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Enantioselective Total Synthesis of (+)-Monocerin, a Dihydroisocoumarin Derivative with Potent Antimalarial Properties

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Abstract

We describe here the enantioselective synthesis of (+)-monocerin and its acetate derivative. The present synthesis features an efficient optically active synthesis of the β -hydroxy- γ -lactone derivative with high enantiomeric purity using a Sharpless dihydroxylation as the key step. The synthesis also highlights a tandem Lewis acid-catalyzed, oxocarbenium ion-mediated diastereoselective syn-allylation reaction and a methoxymethyl group promoted methylenation reaction. A selective CrO_3 -mediated oxidation of isochroman provided the corresponding lactone derivative. We investigated this reaction with a variety of Lewis acids. The synthesis is quite efficient and may be useful for the preparation of derivatives.

Graphical Abstract

Introduction

Dihydrocoumarin and dihydroisocoumarin derivatives frequently occur in nature.^{1,2} These natural products exhibit a wide range of biological properties including antifungal, insecticidal, antiparasitic, and plant pathogenic activity.^{3,4,5} Monocerin (**1**, Figure 1), which was first isolated by Aldridge and Turner from *Exserohilum monoceras* (Drechsler), is a

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ASSOCIATED CONTENT

Supporting Information

The supporting Information is available free of charge on the ACS Publications website <http://pubs.acs.org>.

¹H- and ¹³C-NMR spectra for all new compounds (PDF).

Conflicts of interest

There are no conflicts to declare.

Structural features as well as broad-spectrum biological properties of monocerin led to considerable synthetic attention over the years. Mori and co-workers reported the first synthesis of monocerin in racemic form.¹⁶ Simpson and co-workers then reported a biomimetic synthesis of monocerin.¹⁷ Since then, monocerin and its derivatives have attracted much synthetic interest due to their broad medicinal potentials. A number of total syntheses of monocerin has been reported.^{18–23} Recently, an enantioselective total synthesis of lasionectrin has also been reported.²⁴ Herein, we report a short and practical synthesis of monocerin and its acetate derivative in optically active form. The synthesis features a Sharpless asymmetric dihydroxylation, a Lewis-acid catalyzed oxocarbenium ion-mediated stereoselective allylation, a formulation reaction, and a CrO₃ mediated oxidation of the benzopyran to a dihydroisocoumarin derivative. The synthesis is potentially amenable towards the synthesis of structural variants of monocerin for biological studies.

Results and discussion

Our synthetic strategy for (+)-monocerin is shown in Scheme 1. We planned an oxocarbenium ion-mediated allylation of acetate derivative **6** for stereoselective installation of the propyl chain of monocerin. We also envisioned an intramolecular oxocarbenium ion-mediated formulation of the aromatic ring through the MOM-group to install the isochroman structure. We planned to investigate these transformations in a “one-pot” operation. A related C3-benzyloxy substituted five-membered ring oxocarbenium ion has been shown to promote allylation selectivity to provide the 1,3-*cis* product.^{25,26} The stereochemical outcome and selectivity with a methoxymethyl group is expected to be similar. The key allylation substrate can be synthesized from 3-hydroxy- γ -lactone **7**, which can be synthesized in an optically active manner by asymmetric dihydroxylation of *E*-olefin **8**.^{27,28} The requisite *E*-olefin can be synthesized by a stereoselective Wittig olefination using a γ -oxido-ylid and commercially available 3,4,5-trimethoxy benzaldehyde.^{29,30}

