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# Biomimetically inspired total synthesis of (12*S*)-12-hydroxymonocerin and (12*R*)-12-hydroxymonocerin

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ABSTRACT

A concise asymmetric total synthesis of (12*S*)-12-hydroxymonocerin (**1**) and (12*R*)-12-hydroxymonocerin (**2**) were efficiently achieved from the known 4-bromo-2,6-dimethoxyphenol. The synthetic approach was inspired by our biomimetic synthesis of (+)-monocerin (**3**) and 7-*O*-demethylmonocerin (**4**). The *cis*-fused furobenzopyranones of **1** and **2** was efficiently constructed via an intramolecular nucleophilic trapping of a quinonemethide intermediate, which was obtained by benzylic oxidation of compound **10** using 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).



## 1. Introduction

Monocerin (**3**) and analogues have been isolated as antifungal, insecticidal, and phytotoxic secondary metabolites from several fungal sources (Fig. 1).[1] 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. Due to the unique structural feature and potential for application in the pharmaceutical industry, these natural products attracted the attention of synthetic chemists and several total syntheses of monocerin (**3**) have been reported.[2] Recently, we have completed total synthesis of (+)-monocerin (**3**) and 7-*O*-demethylmonocerin (**4**) by a biomimetically inspired procedure (Scheme 1).[3] The *cis*-fused furobenzopyranones of (+)-monocerin (**3**) and 7-*O*-demethylmonocerin (**4**) was efficiently constructed via an intramolecular nucleophilic trapping of a quinonemethide intermediate **7**, which was obtained by benzylic oxidation of fusarentin 6-methyl ether (**5**) with 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or $PhI(OAc)_2$.

(12*S*)-12-Hydroxymonocerin (**1**) and (12*R*)-12-hydroxym onocerin (**2**) were isolated together with monocerin (**3**) from *Microdochium bolleyi* by Krohn and co-workers in 2008[4] (Fig. 1), they are both 12-oxo epimers of monocerin (**3**). Compound **1** has showed good antifungal, antibacterial, and antialgal activities against *Microbotryum Violaceum*, *Escherichia coli*, *Bacillus megaterium*, and *Chlorella fusca*. Compound **2** was moderately antifungal

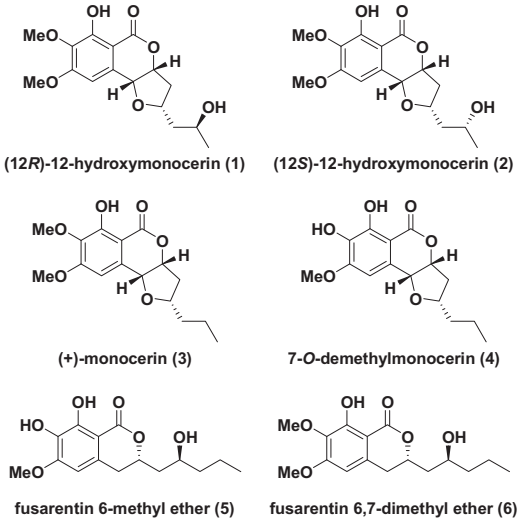


**Fig. 1.** Structures of 12-hydroxymonocerin (**1**), (**2**), and its analogues.

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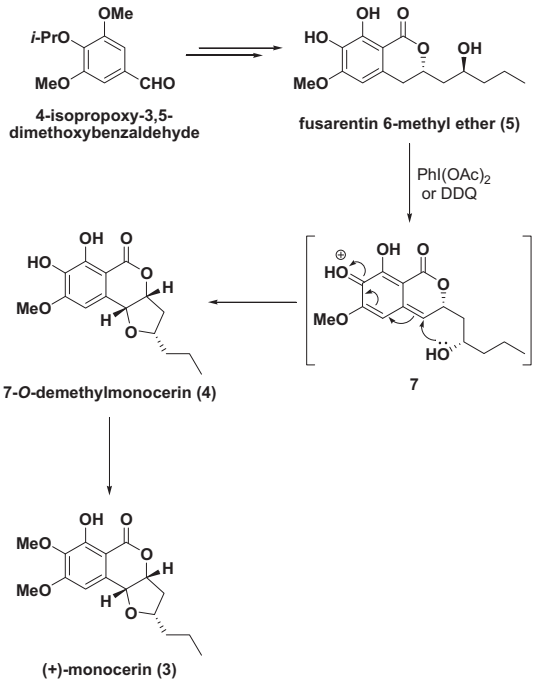



**Scheme 1.** Biomimetic synthesis of (+)-monocerin (**3**) and 7-*O*-demethylmonocerin (**4**).

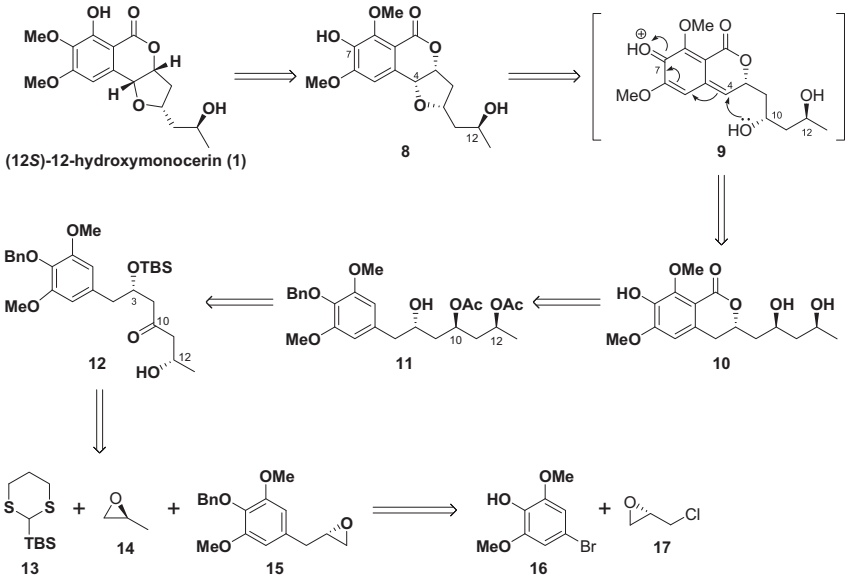
and antialgal. On the basis of our previous biomimetic synthesis of monocerin (**3**),[3] we describe a concise asymmetric total synthesis of the (12*S*)-12-hydroxymonocerin (**1**) and (12*R*)-12-hydroxymonocerin (**2**).

