JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Asymmetric Total Synthesis of Fusarentin 6-Methyl Ether and Its Biomimetic Transformation into Fusarentin 6,7-Dimethyl Ether, 7-*O*-Demethylmonocerin, and (+)-Monocerin

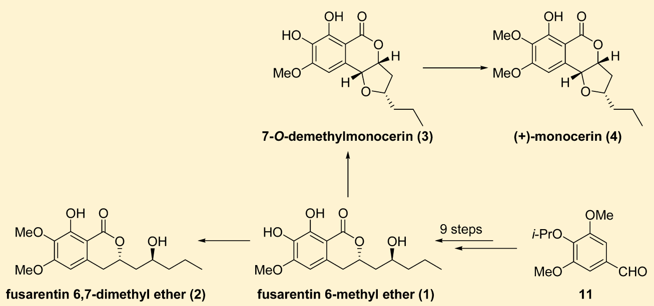
Bowen Fang,[†] Xingang Xie,[†] Changgui Zhao,[†] Peng Jing,[†] Huilin Li,[†] Zhengshen Wang,[†] Jixiang Gu,[†] and Xuegong She*[,†,‡]

[†]State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou, Gansu 730000, People's Republic of China

[‡]State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, Gansu 730000, People's Republic of China

Supporting Information

ABSTRACT: A concise asymmetric total synthesis of a fusarentin ether (**1**) with sequential biomimetic transformation to its analogues fusarentin 6,7-dimethyl ether (**2**), 7-*O*-demethylmonocerin (**3**), and (+)-monocerin (**4**) has been accomplished. The *cis*-fused furobenzopyranones of 7-*O*-demethylmonocerin (**3**) and (+)-monocerin (**4**) were efficiently constructed via an intramolecular nucleophilic trapping of a quinonemethide intermediate, which was obtained by benzylic oxidation of fusarentin 6-methyl ether (**1**) using hypervalent iodine reagent.



The fusarentin ethers **1** and **2** were originally isolated along with 7-*O*-demethylmonocerin (**3**) and (+)-monocerin (**4**) from *Fusarium larvarum* in 1979.[1] Since then, monocerin and a series of its analogues have been isolated from several fungal species (Figure 1).[2−7] The structural features of monocerin and its analogues include a 4-oxyisochroman-1-one skeleton and a 2,3,5-trisubstituted tetrahydrofuran, which are embedded with all-*cis* stereochemistry. The fusarentin ethers **1** and **2** are the ring-opened derivatives of 7-*O*-demethylmonocerin (**3**) and (+)-monocerin (**4**). Along with the elucidation of structures, studies regarding their biological properties have also been performed, showing various antifungal, insecticidal, and plant pathogenic properties and phytotoxic activity.[6−9] Due to their potential for application in the pharmaceutical industry, these natural products attracted the attention of synthetic chemists, and several total syntheses of fusarentin ethers **1** and **2**[10] and monocerin (**4**)[11−15] have been reported. One elegant synthetic study was reported by Simpson, who employed a radical benzylic bromination to initiate the formation of *cis*-tetrahydrofuran.[12] Biosynthetically, monocerin was found to be of heptaketide origin, and ^{13}C labeling studies suggested the *cis*-fused furobenzopyranones arose by intramolecular nucleophilic trapping of a quinonemethide intermediate by a pendant alcohol.[3,16] Herein, we describe a concise asymmetric total synthesis of fusarentin 6-methyl ether (**1**) and its sequential biomimetic transformation into fusarentin 6,7-dimethyl ether (**2**), 7-*O*-demethylmonocerin (**3**), and monocerin (**4**).

The retrosynthetic pathway of fusarentin 6-methyl ether (**1**), fusarentin 6,7-dimethyl ether (**2**), 7-*O*-demethylmonocerin (**3**), and monocerin (**4**) is depicted in Scheme 1. We envisioned that monocerin (**4**) could be readily obtained from 7-*O*-demethylmonocerin (**3**), which contains two phenolic hydroxyl substituents, but since the reactivity of one of them is attenuated by hydrogen bonding to adjacent carbomethoxy groups, **3** can be selectively monomethylated to **4**.[17] As for **3**, on the basis of a previous biosynthetic hypothesis of monocerin[3,16] and Simpson and co-workers' elegant biomimetic total synthesis of monocerin,[12] we envisioned that it could be accomplished via an intramolecular conjugate addition of the 10-hydroxyl group to C-4 of the quinonemethide intermediate **7**, which could be obtained by an oxidation of the arene in fusarentin 6-methyl ether (**1**). Fusarentin 6-methyl ether (**1**) could be synthesized from δ-valerolactone **8**, which in turn could be prepared from homobenzylic alcohol **9** via an oxa-Pictet−Spengler cyclization followed by a proper oxidation. The C-3 stereogenic center in alcohol **9** would be established by a SmI_2-promoted Evans−Tishchenko reduction. In addition, the requisite chiral β-hydroxy ketone **10** could be easily accessed by several steps from the known 4-isopropoxy-3,5-dimethoxybenzaldehyde (**11**).

