL) was added tetra-*n*-propylammonium perruthenate (TPAP, 4.83 mg, 0.0137 mmol), and the mixture was stirred for 2 h at room temperature. After the mixture was filtered through a pad of Celite, the filtrate was concentrated *in vacuo*. The resulted residue was purified by column chromatography (hexane–AcOEt, 15:1) to afford **19** (36.1 mg, 72%) as a white powder. $[\alpha]_D^{20}$ –39.0 (*c*=1.0, CHCl₃). mp 87–89°C. IR (KBr) cm^{–1}: 3478, 3136, 2930, 2856, 1694, 1682, 1668, 1592, 1531, 1470, 1463, 1403, 1372, 1293, 1257, 1191. ¹H-NMR (400 MHz, CDCl₃) δ: 0.09 (3H, s), 0.12 (3H, s), 0.90 (9H, s), 0.99 (3H, t, *J*=7.4 Hz), 1.31 (3H, s), 1.74 (2H, qt, *J*=7.4, 7.4 Hz), 2.79–2.84 (2H, m), 2.86 (1H, dd, *J*=18.0, 9.8 Hz), 3.19–3.28 (1H, brs), 3.46 (1H, dd, *J*=18.0, 5.4 Hz), 4.08 (1H, dd, *J*=9.8, 5.4 Hz), 8.06 (1H, s). ¹³C-NMR (100 MHz, CDCl₃) δ: –4.9, –4.7, 13.8, 17.0, 18.1, 18.3, 25.7 (3C), 29.1, 41.0, 74.1, 78.5, 123.6, 128.5, 146.0, 148.4, 191.1, 195.8. HR-MS (ESI-TOF) Calcd for C₁₉H₃₁O₅Si [M+H]⁺ 367.1941. Found 367.1940.

(5*S*,6*R*)-1-Butyryl-5,6-dihydroxy-5-methyl-6,7-dihydroisobenzofuran-4(5*H*)-one (Proposed **1)** To a stirred solution of **19** (56.2 mg, 0.153 mmol) in THF (1.5 mL) was added dropwise TBAF (1.0 M in THF, 0.307 mL, 0.307 mmol) at 0°C, and the mixture was stirred for 1 h at 0°C. The reaction was quenched with H₂O at 0°C, and extracted with CHCl₃. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (hexane–AcOEt, 5:1) to afford **1** (35.0 mg, 90%) as colorless needles. $[\alpha]_D^{20}$ –14.8 (*c*=0.50, MeOH). mp 84–87°C (AcOEt). IR (KBr) cm^{–1}: 3398, 2965, 1700, 1669, 1636, 1591, 1560, 1527, 1508, 1458, 1405, 1961. ¹H-NMR (400 MHz, CD₃CN) δ: 0.94 (3H, t, *J*=7.4 Hz), 1.28 (3H, s), 1.61–1.70 (2H, m), 2.79 (2H, t, *J*=7.3 Hz), 2.86 (1H, dd, *J*=17.7, 8.2 Hz), 3.36 (1H, dd, *J*=17.7, 4.8 Hz), 3.45–3.53 (1H, brs), 3.80–3.88 (1H, brs), 4.04 (1H, dd, *J*=8.2, 4.8 Hz), 8.16 (1H, s). ¹³C-NMR (100 MHz, CD₃CN) δ: 14.0, 17.6, 18.4, 28.2, 41.7, 74.1, 78.2, 124.9, 129.5, 147.6, 149.4, 191.5, 195.7. HR-MS (ESI-TOF) Calcd for C₁₃H₁₆O₅Na [M+H]⁺ 275.0895. Found 275.0901.

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Conflict of Interest The authors declare no conflict of

interest.

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