## 2. Results and discussions

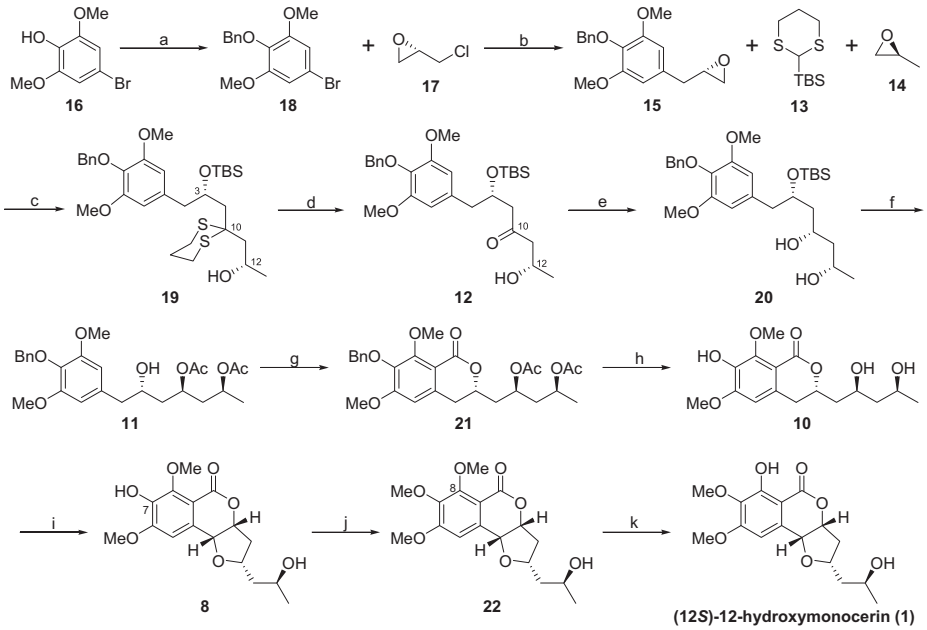
The retrosynthetic pathway of the compound **1** was depicted in Scheme 2. We envisioned that (12*S*)-12-hydroxymonocerin (**1**) could be readily obtained from compound **8**. As for **8**, we envisioned that it could be accomplished via an intramolecular conjugate addition of the 10-hydroxyl group to C-4 of the quinonemethide intermediate **9**, which could be generated in situ by an oxidation of phenol **10**. The δ-valerolactone of compound **10** could be prepared from homo-benzylic alcohol **11** via an oxa-Pictet–Spengler cyclization followed by a proper oxidation. The C-10 stereogenic center in alcohol **11** would be established by a *syn*-diastereoselective reduction. And the requisite chiral β-hydroxyketone **12** could be obtained by an Anion Relay Chemistry[5] based strategy—a multicomponent coupling of *tert*-butyl(1,3-dithian-2-yl)dimethylsilane **13**, (*S*)-2-methyloxirane **14** and epoxide **15**. The epoxide **15** could be easily accessed by several steps from the known 4-bromo-2,6-dimethoxyphenol **16** and commercially available (*S*)-2-(chloromethyl)oxirane **17**.

The synthesis of the (12*S*)-12-hydroxymonocerin (**1**) commenced from the known 4-bromo-2,6-dimethoxyphenol **16**[6] (Scheme 3). The hydroxyl group of **16** was protected as benzyl ether **18**, which was converted into the corresponding Grignard reagent. Treatment of the Grignard reagent with CuI at low temperature, followed by the ring opening of (*S*)-2-(chloromethyl) oxirane **17** and the resulting compound was subjected to NaOH to give epoxide **15** (52% yield over two steps). The synthesis of **19** was initiated by a three-component linchpin coupling employing *tert*-butyl(1,3-dithian-2-yl)dimethylsilane **13** with (*S*)-2-methyloxirane **14** and epoxide **15** to afford β-hydroxydithiane **19** in 61% yield. Removal of the 1,3-dithiane group, followed by *syn*-diastereoselective reduction[7] of the resulting β-hydroxyketone **12** to give diol **20** in 89% yield. Bis-acetylation was easily accomplished under acetic anhydride and pyridine, and then the silyl protecting group was removed in 88% yield employing 6 N aqueous HCl,[8] thus setting the stage for an oxa-Pictet–Spengler reaction of the homobenzylic alcohol in **11**.[9] Treatment of **11** with trimethyl orthoformate and TMSOTf, the oxa-Pictet–Spengler reaction was found to be reliable and the resulting cyclic acetal was directly treated with Jones reagent[10] to afford δ-valerolactone **21** in 81% yield for two consecutive steps. Subsequently, removal of the acetyl group was readily accomplished under slight basic conditions to give diol, which was converted into phenol **10** in 99% overall yield upon debenzylation with 10% Pd/C.

With phenol **10** in hand, we set out to investigate its biomimetic transformation to (12*S*)-12-hydroxymonocerin (**1**). It was found that 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was the effective reagent. The 7-hydroxyl group of phenol **10** was oxidized as carbonyl, occurred with intramolecular nucleophilic trapping of the quinonemethide intermediate **9** by conjugate addition of the