The synthesis of fusarentin 6-methyl ether (**1**) commenced from the known 4-isopropoxy-3,5-dimethoxybenzaldehyde (**11**)[18] (Scheme 2). Homologation of **11** was performed via a Wittig reaction, and the resulting enol ether was directly subjected to 1,3-propanedithiol and $BF_3{\cdot}OEt_2$ to give dithiane

Received: April 10, 2013

dx.doi.org/10.1021/jo400760q | *J. Org. Chem.* XXXX, XXX, XXX−XXX

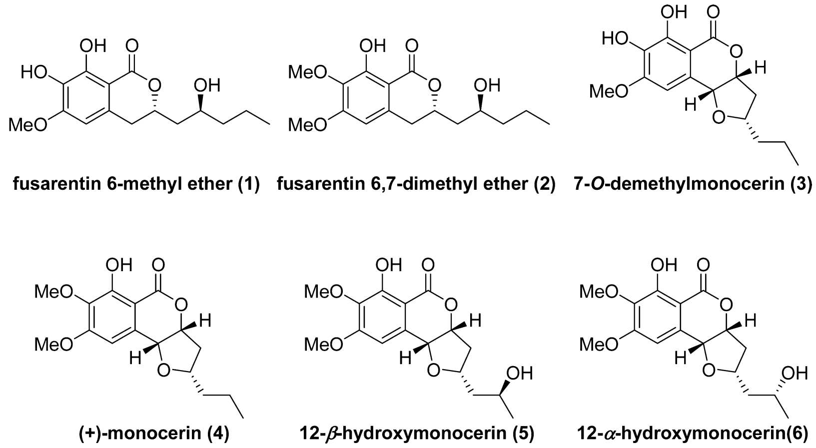
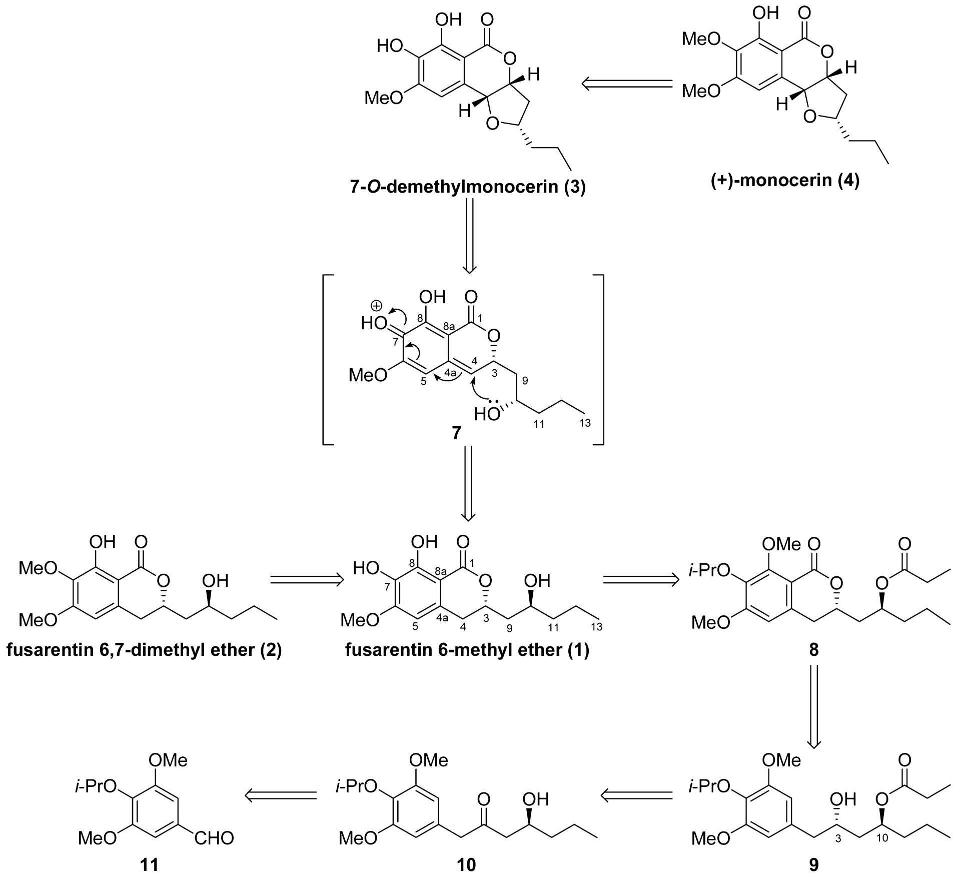


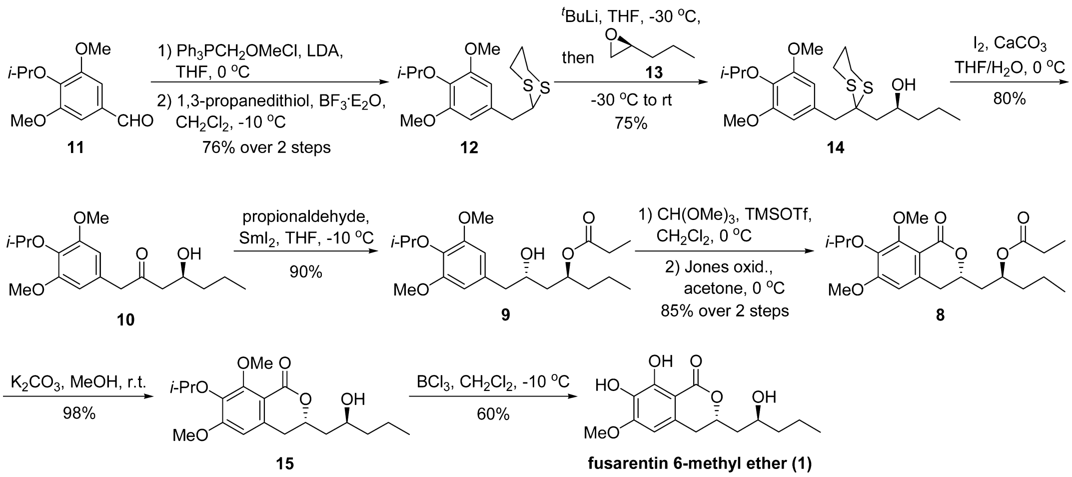
Figure 1. The fusarentin ethers **1** and **2** and monocerin (**4**) and its analogues.