Our synthesis of multigram quantities of γ -lactone **7** and its derivatives is shown in Scheme 2, Wittig olefination of 3,4,5-trimethoxybenzaldehyde **9** was carried out with ylid generated from (2-carboxyethyl)triphenyl phosphonium bromide and potassium *t*-butoxide in THF at -78 °C to 23 °C for 18 h.^{29,31} The resulting β,γ -unsaturated acid was esterified by exposure to TMSCl in MeOH at 0 °C to 23 °C for 12 h to provide methyl ester **8** in 49% yield over 2-steps. Asymmetric dihydroxylation of methyl ester **8** with AD-mix- β in the presence of methanesulfonamide and sodium bicarbonate in aqueous *t*-BuOH at 0 °C for 22 h afforded β -hydroxy- γ -lactone **7** in 90% yield.²⁷ Optical purity of lactone **7** was over 95% *ee* as determined by chiral HPLC analysis using chiralpak IC column. Protection of the hydroxyl group as a MOM ether was achieved by reaction of lactone **7** with MOMCl in THF in the presence of diisopropylethylamine (DIPEA) and a catalytic amount of tetrabutylammonium iodide (TBAI) at 50 °C for 24 h to provide MOM-ether **10** in 95% yield. It was then converted to acetate derivative **6** in a two-step sequence, first, by DIBAL-H reduction in CH_2Cl_2 at -78 °C for 2 h, followed by acetylation of the resulting crude lactol with acetic anhydride and triethylamine in the presence of a catalytic amount of DMAP in CH_2Cl_2 at 0 °C for 2 h to provide **6** as the major anomer along with a small amount of another anomer (ratio 14:1) in 88% combined yield over two-steps. Lactone **7** was converted to TBS-protected acetate derivative **11** by protection of the hydroxyl group as TBS ether followed by DIBAL-H reduction and acetylation as described above. Similarly, lactone **7** was also converted to MEM-derivative **12** as described above. The stereochemistry of the chiral center bearing acetate group for **6**, **11** and **12** was assigned by using ^1H -NMR NOESY experiments (Please see the Supporting Information).

With the synthesis of these acetates, we have investigated allylation promoted by various Lewis acids. We first carried out allylation of **6** with 1.1 equivalent of SnBr_4 and 4 equivalent of allyltrimethylsilane in CH_2Cl_2 at -78 °C for 3 h. This resulted in a mixture (62 : 38) of allyl derivatives **13a** and **14a** in 84% combined yield. The ratio was determined by ^1H -NMR-analysis of diastereomeric protons. We then investigated other Lewis acids under various conditions and the results are shown in Table 1. The use of 2 equivalents of SnBr_4 did not improve diastereoselectivity and the reaction yield was reduced (entry 2). The use of 1.1 equivalent of TiCl_4 resulted in 69% yield of a mixture of diastereomers (60 : 40) similar to SnBr_4 reaction (entry 3). An increase of Lewis acid to 2 equivalents, resulted in a decrease of reaction yields as well as a slight reduction of diastereomeric ratio (entry 4). We also investigated the allylation reaction with $\text{BF}_3\cdot\text{OEt}_2$ and TMSOTf as the Lewis acids. In both cases, the reaction provided similar diastereomeric ratios and the reaction yields were 52% and 57%, respectively (entries 5 and 6). We then examined allylation of TBS-protected acetate derivative **11** with 1.1 equivalent of SnBr_4 and 4 equivalent of allyltrimethylsilane in CH_2Cl_2 at -78 °C for 3 h. This has resulted in a slight improvement in diastereomeric ratio (70 : 30) of allyl derivatives **13b** and **14b** in 81% yield (entry 7). The use of 1.1 equivalent of TiCl_4 also provided comparable diastereoselectivity and yield (entry 8). Interestingly, allylation of MEM-protected acetate derivative **12** with 1.1 equivalent of SnBr_4 and 4 equivalent of allyltrimethylsilane in CH_2Cl_2 at -78 °C for 3 h resulted in allyl derivatives **13c** and **14c** in a 1:1 ratio and 33% yield (entry 9). The reaction of **12** with 1.1 equivalent of $\text{BF}_3\cdot\text{OEt}_2$ and 1.5 equivalent of allyltrimethylsilane provided allyl derivatives **13c** and **14c** in a 63:37 ratio and the reaction yield was 36% (entry 10). While the observed

diastereoselectivity of allylation was moderate, we assigned stereochemical identity of diastereomers **13b** and **14b** by using ^1H -NMR NOESY experiments (Please see the Supporting Information for details).