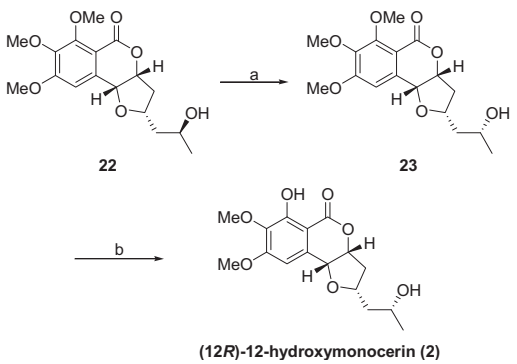

**Scheme 2.** Retrosynthetic plan for synthesis of (12*S*)-12-hydroxymonocerin (**1**).




**Scheme 3.** Synthesis of (12*S*)-12-hydroxymonocerin (**1**). Reagents and conditions: (a) $K_2CO_3$, BnBr, DMF, 40 °C, 94%; (b) (i) Mg, $I_2$, THF, rt then CuI, **17**, −40 °C; (ii) NaOH, $Et_2O$, rt 52% (over two steps); (c) **13**, *n*-BuLi, 0 °C, 10 min, then **15** in $Et_2O$, −35 °C, 1 h, then HMPA and **14** was added, −50 °C to rt, 61%; (d) $I_2$, $CaCO_3$, THF/$H_2O$, 0 °C, 86%; (e) $Me_4NBH(OAc)_3$, $CH_3CN$/AcOH, −30 °C, 89%; (f) (i) $(Ac)_2O$, pyridine, DMAP, rt, 85%; (ii) 6 N HCl, acetone, 0 °C, 88%; (g) (i) $CH(OMe)_3$, TMSOTf, $CH_2Cl_2$, 0 °C; (ii) Jones oxidn, acetone, 0 °C, 81% (over two steps); (h) (i) $K_2CO_3$, $CH_3OH$, rt, 93%; (ii) 10% Pd/C, $H_2$ (1 atm), EtOAc, rt, 99%; (i) DDQ, 1,4-dioxane, rt, 62%; (j) $CH_3I$, $K_2CO_3$, acetone, reflux, 68%; (k) $BCl_3$, $CH_2Cl_2$, −78 °C, 50%.

10-hydroxyl group to C-4, which afforded *cis*-fused furobenzopyranone **8** in 62% yield. To our delight, we did not observe the undesired product, which could be generated by conjugate addition of the 12-hydroxyl group to C-4 in this procedure. Methylation of 7-hydroxyl group of **8** with iodomethane in the presence of anhydrous potassium carbonate in acetone under reflux conditions, gave trimethyl ether **22**, which was converted into (12*S*)-12-hydroxymonocerin (**1**) by partial demethylation[11] with boron trichloride in 50% yield. The characterization data of **1** ($^1H$, $^{13}C$ NMR determined in $CDCl_3$, and optical rotation) is consistent with the prior reported[4] (see the Supplementary data).

Based on the successful synthesis of (12*S*)-12-hydroxymonocerin (**1**), we then turned our attention to the synthesis of (12*R*)-12-hydroxymonocerin (**2**) (Scheme 4). The 12-hydroxyl group of trimethyl ether **22** was converted to α-alcohol **23** through Mitsunobu reaction[12] and deprotection of the resulting 4-nitrobenzoate by $K_2CO_3$ in $CH_3OH$. Finally, the desired product **2** could be obtained by partial demethylation of trimethyl ether **23** with boron trichloride in 55% yield. The characterization data of our synthetic compound **2** ($^1H$, $^{13}C$ NMR determined in $CDCl_3$) is consistent with the prior reported,[4] however, the optical rotation is greatly different from that of prior reported[4] ($[\alpha]_D^{20}$ −12.7 (*c* 0.11, $CH_2Cl_2/CH_3OH$=1/1)), which is $[\alpha]_D^{28}$ +41 (*c* 0.11, $CH_2Cl_2/CH_3OH$=1/1) and $[\alpha]_D^{28}$ +34 (*c* 0.5, $CH_2Cl_2/CH_3OH$=1/1) in our work (see the Supplementary data). To be rigorous, we have completed the synthesis of proposed (12*R*)-12-hydroxymonocerin (**2**).




**Scheme 4.** Synthesis of (12*R*)-12-hydroxymonocerin (**2**). Reagents and conditions: (a) (i) 4-nitrobenzoic acid, DEAD, $Ph_3P$, THF, 0 °C to rt; (ii) $K_2CO_3$, $CH_3OH$, rt, 83% (over two steps); (b) $BCl_3$, $CH_2Cl_2$, −78 °C, 55%.

## 3. Conclusion

In summary, we have achieved the first asymmetric total synthesis of (12*S*)-12-hydroxymonocerin (**1**) and (12*R*)-12-hydroxymonocerin (**2**) from 4-bromo-2,6-dimethoxyphenol with an overall yield of 2.7% over 14 steps, 2.4% over 16 steps, respectively. The strategy was developed based on a biomimetically inspired intramolecular nucleophilic trapping of a quinonemethide intermediate by a pendant alcohol.

## 4. Experimental

### 4.1. General methods

Solvents were purified and dried by standard methods prior to use. All commercially available reagents were used without further purification unless otherwise noted. Oxygen- and moisture-sensitive reactions were carried out under argon atmosphere. Column chromatography was generally performed on silica gel (200–300 mesh) and reactions were monitored by thin layer chromatography (TLC) using silica gel GF254 plates with UV light to visualize the course of reaction. Melting points were determined with a digital Koffer apparatus and were uncorrected. $^1H$ and $^{13}C$ NMR data were recorded on 300 MHz and 400 MHz spectrometer using $CDCl_3$ as solvent at room temperature. The chemical shifts ($\delta$) are reported in parts per million and coupling constants (*J*) in Hertz. High-resolution mass spectra (HRMS) were obtained on an FT-ICR spectrometer.

### 4.2. Experimental procedure and characterization data for compounds

*4.2.1. 2-(Benzyloxy)-5-bromo-1,3-dimethoxybenzene (**18**).* To a solution of 4-bromo-2,6-dimethoxyphenol **16** (22.1 g, 94.8 mmol) in

anhydrous DMF (90 mL) were added $K_2CO_3$ (27.6 g, 200 mmol), and (bromomethyl)benzene (12.4 mL, 104.6 mmol) at 0 °C. After being stirred for 6 h at 40 °C, the reaction was quenched with $H_2O$ (40 mL) and extracted with $Et_2O$ (4×30 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated in vacuum. Purification by column chromatography (petroleum ether/EtOAc 20/1) gave benzyl ether **18** (28.9 g, 94% yield) as white solid: mp 53–54 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.51–7.48 (m, 2H), 7.40–7.29 (m, 3H), 6.73 (s, 2H), 5.00 (s, 2H), 3.81 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.0, 137.4, 135.9, 128.4, 128.1, 127.8, 116.2, 108.8, 74.9, 56.1, 56.1; IR ($CHCl_3$): $\nu_{max}$ 2935, 1587, 1493, 1407, 1223, 1126, 812, 731 cm$^{-1}$; HRMS (ESI) calcd for $C_{15}H_{16}BrO_3$ $[M+H]^+$ 323.0277, found 323.0277.