Scheme 1. Retrosynthetic Plan for Synthesis of (+)-Monocerin (4) and Isocoumarin Derivatives



12 (76% yield over two steps). Treatment of **12** with *t*-BuLi in THF was followed by the ring opening of (*S*)-2-propyloxirane (**13**)[19] to afford *β*-hydroxydithiane **14** in 75% yield. Removal of the 1,3-dithiane group was achieved under mild conditions by I_2 and $CaCO_3$ to give *β*-hydroxy ketone **10**. Then an SmI_2-promoted Evans−Tishchenko reduction[20] was employed with ketone **10**, generating the desired homobenzylic alcohol **9** with high diastereoselectivity (the diastereoselectivity is calculated on the basis of ^{1}H NMR integration of the crude mixture, dr > 15:1). Moreover, the hydroxy group of C-10 was protected as a propionate. Subsequently, treatment of alcohol **9** with trimethyl orthoformate and TMSOTf, the oxa-Pictet−Spengler reaction,[21] was found to be reliable and the resulting cyclic acetal was directly treated with Jones reagent[22] to afford *δ*-valerolactone **8** in 85% yield in two consecutive steps. Finally, removal of the propionyl group was readily accomplished under slightly basic conditions to give the alcohol *δ*-valerolactone **15**, which was converted into fusarentin 6-methyl ether (**1**) upon deisopropylation[23] and partial demethylation[24] with boron trichloride in 60% overall yield. The deisopropylation is favored over demethylation probably because isopropyl ether is less stable with the Lewis acid. The C-8 methoxy group is attenuated by hydrogen bonding to adjacent carbomethoxy groups, which can be selectively demethylated. The yield of the last step, a dealkylation reaction, was moderate, probably due to

Scheme 2. Synthesis of Fusarentin 6-Methyl Ether (1)



Scheme 3. Synthesis of Fusarentin 6,7-Dimethyl Ether (2), 7-*O*-Demethylmonocerin (3), and Monocerin (4)

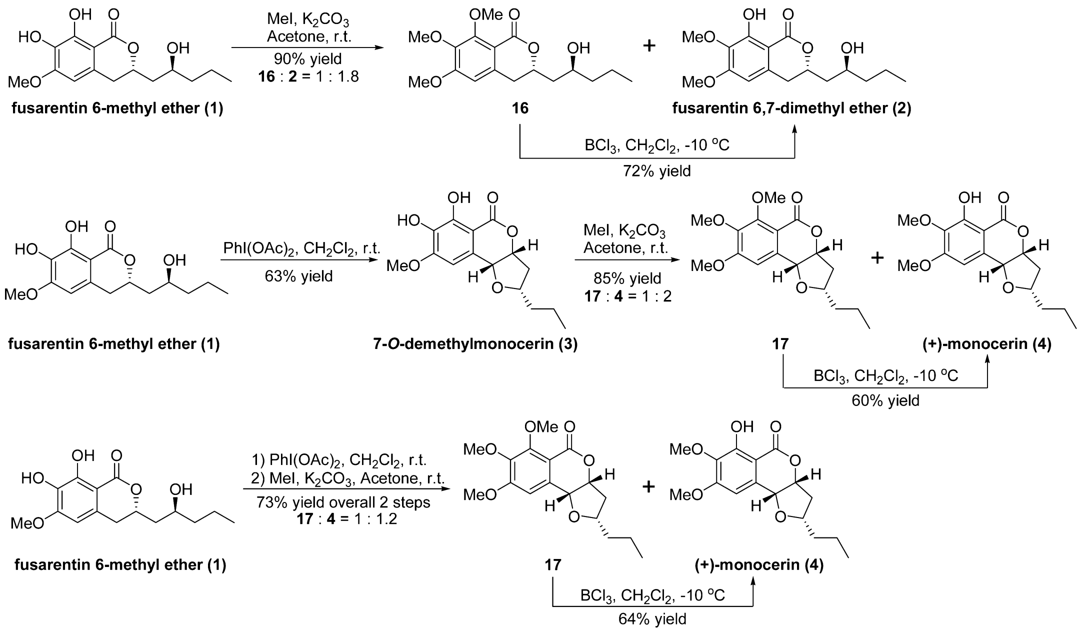
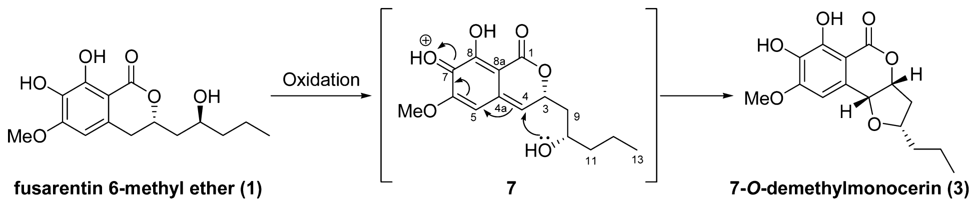


Table 1. Synthesis of 7-*O*-Demethylmonocerin (3) from Fusarentin 6-Methyl Ether (1)[a]



entry	reagent (amt (equiv))	solvent	temp	time (h)	yield (%)[b]
1	$K_2S_2O_8$ (2)	CH_3CN	reflux	1	0[c]
2	$Ce(NH_4)_2(NO_3)_6$ (1.5)	CH_3CN/H_2O	reflux	8	10[d]
3	$K_3Fe(CN)_6$ (10)	$CHCl_3$	room temp	24	0[e]
4	DDQ (1.1)	1,4-dioxane	room temp	1	60
5	$PhI(OAc)_2$ (1.1)	DCM	room temp	1	63

[a]**1** (30 mg, 0.1 mmol) and 1 mL of solvent were mixed. [b]Isolated yield. [c]Starting material decomposition. [d]Recovery of most of the starting material. [e]Quantitative recovery of the starting material.

the fact that fusarentin 6-methyl ether (**1**) was unstable during the column chromatography purification process.