The observed *cis*-diastereoselectivity is consistent with C3-alkoxy substituted tetrahydrofuranyl substrates examined by Worerpel and co-workers.^{25,26} However, the extent of diastereoselectivity of allylation is significantly lower presumably due to competing stereoelectronic effects. As shown in Figure 2, allylation of acetates can proceed through oxocarbenium ion intermediates **15** and **16**. Intermediate **15** is preferred over **16** due to the pseudoequatorial orientation of the bulky trimethoxyphenyl group at the C4-position.^{26,32,33} The axial alkoxy group forms a gauche interaction with the aromatic group. Inside attack on the oxocarbenium ion intermediate **15** leads to major diastereomer **13**. Intermediate **16** also shows a gauche interaction as well as 1,3-interactions between the bulky aromatic group and the C2-axial hydrogen. Changing of Lewis acids did not make much difference in selectivity. The size and nature of protecting groups also did not show much influence in diastereoselectivity. Moreover, the protecting groups remained unaffected under the reaction conditions.

We then investigated a Lewis acid-catalyzed allylation reaction at $-78\text{ }^\circ\text{C}$ to $23\text{ }^\circ\text{C}$ in an effort to promote selective allylation, as well as to carry out Friedel-Crafts alkylation through the MOM or MEM groups on to the aromatic ring in a one-pot operation.^{34,35} The results of these tandem allylation and Oxa-Pictet-Spengler cyclization are shown in Table 2. Initial reaction of MOM derivative **6** with 1.6 equivalent of SnBr_4 in the presence of allyltrimethylsilane at $-78\text{ }^\circ\text{C}$ to $23\text{ }^\circ\text{C}$ for 3 h provided diastereomeric mixture of allylated products **13a** and **14a** in 54% yield as well as isochroman derivatives **17** and **18** in 22% yield (entry 1, Table 2). To promote complete formation of isochroman derivatives, we examined the reaction with additional equivalents of Lewis acid and the reaction was carried out for a longer period of time. Thus, reaction of MOM derivative **6** was carried out with 1.6 equivalent of SnBr_4 in the presence of allyltrimethylsilane at $-78\text{ }^\circ\text{C}$ to $23\text{ }^\circ\text{C}$ for 4 h. Reaction was monitored by TLC and showed complete consumption of the starting acetate derivatives. After this period, the reaction was cooled to $0\text{ }^\circ\text{C}$ and 2 equivalents of SnBr_4 was added, and the resulting mixture was warmed to $23\text{ }^\circ\text{C}$ for 12 h. This resulted in the formation of isochroman derivatives **17** and **18** in 52% yield. The diastereomeric ratio was determined to be 4:1 by ^1H NMR analysis (entry 2). Addition of additional equivalent of Lewis acid was then investigated at lower temperature. Acetate **6** was treated with 1.1 equivalent of SnBr_4 at $-78\text{ }^\circ\text{C}$ to $23\text{ }^\circ\text{C}$ for 3 h and 2 equivalents of SnBr_4 was added at $-78\text{ }^\circ\text{C}$. The resulting mixture was allowed to warm from $-78\text{ }^\circ\text{C}$ to $23\text{ }^\circ\text{C}$ for 12 h. This reaction protocol furnished products **17** and **18** as a mixture (3.2 : 1) of diastereomers in 35% yield (entry 3). In a further optimization effort, acetate **6** was treated with 1.1 equivalent of SnBr_4 at $-78\text{ }^\circ\text{C}$ to for 3 h and then 2 equivalents of SnBr_4 was added at $-78\text{ }^\circ\text{C}$ and the reaction was warmed to $23\text{ }^\circ\text{C}$ for 12 h. This has resulted products **17** and **18** as 3:1 mixture in 42% combined yield (entry 4). Oxa-Pictet-Spengler cyclization of acetate derivative **6** with TiCl_4 in place of SnBr_4 under similar reaction conditions, however, provided only trace amount of the products (entry 5). Interestingly, the reaction of MEM derivative **12** with SnBr_4 and allyltrimethylsilane using conditions described in entry 2

provided a mixture (1.7:1) of isochroman derivatives **17** and **18** in 21% combined yield (entry 6).