*4.2.2. (S)-2-(4-(Benzyloxy)-3,5-dimethoxybenzyl)oxirane (**15**).* To a suspension of Mg (1.2 g, 50 mmol) in THF (10 mL) was added $I_2$ to activate Mg, and a solution of **18** (12.9 g, 40 mmol) in THF (80 mL) was added dropwise under Ar. After the addition (about 1 h), the mixture was stirred at room temperature for 2 h and then cooled to −40 °C. To this cold Grignard reagent solution was added CuI (760 mg, 4 mmol), followed by the addition of (*S*)-2-(chloromethyl) oxirane **17** (3.2 mL, 41 mmol) in THF (50 mL). The mixture was stirred at −40 °C overnight, and then quenched by addition of saturated aqueous $NH_4Cl$ solution (10 mL). After being stirred for 30 min, the mixture was extracted with ethyl acetate (3×10 mL), the combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated in vacuum. Purification by column chromatography (petroleum ether/EtOAc 5/1) gave *(S)-1-(4-(benzyloxy)-3,5-dimethoxyphenyl)-3-chloropropan-2-ol* (8.28 g, 62% yield) as colorless oil: $[\alpha]_D^{28}$ +5.0 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.53–7.48 (m, 2H), 7.39–7.28 (m, 3H), 6.45 (s, 2H), 5.00 (s, 2H), 4.04 (s, 1H), 3.82 (s, 6H), 3.61 (dd, *J*=11.1, 4.1 Hz, 1H), 3.51 (dd, *J*=11.1, 5.9 Hz, 1H), 2.87–2.77 (m, 1H), 2.42 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 153.4, 137.7, 135.6, 132.7, 128.4, 128.0, 127.7, 106.1, 74.9, 71.9, 56.0, 48.9, 40.8; IR ($CHCl_3$): $\nu_{max}$ 3458, 2928, 1590, 1460, 1241, 1127, 736 cm$^{-1}$; HRMS (ESI) calcd for $C_{18}H_{22}ClO_4$ $[M+H]^+$ 337.1201, found 337.1201.

To a solution of above compound (5.07 g, 15 mmol) in anhydrous $Et_2O$ (100 mL) was added NaOH (2.4 g, 60 mmol). After being stirred for 8 h at room temperature, the mixture was filtered and the filtration residue was wash with $Et_2O$ (3×10 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, and concentrated in vacuum. Purification by column chromatography (petroleum ether/EtOAc 15/1) gave epoxide **15** (3.83 g, 85% yield) as a colorless oil: $[\alpha]_D^{28}$ −12.0 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.52 (d, *J*=7.1 Hz, 2H), 7.41–7.28 (m, 3H), 6.49 (s, 2H), 5.01 (s, 2H), 3.84 (s, 6H), 3.19–3.15 (m, 1H), 2.87–2.75 (m, 3H), 2.57 (dd, *J*=4.9, 2.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 153.4, 137.8, 135.6, 133.0, 128.3, 127.9, 127.6, 105.9, 74.9, 56.0, 52.3, 46.7, 38.9; IR ($CHCl_3$): $\nu_{max}$ 2925, 1589, 1459, 1241, 1127, 981, 738 cm$^{-1}$; HRMS (ESI) calcd for $C_{18}H_{21}O_4$ $[M+H]^+$ 301.1434, found 301.1432.

*4.2.3. (S)-1-(2-((S)-3-(4-(Benzyloxy)-3,5-dimethoxyphenyl)-2-(tert-butyldimethylsilyloxy)propyl)-1,3-dithian-2-yl)propan-2-ol (**19**).* A solution of TBS–dithiane **13** (1.83 g, 7.8 mmol) in anhydrous tetrahydrofuran (15 mL), under an argon atmosphere, was treated with *n*-BuLi (3.0 mL, 7.5 mmol, 2.5 M) at 0 °C and stirred at this temperature for 10 min. Then, the solution was transferred via cannula to a pre-cooled solution of epoxide **15** (1.8 g, 6.0 mmol) in anhydrous diethyl ether (50 mL) under an argon atmosphere at −35 °C. The reaction mixture was then stirred at this temperature for 1 h, and then cooled to −50 °C, anhydrous hexamethyl phosphorous amide (2.5 mL, 11.1 mmol) and a solution of (*S*)-2-methyloxirane **14** (0.84 mL, 12.0 mmol) in diethyl ether (20 mL) were added dropwise. The reaction was then allowed to warm up to room temperature with stirring overnight. The reaction 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 vacuum. Purification by column chromatography (petroleum ether/EtOAc 8/1) gave β-hydroxydithiane **19** (2.16 g, 61%) as yellow oil: $[\alpha]_D^{28}$ +23.0 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.50–7.47 (m, 2H), 7.37–7.28 (m, 3H), 6.43 (s, 2H), 4.98 (s, 2H), 4.39–4.29 (m, 1H), 4.22–4.12 (m, 1H), 3.82 (s, 6H), 3.73 (d, *J*=2.9 Hz, 1H), 2.95 (dd, *J*=13.2, 4.6 Hz, 1H), 2.72–2.54 (m, 3H), 2.48 (dt, *J*=14.2, 4.8 Hz, 1H), 2.27 (d, *J*=2.3 Hz, 1H), 2.21–2.12 (m, 3H), 2.02 (d, *J*=15.1 Hz, 1H), 1.81–1.72 (m, 2H), 1.16 (d, *J*=6.2 Hz, 3H), 0.94 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 153.4, 137.6, 135.4, 134.2, 128.4, 128.1, 127.8, 106.4, 75.0, 72.4, 63.9, 56.1, 56.0, 51.5, 48.1, 45.6, 42.9, 26.3, 26.0, 25.5, 24.8, 24.5, 18.0, −3.3, −4.2; IR ($CHCl_3$): $\nu_{max}$ 3458, 2928, 1589, 1460, 1240, 1128, 835, 776 cm$^{-1}$; HRMS (ESI) calcd for $C_{31}H_{48}O_5S_2SiNa$ $[M+Na]^+$ 615.2605, found 615.2603.