With fusarentin 6-methyl ether (**1**) in hand, we set out to investigate its biomimetic transformation to fusarentin 6,7-

dx.doi.org/10.1021/jo400760q | J. Org. Chem. XXXX, XXX, XXX−XXX

dimethyl ether (**2**), 7-*O*-demethylmonocerin (**3**), and monocerin (**4**) (Scheme 3). It was found that selective monomethylation of **1** with iodomethane in the presence of anhydrous potassium carbonate in acetone at room temperature[17] gave a 58% yield of fusarentin 6,7-dimethyl ether (**2**) and a 32% yield of the dimethyl ether **16**. The desired product **2** could be easily isolated by silica-based column chromatography, and regioselective demethylation of **16** also generated fusarentin 6,7-dimethyl ether (**2**) in 72% yield.

Subsequent oxidation of fusarentin 6-methyl ether (**1**) was tested using various conditions, and the results are summarized in Table 1. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and $PhI(OAc)_2$ were found to be the most effective reagents. The 7-hydroxyl group of phenol **1** was oxidized as carbonyl, along with intramolecular nucleophilic trapping of the quinonemethide intermediate **7** by conjugate addition of the 10-hydroxyl group to C-4, which afforded 7-*O*-demethylmonocerin (**3**). The isolated yield was moderate, probably due to the product's instability against column chromatography. The structure of **3** was characterized by X-ray diffraction analysis, confirming the *cis*-fused furobenzopyranones (see the Supporting Information).

Regioselective methylation of 7-*O*-demethylmonocerin (**3**) afforded a 56% yield of monocerin (**4**), along with a 29% yield of the diprotected product **17**, which also could be converted into **4** in 60% yield (Scheme 3). Treatment of fusarentin 6-methyl ether (**1**) with $PhI(OAc)_2$, followed by regioselective methylation, smoothly furnished monocerin (**4**) and compound **17** in 73% combined yield (**4**:**17** = 1:1.2) for two consecutive steps. Monocerin (**4**) was obtained in 61% yield in these procedures.

In summary, we have achieved a concise asymmetric total synthesis of fusarentin 6-methyl ether with an overall yield of 20.5% over nine steps. Utilizing this compound as the key intermediate, we have achieved biomimetic total syntheses of fusarentin 6,7-dimethyl ether (**2**), 7-*O*-demethylmonocerin (**3**), and monocerin (**4**) with an overall yield of 16.5% over 11 steps, 12.9% over 10 steps, and 12.5% over 12 steps.

■ EXPERIMENTAL SECTION

Synthesis of 2-(4-Isopropoxy-3,5-dimethoxybenzyl)-1,3-dithiane (12). To a suspension of methoxymethylphosphonium chloride (6.5 g, 19 mmol) in anhydrous THF (50 mL) was added LDA (2.0 M, 9.4 mL, 18.8 mmol) at 0 °C under Ar, and the mixture was stirred for 0.5 h at 0 °C. A solution of 4-isopropoxy-3,5-dimethoxybenzaldehyde (**11**; 2.82 g, 12.6 mmol) in THF (30 mL) was added dropwise. After it was stirred for 2 h, the mixture was quenched with saturated aqueous NH_4Cl (15 mL) at 0 °C, and the resulting mixture was diluted with Et_2O (20 mL). The organic layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was dissolved in petroleum ether, after removal of triphenylphosphine oxide by filtration; the filtrate was concentrated in vacuo to give the crude product, which was used immediately without further purification.

The crude residue was dissolved in CH_2Cl_2 (50 mL), and 1,3-propanedithiol (1.5 mL, 15 mmol) was added at −10 °C. To the resultant solution was added $BF_3 \cdot Et_2O$ (3.2 mL, 25 mmol) dropwise and the solution stirred at −10 °C for 2 h. Saturated aqueous $NaHCO_3$ was added slowly at −10 °C to quench the excess $BF_3 \cdot Et_2O$. After it was warmed to room temperature, the mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc 20/1) gave dithiane **12** (3.15 g, 76% yield for two steps) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 6.44 (s, 2H), 4.31 (dt, *J* = 12.4, 6.2 Hz, 1H), 4.23 (t, *J* = 7.2 Hz, 1H), 3.82 (s, 6H), 2.94 (d, *J* = 7.2 Hz, 2H), 2.91−2.78 (m, 4H), 2.16−2.08 (m, 1H), 1.92−1.81 (m, 1H), 1.29 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 135.0, 132.4, 106.2, 75.1, 55.9, 48.4, 42.2, 30.5, 25.6, 22.4; HRMS (ESI) calcd for $C_{16}H_{25}O_3S_2$ $[M + H]^+$ 329.1240, found 329.1245.

Synthesis of (*S*)-1-(2-(4-Isopropoxy-3,5-dimethoxybenzyl)-1,3-dithian-2-yl)pentan-2-ol (14). To a solution of 1,3-dithiane **12** (1.97 g, 6 mmol) in anhydrous THF (20 mL) was added *t*-BuLi (1.3 M in pentane, 6 mL, 7.8 mmol) at −40 °C under Ar, and the mixture was stirred for 0.5 h at −40 °C. A solution of (*S*)-2-propyloxirane (**13**; 725 mg, 8.4 mmol) in THF (10 mL) was added dropwise. After it was stirred for 1 h at −40 °C, the reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc 8/1) gave β-hydroxydithiane **14** (1.86 g, 75% yield) as a pale yellow oil: $[\alpha]^{20}_D$ = +16.0° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.52 (s, 2H), 4.32 (dt, *J* = 12.4, 6.2 Hz, 1H), 4.05 (s, 1H), 3.80 (s, 6H), 3.50 (s, 1H), 3.25 (d, *J* = 14.1 Hz, 1H), 3.15 (d, *J* = 14.1 Hz, 1H), 3.06 (ddd, *J* = 13.8, 10.7, 2.8 Hz, 1H), 2.91 (dd, *J* = 10.6, 3.0 Hz, 1H), 2.83−2.73 (m, 2H), 2.24 (dd, *J* = 15.2, 9.4 Hz, 1H), 2.12−1.99 (m, 1H), 1.97−1.75 (m, 2H), 1.52−1.40 (m, 2H), 1.39−1.29 (m, 2H), 1.28 (s, 3H), 1.27 (s, 3H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 135.2, 130.1, 108.3, 75.1, 68.5, 55.9, 52.5, 46.5, 43.5, 39.7, 26.8, 26.3, 24.6, 22.4, 22.4, 18.6, 14.0; HRMS (ESI) calcd for $C_{21}H_{35}O_4S_2$ $[M + H]^+$ 415.1971, found 415.1977.

Synthesis of (*S*)-4-Hydroxy-1-(4-isopropoxy-3,5-dimethoxyphenyl)heptan-2-one (10). To a solution of β-hydroxydithiane **14** (1.86 g, 4.5 mmol) in THF/H_2O (4/1, 45 mL) was added $CaCO_3$ (4.5 g, 45.0 mmol) at 0 °C, and then iodine (4.5 g, 18 mmol) was added portionwise. The mixture was stirred for 0.5 h and quenched with saturated aqueous $Na_2S_2O_3$ (20 mL). The aqueous phase was separated and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc 3/1) gave β-hydroxy ketone **10** (1.16 g, 80% yield) as a colorless oil: $[\alpha]^{20}_D$ = +44.0° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.38 (s, 2H), 4.35−4.27 (m, 1H), 4.01 (dd, *J* = 7.5, 3.7 Hz, 1H), 3.80 (s, 6H), 3.62 (s, 2H), 2.97 (d, *J* = 3.3 Hz, 1H), 2.59 (qd, *J* = 17.6, 5.9 Hz, 2H), 1.48−1.36 (m, 2H), 1.35−1.21 (m, 2H), 1.28 (s, 3H), 1.27 (s, 3H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 153.9, 135.2, 128.6, 106.3, 75.1, 67.3, 55.9, 50.9, 48.0, 38.4, 22.3, 18.5, 13.8; HRMS (ESI) calcd for $C_{18}H_{29}O_5$ $[M + H]^+$ 325.2010, found 325.2014.

Synthesis of (2*S*,4*S*)-2-Hydroxy-1-(4-isopropoxy-3,5-dimethoxyphenyl)heptan-4-yl Propionate (9). To a solution of β-hydroxy ketone **10** (1.16 g, 3.6 mmol) in anhydrous THF (8 mL) were added propionaldehyde (2.1 mL, 28.8 mmol) and SmI_2 (0.1 M, 18 mL, 1.8 mmol) at −10 °C under Ar. After it was stirred for 4 h at −10 °C, the mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc 3/1) gave alcohol **9** (1.24 g, 90% yield) as a colorless oil: $[\alpha]^{20}_D$ = −3.0° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.41 (s, 2H), 5.13 (ddd, *J* = 12.6, 8.1, 4.2 Hz, 1H), 4.30 (dt, *J* = 12.3, 6.2 Hz, 1H), 3.80 (s, 6H), 3.72 (s, 1H), 2.88 (d, *J* = 3.4 Hz, 1H), 2.67 (qd, *J* = 13.7, 6.4 Hz, 2H), 2.34 (q, *J* = 7.6 Hz, 2H), 1.72−1.44 (m, 4H), 1.39−1.31 (m, 2H), 1.29 (s, 3H), 1.27 (s, 3H), 1.14 (t, *J* = 7.6 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 153.6, 134.6, 133.7, 106.3, 75.1, 71.2, 68.3, 55.9, 43.9, 42.1, 36.9, 27.7, 22.4, 18.6, 13.7, 9.2; HRMS (ESI) calcd for $C_{21}H_{34}O_6Na$ $[M + Na]^+$ 405.2248, found 405.2252.

Synthesis of (*S*)-1-((*S*)-7-Isopropoxy-6,8-dimethoxy-1-oxoisochroman-3-yl)pentan-2-yl Propionate (8). To a solution of alcohol **9** (1.24 g, 3.2 mmol) and trimethyl orthoformate (8.3 mL) in

CH_2Cl_2 (20 mL) was added TMSOTf (0.06 mL, 0.35 mmol) at 0 °C. After it was stirred for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Concentration in vacuo gave the crude product as an oil, which was used immediately without further purification.

The crude product was dissolved in acetone (18 mL), and Jones oxidant (3.0 M, 3.2 mL, 9.6 mmol) was added at 0 °C. After it was stirred for 1 h, the mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc 2/1) gave δ-valerolactone **8** (1.11 g, 85% yield) as a pale yellow oil: $[\alpha]^{20}_D = -68.0°$ (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (s, 1H), 5.12 (t, J = 3.2 Hz, 1H), 4.46−4.35 (m, 2H), 3.92 (s, 3H), 3.86 (s, 3H), 2.81 (ddd, J = 18.8, 16.0, 7.3 Hz, 2H), 2.29 (q, J = 7.6 Hz, 2H), 2.04 (ddd, J = 14.5, 8.3, 3.8 Hz, 1H), 1.87 (ddd, J = 14.6, 8.4, 3.9 Hz, 1H), 1.67−1.48 (m, 2H), 1.40−1.29 (m, 2H), 1.28 (d, J = 2.8 Hz, 3H), 1.26 (d, J = 2.8 Hz, 3H), 1.10 (t, J = 7.6 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 161.7, 158.1, 156.6, 140.1, 136.3, 111.8, 105.5, 76.0, 74.4, 70.4, 61.3, 55.9, 39.5, 36.7, 34.6, 27.6, 22.4, 22.3, 18.2, 13.8, 9.0; HRMS (ESI) calcd for $C_{22}H_{33}O_7$ $[M + H]^+$ 409.2221, found 409.2226.