*4.2.4. (2S,6S)-1-(4-(Benzyloxy)-3,5-dimethoxyphenyl)-2-(tert-butyldimethylsilyloxy)-6-hydroxyheptan-4-one (**12**).* To a solution of β-hydroxydithiane **19** (2.16 g, 3.65 mmol) in THF/$H_2O$ (4/1, 35 mL) was added $CaCO_3$ (3.65 g, 36.5 mmol) at 0 °C, then iodine (4.6 g, 18 mmol) was added portion wise. The mixture was stirred for 0.5 h and quenched with saturated aqueous $Na_2S_2O_3$ (10 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 vacuum. Purification by column chromatography (petroleum ether/EtOAc 3/1) gave β-hydroxyketone **12** (1.58 g, 86% yield) as colorless oil: $[\alpha]_D^{28}$ +25.0 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.51–7.47 (m, 2H), 7.37–7.27 (m, 3H), 6.39 (s, 2H), 4.98 (s, 2H), 4.37 (p, *J*=6.1 Hz, 1H), 4.22 (s, 1H), 3.81 (s, 6H), 3.09 (s, 1H), 2.70 (qd, *J*=13.5, 6.0 Hz, 2H), 2.63–2.44 (m, 4H), 1.18 (d, *J*=6.3 Hz, 3H), 0.85 (s, 9H), −0.02 (s, 3H), −0.11 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 210.9, 153.2, 137.8, 135.4, 133.9, 128.4, 128.0, 127.7, 106.7, 74.9, 69.8, 63.5, 56.0, 52.3, 50.2, 44.2, 25.7, 22.2, 17.8, −4.9, −5.0; IR ($CHCl_3$): $\nu_{max}$ 3502, 2928, 1706, 1590, 1460, 1242, 1128, 835, 776 cm$^{-1}$; HRMS (ESI) calcd for $C_{28}H_{46}O_6SiN$ $[M+NH_4]^+$ 520.3089, found 520.3088.

*4.2.5. (2S,4S,6S)-7-(4-(Benzyloxy)-3,5-dimethoxyphenyl)-6-(tert-butyldimethylsilyloxy)heptane-2,4-diol (**20**).* To a solution of **12** (1.44 g, 2.86 mmol) in THF (30 mL) and methanol (3 mL) at −78 °C was added diethylmethoxyborane (3.43 mL, 1 M in THF) under Ar. After being stirred for 1 h at −78 °C, sodium borohydride (326 mg, 8.58 mmol) was added and the reaction mixture was stirred for 8 h at −78 °C then the temperature was slowly increased to −35 °C over a period of 5 h. The resulting mixture was allowed to stand in a −20 °C refrigerator for 10 h without stirring, then warmed to room temperature, and stirred for 10 min. It was diluted with 100 mL of EtOAc and then washed with water and with brine. The organic phase was dried over anhydrous $Na_2SO_4$ and concentrated in vacuum. The Crude product was diluted with methanol then hydrogen peroxide (30%, 10 mL) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with EtOAc (3×10 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, and concentrated in vacuum. Purification by chromatography on silica gel (petroleum ether/EtOAc 5/1) gave alcohol **20** (1.28 g, 89% yield) as colorless oil: $[\alpha]_D^{28}$ −7.0 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.51–7.48 (m, 2H), 7.37–7.28 (m, 3H), 6.39 (s, 2H), 4.99 (s, 2H), 4.31 (t, *J*=9.9 Hz, 1H), 4.25–4.17 (m, 2H), 4.12–4.03 (m, 1H), 3.81 (s, 6H), 3.78 (s, 1H), 2.86 (dd, *J*=13.5, 7.5 Hz, 1H), 2.76 (dd, *J*=13.5, 5.8 Hz, 1H), 1.72 (ddd, *J*=14.1, 10.1, 3.8 Hz, 1H), 1.62–1.50 (m, 2H), 1.45 (dt, *J*=14.1, 2.4 Hz, 1H), 1.20 (d, *J*=6.2 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), −0.18 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 153.2, 137.7, 135.5, 134.4, 128.4, 127.9, 127.6, 106.6, 74.9, 72.8, 69.5, 68.3, 55.9, 45.6, 43.3, 42.3, 25.7, 23.7, 17.8, −5.0, −5.1; IR ($CHCl_3$): $\nu_{max}$ 3430, 2930, 1590, 1460, 1242, 1128,

834, 775 $cm^{-1}$; HRMS (ESI) calcd for $C_{28}H_{44}O_6Si$ $[M+H]^+$ 505.2980, found 505.2978.

*4.2.6. (2S,4R,6S)-7-(4-(Benzyloxy)-3,5-dimethoxyphenyl)-6-hydroxyheptane-2,4-diyl diacetate (**11**).* To a solution of **20** (857 mg, 1.7 mmol) in pyridine (17 mL) at 0 °C was added acetic anhydride (3.5 g, 34 mmol) and DMAP (105 mg, 0.85 mmol). After being stirred for 1 h at room temperature, the solvent was concentrated in vacuum. Purification by chromatography on silica gel (petroleum ether/EtOAc 15/1) gave *(2S,4S,6S)-7-(4-(benzyloxy)-3,5-dimethoxyphenyl)-6-(tert-butyldimethylsilyloxy)heptane-2,4-diyl diacetate* (846 mg, 85% yield) as colorless oil: $[\alpha]_D^{28}$ +8.0 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.52–7.47 (m, 2H), 7.38–7.27 (m, 3H), 6.38 (s, 2H), 5.10–5.01 (m, 1H), 4.99 (s, 2H), 4.91 (dd, *J*=13.2, 6.2 Hz, 1H), 3.98–3.90 (m, 1H), 3.81 (s, 6H), 2.70 (ddd, *J*=29.8, 13.7, 6.2 Hz, 2H), 2.03 (s, 3H), 1.99 (s, 3H), 2.01–1.91 (m, 1H), 1.76–1.56 (m, 3H), 1.23 (d, *J*=6.3 Hz, 3H), 0.88 (s, 9H), 0.01 (s, 3H), −0.08 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.3, 170.2, 153.2, 137.9, 135.5, 134.2, 128.4, 128.0, 127.6, 106.7, 74.9, 70.1, 68.9, 67.8, 56.1, 44.7, 41.6, 40.7, 25.8, 21.2, 20.1, 17.9, −4.4, −5.0; IR ($CHCl_3$): $\nu_{max}$ 2928, 1736, 1590, 1460, 1371, 1243, 1127, 836, 759 $cm^{-1}$; HRMS (ESI) calcd for $C_{32}H_{49}O_8Si$ $[M+H]^+$ 589.3191, found 589.3194.