Synthesis of (*S*)-3-((*S*)-2-Hydroxypentyl)-7-isopropoxy-6,8-dimethoxyisochroman-1-one (15). To a solution of δ-valerolactone **8** (1.11 g, 2.71 mmol) in CH_3OH (10 mL) was added anhydrous K_2CO_3 (1.12 g, 8.1 mmol) at room temperature. After it was stirred for 3 h, the reaction mixture was quenched with H_2O (10 mL) and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc 1.5/1) gave alcohol **15** (936 mg, 98% yield) as a pale yellow oil: $[\alpha]^{20}_D = -85.0°$ (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.47 (s, 1H), 4.70 (t, J = 10.3 Hz, 1H), 4.39 (dt, J = 12.2, 6.0 Hz, 1H), 4.04 (s, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 2.83 (dt, J = 15.9, 14.8 Hz, 2H), 2.25 (s, 1H), 1.97−1.86 (m, 1H), 1.64 (dd, J = 17.7, 6.5 Hz, 1H), 1.52−1.31 (m, 4H), 1.27 (t, J = 6.1 Hz, 6H), 0.91 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 158.1, 156.6, 140.0, 136.9, 111.7, 105.5, 76.0, 74.7, 66.9, 61.2, 55.9, 42.2, 40.1, 34.8, 22.4, 22.3, 18.6, 13.9; HRMS (ESI) calcd for $C_{19}H_{29}O_6$ $[M + H]^+$ 353.1959, found 353.1954.

Synthesis of Fusarentin 6-Methyl Ether (1). To a solution of alcohol **15** (353 mg, 1.0 mmol) in dry CH_2Cl_2 (10 mL) was added BCl_3 (1.0 M, 2.1 mL, 2.1 mmol) at −10 °C under Ar. After it was stirred for 3 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (3 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc 1/1) gave fusarentin 6-methyl ether (**1**; 177 mg, 60% yield) as a white solid: mp 139−140 °C; $[\alpha]^{20}_D = -35.0°$ (c = 1.0, $CHCl_3$) (lit.[1] mp 137 °C; $[\alpha]^{20}_D = -30°$); ^1H NMR (400 MHz, $CDCl_3$) δ 10.91 (s, 1H), 6.27 (s, 1H), 5.74 (s, 1H), 4.83 (t, J = 10.4 Hz, 1H), 4.03 (s, 1H), 3.90 (s, 3H), 2.84 (qd, J = 16.2, 7.6 Hz, 2H), 2.39 (s, 1H), 1.94 (ddd, J = 14.2, 9.8, 1.8 Hz, 1H), 1.72−1.64 (m, 1H), 1.55−1.30 (m, 4H), 0.92 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 152.1, 149.3, 132.0, 131.2, 102.4, 101.7, 76.9, 66.9, 56.1, 42.1, 40.0, 33.1, 18.6, 13.9; HRMS (ESI) calcd for $C_{15}H_{21}O_6$ $[M + H]^+$ 297.1333, found 297.1330.

Synthesis of Fusarentin 6,7-Dimethyl Ether (2) and (*S*)-3-((*S*)-2-Hydroxypentyl)-6,7,8-trimethoxyisochroman-1-one (16). To a solution of fusarentin 6-methyl ether (**1**; 26 mg, 0.088 mmol) in acetone (1.5 mL) were added anhydrous K_2CO_3 (14 mg, 0.1 mmol) and MeI (44 μL, 0.7 mmol) at room temperature under Ar. After it was stirred for 3 days in the dark, the reaction mixture was quenched with H_2O (1 mL) and the mixture was extracted with ethyl acetate (3 × 2 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc 2/1) yielded 16 mg (58%) of fusarentin 6,7-dimethyl ether (**2**) and 9 mg of (32%) (*S*)-3-((*S*)-2-hydroxypentyl)-6,7,8-trimethoxyisochroman-1-one (**16**).

Fusarentin 6,7-dimethyl ether (**2**): white solid: mp 102−104 °C; $[\alpha]^{20}_D = -25.0°$ (c = 1.0, $CHCl_3$) (lit.[1] mp 103 °C; $[\alpha]^{20}_D = -29°$); ^1H NMR (400 MHz, $CDCl_3$) δ 11.04 (s, 1H), 6.26 (s, 1H), 4.85−4.77 (m, 1H), 4.00 (s, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 2.85 (qd, J = 16.3, 7.6 Hz, 2H), 2.43 (s, 1H), 1.92 (ddd, J = 14.4, 9.7, 2.0 Hz, 1H), 1.72−1.60 (m, 1H), 1.51−1.27 (m, 4H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 158.3, 155.9, 135.6, 135.1, 102.7, 102.0, 76.5, 66.7, 60.5, 56.0, 42.2, 40.0, 33.4, 18.5, 13.9; HRMS (ESI) calcd for $C_{16}H_{23}O_6$ $[M + H]^+$ 311.1489, found 311.1485.