A solution of HCl (6 N, 1.5 mL) was added to a stirred solution of above compound (846 mg, 1.44 mmol) in acetone (15 mL) at 0 °C, and the mixture was stirred for 2 h at 0 °C. The reaction was diluted with $Et_2O$ (10 mL), washed with saturated aqueous $NaHCO_3$, dried over $Na_2SO_4$, filtered, and concentrated in vacuum. Purification by chromatography on silica gel (petroleum ether/EtOAc 2/1) gave **11** (600 mg, 88% yield) as colorless oil: $[\alpha]_D^{28}$ +10.0 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.49 (d, *J*=7.1 Hz, 2H), 7.37–7.27 (m, 3H), 6.42 (s, 2H), 5.19 (ddd, *J*=12.7, 8.1, 4.4 Hz, 1H), 4.98 (s, 2H), 4.99–4.91 (m, 1H), 3.81 (s, 6H), 3.71 (s, 1H), 2.73–2.64 (m, 2H), 2.08 (s, 3H), 2.02 (s, 3H), 2.06–1.96 (m, 1H), 1.80–1.59 (m, 3H), 1.24 (d, *J*=6.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 171.6, 170.4, 153.4, 137.9, 135.7, 134.0, 128.3, 128.0, 127.7, 106.4, 74.9, 68.8, 68.2, 67.9, 56.1, 44.0, 42.1, 40.7, 21.2, 21.0, 19.9; IR ($CHCl_3$): $\nu_{max}$ 3502, 2922, 1732, 1589, 1458, 1374, 1241, 1125, 1021, 739 $cm^{-1}$; HRMS (ESI) calcd for $C_{26}H_{34}O_8Na$ $[M+Na]^+$ 497.2146, found 497.2142.

*4.2.7. (2S,4S)-1-((S)-7-(Benzyloxy)-6,8-dimethoxy-1-oxoisochroman-3-yl)pentane-2,4-diyl diacetate (**21**).* To a solution of alcohol **11** (600 mg, 1.26 mmol) and trimethyl orthoformate (3.2 mL) in $CH_2Cl_2$ (13 mL) was added TMSOTf (0.05 mL, 0.13 mmol) at 0 °C. After stirring for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with brine and dried over anhydrous $Na_2SO_4$. Concentration in vacuum gave crude product as oil, which was used immediately without further purification.

The crude product was dissolved in acetone (12 mL) and Jones oxidant (3.0 M, 1.2 mL, 3.6 mmol) was added at 0 °C. After stirring for 1 h, the mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3×5 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, and concentrated in vacuum. Purification by column chromatography (petroleum ether/EtOAc 2/1) gave δ-valerolactone **21** (512 mg, 81% yield for two steps) as pale yellow oil: $[\alpha]_D^{28}$ −68.0 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.49 (d, *J*=7.0 Hz, 2H), 7.40–7.30 (m, 3H), 6.48 (s, 1H), 5.25–5.17 (m, 1H), 4.99 (s, 2H), 5.03–4.93 (m, 1H), 4.44 (ddt, *J*=11.6, 8.7, 3.0 Hz, 1H), 3.97 (s, 3H), 3.86 (s, 3H), 2.91 (dd, *J*=15.9, 11.7 Hz, 1H), 2.74 (dd, *J*=16.0, 2.7 Hz, 1H), 2.13–2.00 (m, 8H), 2.05 (s, 6H), 1.95–1.88 (m, 1H), 1.84–1.78 (m, 1H), 1.26 (d, *J*=6.3 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.4, 170.2, 161.4, 157.8, 156.5, 141.1, 137.2, 136.7, 128.3, 128.2, 127.9, 111.8, 105.7, 75.4, 74.1, 68.1, 67.7, 61.9, 56.0, 40.4, 39.5, 34.6, 21.3, 21.1, 20.1; IR ($CHCl_3$): $\nu_{max}$ 2925, 1734, 1593, 1459, 1372, 1246, 1114, 1020, 751 $cm^{-1}$; HRMS (ESI) calcd for $C_{27}H_{33}O_9$ $[M+H]^+$ 501.2119, found 501.2119.

*4.2.8. (S)-3-((2S,4S)-2,4-Dihydroxypentyl)-7-hydroxy-6,8-dimethoxyisochroman-1-one (**10**).* To a solution of δ-valerolactone **21** (472 mg, 0.94 mmol) in $CH_3OH$ (10 mL) was added anhydrous $K_2CO_3$ (130 mg, 0.94 mmol) at room temperature. After stirring for 3 h, the reaction was quenched with $H_2O$ (5 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 vacuum. Purification by column chromatography ($CH_2Cl_2$/$CH_3OH$, 40/1) gave *(S)-7-(benzyloxy)-3-((2S,4S)-2,4-dihydroxypentyl)-6,8-dimethoxyisochroman-1-one* (364 mg, 93% yield) as pale yellow oil: $[\alpha]_D^{28}$ −41.0 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.47 (d, *J*=6.7 Hz, 2H), 7.39–7.28 (m, 3H), 6.49 (s, 1H), 5.00–4.94 (m, 2H), 4.75–4.68 (m, 1H), 4.27 (s, 2H), 4.14–4.04 (m, 1H), 3.93 (s, 3H), 3.85 (s, 3H), 3.49 (s, 1H), 2.85 (qd, *J*=16.2, 7.4 Hz, 2H), 1.93–1.86 (m, 1H), 1.78–1.69 (m, 1H), 1.57 (dd, *J*=9.4, 4.5 Hz, 2H), 1.20 (d, *J*=6.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 162.5, 157.9, 156.4, 140.9, 137.4, 137.2, 128.3, 128.2, 127.9, 111.6, 105.8, 75.3, 74.4, 68.7, 68.0, 61.8, 56.0, 44.9, 42.9, 34.8, 24.2; IR ($CHCl_3$): $\nu_{max}$ 3416, 2928, 1713, 1593, 1457, 1340, 1260, 1117, 757 $cm^{-1}$; HRMS (ESI) calcd for $C_{23}H_{29}O_7$ $[M+H]^+$ 417.1908, found 417.1906.