(*S*)-3-((*S*)-2-Hydroxypentyl)-6,7,8-trimethoxyisochroman-1-one (**16**): colorless oil; $[\alpha]^{20}_D = -65.0°$ (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.47 (s, 1H), 4.75−4.62 (m, 1H), 4.02 (s, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.82 (s, 3H), 2.82 (ddd, J = 19.2, 16.1, 7.3 Hz, 2H), 2.26 (s, 1H), 1.90 (ddd, J = 14.2, 9.5, 1.9 Hz, 1H), 1.68−1.59 (m, 1H), 1.68−1.59 (m, 4H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 157.4, 156.1, 141.9, 137.2, 111.6, 105.6, 74.7, 66.9, 61.6, 60.9, 56.0, 42.1, 40.1, 34.8, 18.6, 13.9; HRMS (ESI) calcd for $C_{17}H_{25}O_6$ $[M + H]^+$ 325.1646, found 325.1643.

Synthesis of Fusarentin 6,7-Dimethyl Ether (2) from 16. To a solution of alcohol **16** (9 mg, 0.028 mmol) in dry CH_2Cl_2 (0.5 mL) was added BCl_3 (1.0 M, 31 μL, 0.031 mmol) at −10 °C under Ar. The mixture was stirred at −10 °C for 1 h and quenched with saturated aqueous $NaHCO_3$ (0.5 mL). The mixture was extracted with ethyl acetate (10 mL), and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc 2/1) gave fusarentin 6,7-dimethyl ether (**2**; 6 mg, 72% yield). The characterization data of **2** are consistent with those reported previously.

Synthesis of 7-*O*-Demethylmonocerin (3). To a solution of fusarentin 6-methyl ether (**1**; 36 mg, 0.12 mmol) in CH_2Cl_2 (3 mL) was added $PhI(OAc)_2$ (45 mg, 0.13 mmol) at room temperature. The mixture was stirred for 1 h and quenched with saturated aqueous $Na_2S_2O_3$ (1 mL). The mixture was extracted with ethyl acetate (10 mL), and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (CH_2Cl_2/CH_3OH, 30/1) yielded 22 mg (63%) of 7-*O*-demethylmonocerin (**3**) as a white solid: mp 173−175 °C; $[\alpha]^{20}_D$ = +33.0° (c = 1.0, $CHCl_3$) (lit.[1] mp 172−175 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 11.15 (s, 1H), 6.62 (s, 1H), 5.60 (s, 1H), 5.07 (dd, J = 5.5, 3.0 Hz, 1H), 4.56 (d, J = 3.1 Hz, 1H), 4.12 (dq, J = 12.7, 6.4 Hz, 1H), 3.98 (s, 3H), 2.60 (ddd, J = 14.6, 8.5, 6.3 Hz, 1H), 2.16 (dd, J = 14.4, 5.8 Hz, 1H), 1.77−1.64 (m, 1H), 1.64−1.52 (m, 1H), 1.49−1.29 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 152.1, 149.4, 134.1, 126.9, 104.0, 101.7, 81.5, 78.5, 74.4, 56.3, 39.0, 38.0, 19.0, 13.9; HRMS (ESI) calcd for $C_{15}H_{19}O_6$ $[M + H]^+$ 295.1176, found 295.1172.

Synthesis of (+)-Monocerin (4) and (2*S*,3a*R*,9b*R*)-6,7,8-Trimethoxy-2-propyl-3,3a-dihydro-2*H*-furo[3,2-*c*]isochromen-5(9b*H*)-one (17). Following the procedure described for the preparation of **2** and **16**, (+)-monocerin (**4**; 13 mg, 56%) and **17** (7 mg, 29%) were obtained as colorless oils.

(+)-Monocerin (**4**): $[\alpha]^{25}_D$ = +53° (c = 1, $CHCl_3$), $[\alpha]^{25}_D$ = +60° (c = 0.2, CH_3OH) (lit.[1] $[\alpha]^{24}_D$ = +53°); ^1H NMR (400 MHz, $CDCl_3$) δ 11.29 (s, 1H), 6.60 (s, 1H), 5.06 (dd, J = 5.3, 3.0 Hz, 1H), 4.55 (d, J = 3.0 Hz, 1H), 4.13 (dt, J = 14.8, 6.3 Hz, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 2.60 (ddd, J = 14.6, 8.5, 6.2 Hz, 1H), 2.17 (dd, J = 14.5, 5.8 Hz, 1H), 1.74−1.66 (m, 1H), 1.64−1.52 (m, 1H), 1.50−1.29 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 158.6, 156.2, 137.2, 131.1, 104.3, 102.0, 81.2, 78.7, 74.4, 60.7, 56.2, 38.9, 38.0, 19.1, 13.9; HRMS (ESI) calcd for $C_{16}H_{21}O_6$ $[M + H]^+$ 309.1333, found 309.1328.

Compound **17**: $[\alpha]^{25}_D$ = +45° (c = 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H), 4.94 (dd, J = 5.3, 2.8 Hz, 1H), 4.52 (d, J = 2.8 Hz, 1H), 4.17−4.10 (m, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.88 (s, 3H), 2.51 (ddd, J = 14.4, 8.8, 5.8 Hz, 1H), 2.15 (dd, J = 14.2, 5.4 Hz, 1H), 1.75−1.65 (m, 1H), 1.64−1.52 (m, 1H), 1.48−1.28 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 157.9, 156.5, 144.2, 132.5, 111.2, 108.1, 79.5, 78.9, 75.1, 61.8, 61.1, 56.2, 39.0, 38.1, 19.2, 13.9; HRMS (ESI) calcd for $C_{17}H_{23}O_6$ $[M + H]^+$ 323.1489, found 323.1493. Following the procedure described for the preparation of **2** from **16**, 4 mg of (+)-monocerin (**4**; 60%) was obtained from **17**. The characterization data of **4** are consistent with those reported previously.