To a solution of above diol (323 mg, 0.78 mmol) in EtOAc (8 mL) was added 10% Pd/C (82 mg, 0.08 mmol) under 1atm a hydrogen atmosphere at room temperature. After stirring for 6 h, the mixture was filtered and the filtration residue was wash with $CH_3OH$ (3×10 mL). The combined organic layers were concentrated in vacuum. Purification by column chromatography ($CH_2Cl_2$/$CH_3OH$, 15/1) gave phenol **10** (252 mg, 99% yield) as colorless crystal: mp 183–184 °C: $[\alpha]_D^{28}$ −65.0 (*c* 1.0, $CH_3OH$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.49 (s, 1H), 4.71 (t, *J*=10.4 Hz, 1H), 4.27 (s, 1H), 4.06 (dd, *J*=11.8, 5.9 Hz, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.47 (s, 1H), 2.93–2.73 (m, 2H), 1.94–1.82 (m, 1H), 1.78–1.68 (m, 1H), 1.63–1.32 (m, 2H), 1.20 (d, *J*=6.0 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 162.8, 151.8, 148.8, 138.4, 132.9, 110.8, 105.4, 74.7, 68.9, 68.0, 61.8, 56.2, 44.9, 42.9, 34.5, 24.2; IR ($CHCl_3$): $\nu_{max}$ 3362, 2931, 1699, 1604, 1501, 1270, 1228, 1102 $cm^{-1}$; HRMS (ESI) calcd for $C_{16}H_{23}O_7$ $[M+H]^+$ 327.1438, found 327.1439.

*4.2.9. (2S,3aR,9bR)-7-Hydroxy-2-((S)-2-hydroxypropyl)-6,8-dimethoxy-3,3a-dihydro-2H-furo[3,2-c]isochromen-5(9bH)-one (**8**).* To a solution of phenol **10** (240 mg, 0.73 mmol) in 1,4-dioxane (8 mL) was added DDQ (176 mg, 0.78 mmol) at room temperature. After stirring for 3 h, the mixture was filtered and the filtration residue was wash with $CH_2Cl_2$ (3×10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $Na_2SO_4$, and concentrated in vacuum. Purification by column chromatography ($CH_2Cl_2$/$CH_3OH$, 40/1) yielded 147 mg (62%) of *cis*-fused furobenzopyranone **8** as colorless oil: $[\alpha]_D^{28}$ +16.0 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.76 (s, 1H), 6.14 (s, 1H), 4.96 (dd, *J*=5.1, 2.9 Hz, 1H), 4.57 (d, *J*=2.9 Hz, 1H), 4.39–4.30 (m, 1H), 3.98 (s, 3H), 3.97 (s, 3H), 4.00–3.94 (m, 1H), 2.71 (s, 1H), 2.60 (ddd, *J*=14.4, 8.8, 5.7 Hz, 1H), 2.20 (dd, *J*=14.3, 5.3 Hz, 1H), 1.92–1.82 (m, 1H), 1.75 (ddd, *J*=14.3, 4.1, 3.2 Hz, 1H), 1.17 (d, *J*=6.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 159.9, 151.9, 148.9, 140.7, 127.9, 110.4, 107.7, 79.3, 78.5, 75.5, 67.3, 61.9, 56.4, 44.7, 39.6, 23.5; IR ($CHCl_3$): $\nu_{max}$ 3500, 2935, 1716, 1605, 1461, 1374, 1265, 1108, 739 $cm^{-1}$; HRMS (ESI) calcd for $C_{16}H_{21}O_7$ $[M+H]^+$ 325.1282, found 325.1281.

*4.2.10. (2S,3aR,9bR)-2-((S)-2-Hydroxypropyl)-6,7,8-trimethoxy-3,3a-dihydro-2H-furo[3,2-c]isochromen-5(9bH)-one (**22**).* To a solution of **8** (147 mg, 0.45 mmol) in acetone (5 mL) were added anhydrous $K_2CO_3$ (68 mg, 0.5 mmol) and MeI (0.2 mL, 3.1 mmol) at room temperature. After stirring for 4 h under refluxing conditions, the reaction 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 vacuum. Purification by column chromatography ($CH_2Cl_2/CH_3OH$, 30/1) gave trimethyl ether **22** (105 mg, 68% yield) as orange oil: $[\alpha]_D^{28}$ +26.0 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.76 (s, 1H), 4.95 (dd, *J*=4.9, 2.9 Hz, 1H), 4.58 (d, *J*=2.9 Hz, 1H), 4.41–4.32 (m, 1H), 4.01–3.93 (m, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.89 (s, 3H), 2.60 (ddd, *J*=14.4, 8.9, 5.6 Hz, 1H), 2.22 (dd, *J*=14.3, 5.1 Hz, 1H), 1.88 (dt, *J*=14.3, 9.0 Hz, 1H), 1.75 (ddd, *J*=14.4, 4.2, 3.1 Hz, 1H), 1.17 (d, *J*=6.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 159.6, 157.9, 156.5, 144.4, 132.1, 111.1, 108.2, 79.1, 78.6, 75.5, 67.2, 61.8, 61.1, 56.2, 44.8, 39.5, 23.5; IR ($CHCl_3$): $\nu_{max}$ 3481, 2928, 1715, 1594, 1462, 1369, 1261, 1112, 1037, 737 $cm^{-1}$; HRMS (ESI) calcd for $C_{17}H_{23}O_7$ $[M+H]^+$ 339.1438, found 339.1445.