Synthesis of (+)-Monocerin (4) and (2*S*,3a*R*,9b*R*)-6,7,8-Trimethoxy-2-propyl-3,3a-dihydro-2*H*-furo[3,2-*c*]isochromen-5(9b*H*)-one (17) from Fusarentin 6-Methyl Ether (1). To a solution of fusarentin 6-methyl ether (**1**; 44 mg, 0.148 mmol) in CH_2Cl_2 (3 mL) was added $PhI(OAc)_2$ (55 mg, 0.16 mmol) at room temperature. The mixture was stirred for 1 h and quenched with saturated aqueous $Na_2S_2O_3$ (1 mL). The mixture was extracted with ethyl acetate (10 mL), and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was dissolved in acetone (2 mL), and anhydrous K_2CO_3 (22 mg, 0.16 mmol) and MeI (68 μL, 1.1 mmol) were added at room temperature under Ar. After it was stirred for 3 days in the dark, the reaction mixture was quenched with H_2O (1 mL) and extracted with ethyl acetate (3 × 2 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc 3/1) yielded 19 mg (41%) of (+)-monocerin (**4**) and 15 mg (32%) of **17**. Following the procedure described for the preparation of **2** from **16**, 9 mg of (+)-monocerin (**4**; 64%) was obtained from 15 mg of **17**. The characterization data of **17** and **4** are consistent with those reported previously.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, tables, figures, and a CIF file giving crystallographic data for **3** and ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for X.S.: shexg@lzu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this research was provide by the NSFC (21125207, 21102062, 21072086), the MOST (2010CB833203), PCSIRT (IRT1138), the FRFCU (lzujbky-2013-49,lzujbky-2013-ct02), and Program 111.

■ REFERENCES

(1) Grove, J. F.; Pople, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2048−2051.
(2) Aldridge, D. C.; Turner, W. B. *J. Chem. Soc. C* **1970**, *18*, 2598−2600.
(3) Scott, F. E.; Simpson, T. J.; Trimble, L. A.; Vederas, J. C. *J. Chem. Soc., Chem. Commun.* **1984**, 756−758.
(4) Cuq, F.; Herrmann-Gorline, S.; Klaebe, A.; Rossignol, M.; Petitprez, M. *Phytochemistry* **1993**, *34*, 1265−1270.
(5) Lim, C.-H. *Agric. Chem. Biotechnol. (Engl. Ed.)* **1999**, *42*, 45−47.
(6) Sappapan, R.; Sommit, D.; Ngamrojanavanich, N.; Pengpreecha, S.; Wiyakrutta, S.; Sriubolmas, N.; Pudhom, K. *J. Nat. Prod.* **2008**, *71*, 1657−1659.
(7) Zhang, W.; Krohn, K.; Draeger, S.; Schulz, B. *J. Nat. Prod.* **2008**, *71*, 1078−1081.
(8) Claydon, N.; Grove, J. F.; Pople, M. *J. Invertebr. Pathol.* **1979**, 33, 364−367.
(9) Grove, J. F.; Pople, M. *Mycopathologia* **1981**, *76*, 65−67.
(10) For the synthesis of fusarentin ethers **1** and **2**, see: McNicholas, C.; Simpson, T. J.; Willett, N. J. *Tetrahedron Lett.* **1996**, *37*, 8053−8056.
(11) Mori, K.; Takaishi, H. *Tetrahedron* **1989**, *45*, 1639−1646.
(12) Dillon, M. P.; Simpson, T. J.; Sweeney, J. B. *Tetrahedron Lett.* **1992**, *33*, 7569−7572.
(13) Cassidy, J. H.; Farthing, C. N.; Marsden, S. P.; Pedersen, A.; Slater, M.; Stemp, G. *Org. Biomol. Chem.* **2006**, *4*, 4118−4126.
(14) Kwon, H. K.; Lee, Y. E.; Lee, E. *Org. Lett.* **2008**, *10*, 2995−2996.
(15) Fujita, M.; Mori, K.; Shimogaki, M.; Sugimura, T. *Org. Lett.* **2012**, *14*, 1294−1297.
(16) Axford, L. C.; Simpson, T. J.; Willis, C. L. *Angew. Chem, Int. Ed.* **2004**, *43*, 727−730.
(17) Kelly, T. R.; Bell, S. H.; Ohashi, N.; Armstrong-Chong, R. J. *J. Am. Chem. Soc.* **1988**, *110*, 6471−6480.
(18) For the synthesis of 4-isopropoxy-3,5-dimethoxybenzaldehyde (**11**), see: Shirali, A.; Sriram, M.; Hall, J. J.; Nguyen, B. L.; Guddneppanavar, R.; Hadimani, M. B.; Ackley, J. F.; Siles, R.; Jelinek, C. J.; Arthasery, P.; Brown, R. C.; Murrell, V. L.; McMordie, A.; Sharma, S.; Chaplin, D. J.; Pinney, K. G. *J. Nat. Prod.* **2009**, *72*, 414−421.
(19) For the synthesis of (*S*)-2-propyloxirane (**13**), see: Bates, R. W.; Lu, Y. *J. Org. Chem.* **2009**, *74*, 9460−9465.
(20) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447−6449.
(21) For intramolecular oxa-Pictet−Spengler cyclizations, see: Zheng, H.; Zhao, C.; Fang, B.; Jing, P.; Yang, J.; Xie, X.; She, X. *J. Org. Chem.* **2012**, *77*, 9460−9465.
(22) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39−45.
(23) Li, Q.; Jiang, J.; Fan, A.; Cui, Y.; Jia, Y. *Org. Lett.* **2011**, *13*, 312−315.
(24) Dean, F. M.; Goodchild, J.; Houghton, L. E.; Martin, J. A.; Morton, R. B.; Parton, B.; Price, A. W.; Somvichien, N. *Tetrahedron Lett.* **1966**, *7*, 4153−4159.