*4.2.11. (12S)-12-Hydroxymonocerin (**1**).* To a solution of trimethyl ether **22** (46 mg, 0.14 mmol) in dry $CH_2Cl_2$ (1.5 mL) was added $BCl_3$ (1.0 M, 0.27 mL, 0.27 mmol) at −78 °C under Ar. The mixture was stirred at −78 °C for 1 h and quenched with saturated aqueous $NaHCO_3$ (1 mL). The mixture was extracted with ethyl acetate (15 mL) and the organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated in vacuum. Purification by column chromatography ($CH_2Cl_2/CH_3OH$, 40/1) gave (12*S*)-12-hydroxymonocerin (**1**) (22 mg, 50% yield) as yellow oil: $[\alpha]_D^{28}$ +5.8 (*c* 0.17, $CH_2Cl_2/CH_3OH$=1/1), (lit.,[4] $[\alpha]_D^{20}$ +4.7 (*c* 0.17, $CH_2Cl_2/CH_3OH$=1/1)); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 11.23 (s, 1H), 6.57 (s, 1H), 5.06 (dd, *J*=4.9, 3.1 Hz, 1H), 4.60 (d, *J*=3.1 Hz, 1H), 4.34 (ddd, *J*=14.1, 8.7, 4.9 Hz, 1H), 4.00–3.96 (m, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 2.67 (ddd, *J*=14.6, 8.7, 6.0 Hz, 1H), 2.22 (dd, *J*=14.0, 5.2 Hz, 1H), 1.84 (dt, *J*=14.4, 8.9 Hz, 1H), 1.78–1.72 (m, 1H), 1.18 (d, *J*=6.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 167.6, 158.7, 156.3, 137.5, 130.6, 104.5, 101.9, 80.8, 78.5, 75.0, 67.2, 60.7, 56.3, 44.8, 39.6, 23.6; IR ($CHCl_3$): $\nu_{max}$ 3513, 2929, 1669, 1619, 1520, 1379, 1277, 1122, 734 $cm^{-1}$; HRMS (ESI) calcd for $C_{16}H_{21}O_7$ $[M+H]^+$ 325.1282, found 325.1281.

*4.2.12. (2S,3aR,9bR)-2-((R)-2-Hydroxypropyl)-6,7,8-trimethoxy-3,3a-dihydro-2H-furo[3,2-c]isochromen-5(9bH)-one (**23**).* To a stirred, cooled (0 °C) mixture of trimethyl ether **22** (75 mg, 0.22 mmol), triphenylphosphine (291 mg, 1.1 mmol), and 4-nitrobenzoic acid (185 mg, 1.1 mmol) in THF (3 mL) was added dropwise diethyl azodicarboxylate (224 g, 1.1 mmol), and the mixture was stirred at room temperature overnight. After removing of the solvent in vacuum, the residue was purified by column chromatography (petroleum ether/EtOAc, 1/1) to give the desired 4-nitrobenzoate as crude product.

To a solution of above mixture in $CH_3OH$ (3 mL) was added anhydrous $K_2CO_3$ (30 mg, 0.22 mmol) at room temperature. After stirring for 1 h, the reaction was quenched with $H_2O$ (1 mL). The mixture was extracted with ethyl acetate (15 mL) and the organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated in vacuum. Purification by column chromatography ($CH_2Cl_2/CH_3OH$, 30/1) gave trimethyl ether **23** (62 mg, 83% yield for two steps) as orange oil: $[\alpha]_D^{28}$ −7.0 (*c* 1.0, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.78 (s, 1H), 4.96 (dd, *J*=5.1, 3.0 Hz, 1H), 4.55 (d, *J*=2.8 Hz, 1H), 4.49–4.39 (m, 1H), 4.05–3.99 (m, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.89 (s, 3H), 2.59 (ddd, *J*=14.5, 9.0, 5.6 Hz, 1H), 2.20 (dd, *J*=14.4, 5.5 Hz, 1H), 1.88 (ddd, *J*=14.4, 8.9, 3.1 Hz, 1H), 1.77–1.67 (m, 1H), 1.19 (d, *J*=6.3 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 159.8, 157.9, 156.5, 144.3, 132.3, 111.2, 108.2, 79.5, 76.0, 75.4, 65.1, 61.8, 61.1, 56.2, 44.7, 39.5, 23.9; IR ($CHCl_3$): $\nu_{max}$ 3474, 2935, 1714, 1594, 1464, 1369, 1262, 1114, 1037, 755 $cm^{-1}$; HRMS (ESI) calcd for $C_{17}H_{23}O_7$ $[M+H]^+$ 339.1438, found 339.1438.

*4.2.13. (12R)-12-Hydroxymonocerin (**2**).* To a solution of trimethyl ether **23** (59 mg, 0.17 mmol) in dry $CH_2Cl_2$ (2 mL) was added $BCl_3$ (1.0 M, 0.34 mL, 0.34 mmol) at −78 °C under Ar. The mixture was stirred at −78 °C for 1 h and quenched with saturated aqueous $NaHCO_3$ (1 mL). The mixture was extracted with ethyl acetate (15 mL) and the organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated in vacuum. Purification by column chromatography ($CH_2Cl_2/CH_3OH$, 40/1) gave (12*R*)-12-hydroxymonocerin (**2**) (31 mg, 55% yield) as yellow oil: $[\alpha]_D^{28}$ +41 (*c* 0.11, $CH_2Cl_2/CH_3OH$=1/1), $[\alpha]_D^{28}$ +34 (*c* 0.5, $CH_2Cl_2/CH_3OH$=1/1); (lit.,[4] $[\alpha]_D^{20}$ −12.7 (*c* 0.11, $CH_2Cl_2/CH_3OH$=1/1)); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 11.24 (s, 1H), 6.58 (s, 1H), 5.05 (dd, *J*=5.6, 3.1 Hz, 1H), 4.55 (d, *J*=3.0 Hz, 1H), 4.45–4.33 (m, 1H), 4.05–3.96 (m, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 2.65 (ddd, *J*=14.6, 8.7, 6.1 Hz, 1H), 2.18 (dd, *J*=14.6, 5.9 Hz, 1H), 1.84 (dt, *J*=14.4, 8.9 Hz, 1H), 1.78–1.71 (m, 1H), 1.18 (d, *J*=6.2 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 167.7, 158.6, 156.1, 137.2, 130.9, 104.5, 101.9, 81.2, 75.8, 74.6, 64.9, 60.6, 56.2, 44.5, 39.3, 23.8; IR ($CHCl_3$): $\nu_{max}$ 3520, 2948, 1656, 1617, 1543, 1379, 1278, 1123, 745 $cm^{-1}$; HRMS (ESI) calcd for $C_{16}H_{21}O_7$ $[M+H]^+$ 325.1282, found 325.1281.

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## Supplementary data

NMR spectra ($^1H$ and $^{13}C$) for all products. This material is available free of charge. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.09.075. These data include MOL files and InChiKeys of the most important compounds described in this article.

## References and notes

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