The synthesis of (+)-monocerin is shown in Scheme 3. MOM ether **6** was converted to allylated oxa Pictet-Spengler products **17** and **18**. The diastereomers were separated by silica-gel chromatography and the major isomer **17** was hydrogenated under a hydrogen-filled balloon in the presence of a catalytic amount of 10% Pd-C in ethyl acetate at 23 °C for 12 h to provide saturated bicyclic ether **19** in 88% yield. The ¹H-NMR and ¹³C-NMR spectra of our synthetic bicyclic ether **19** showed excellent agreement with reported derivative.¹⁸ Furthermore, NOESY correlation of *cis*-hydrogens in compound **17** supported stereochemistry of **17** and **19** (Please see the Supporting Information for details). Oxidation of the isochroman ring was carried out with CrO₃ and pyridine in CH₂Cl₂ at 0 °C to 23 °C for 36 h to provide lactone derivative **20** in 40% yield (60% brsm). To complete the synthesis of monocerin, selective deprotection of methyl ether was carried out by exposure to BCl₃ in CH₂Cl₂ at -10 °C for 2 h to provide synthetic (+)-monocerin, **1** in 41% yield (88% brsm). The ¹H- and ¹³C-NMR spectra of synthetic (+)-monocerin {[α]_D²³ +57.8 (c, 0.29, CHCl₃)} are in complete agreement with spectra reported for the natural (+)-monocerin {[α]_D²⁴ +53 (c, 0.85, CHCl₃)}.⁶ We have also synthesized (+)-acetoxymonocerin **2** by treatment of **1** with acetic anhydride and pyridine in the presence of a catalytic amount of DMAP at 0 °C to 23 °C for 5 h to furnish acetate derivative **2** in 96% yield. {[α]_D²³ +3.6 (c, 0.29, CHCl₃)}. Thus, (+)-monocerin **1** was synthesized in 10 steps in an overall 9% yield. The acetate derivative **2** was obtained in 11 steps in an overall 8.6% yield.

Conclusions

In summary, we have accomplished an enantioselective total synthesis of (+)-monocerin and its acetate derivative. The synthesis highlights a Lewis acid catalyzed tandem oxocarbenium ion-mediated stereoselective allylation and Friedel-Crafts type alkylation to provide the isochroman frame work in a one-pot operation. The allylation reaction was investigated with various Lewis acids and by varying protecting groups at the C3 position. While the stereochemical outcome for the major product has all *cis*-stereochemistry, the extent of diastereoselectivity was moderate due to competing stereoelectronic effects. The allylation substrate β-hydroxy-γ-lactone was synthesized conveniently in optically active form using Sharpless asymmetric dihydroxylation as the key step. The corresponding *E*-olefin was prepared selectively by olefination with γ-oxido-ylid. Since monocerin and derivatives show a broad-range of biological activity, the current synthesis will provide access to structural variants in optically active form.

Experimental Section

All chemical and reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. The following reaction solvents were distilled prior to use: CH₂Cl₂ from calcium hydride, diethyl ether and tetrahydrofuran from Na/benzophenone, methanol from activated magnesium under argon. All reactions were carried out under an argon atmosphere in either flame or oven-dried (120 °C) glassware. TLC analysis was conducted using glass-backed Thin-Layer Silica Gel Chromatography Plates

(60 Å, 250 µm thickness, F-254 indicator). Column chromatography was performed using 230–400 mesh, 60 Å pore diameter silica gel. ¹H-NMR spectra were recorded at room temperature on a 400 MHz spectrometer. ¹³C-NMR spectra were recorded on 100 and 200 MHz spectrometers. Chemical shifts (δ values) are reported in parts per million and are referenced to the deuterated residual solvent peak. NMR data is reported as: δ value (chemical shift, *J*-value (Hz), integration, where s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sep = septet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, dq = doublet of quartets, brs = broad singlet, app = apparent). Optical rotations were recorded on a digital polarimeter. LRMS and HRMS spectra were recorded at the Purdue University Department of Chemistry Mass Spectrometry Center. These experiments were performed under ESI+ and positive atmosphere pressure chemical ionization (APCI+) conditions using an Orbitrap XL Instrument.

Methyl (E)-4-(3,4,5-Trimethoxyphenyl) But-3-enoate (8).—To a cooled suspension of (2-carboxyethyl) triphenylphosphonium bromide (2.99 g, 7.2 mmol, 1.2 equiv) and 3,4,5-trimethoxybenzaldehyde (1.18 g, 6 mmol, 1.0 equiv) in THF (45 mL) at –78 °C was slowly added a solution of *t*-BuOK (15 mL, 15 mmol, 1.0 THF solution, 2.5 equiv). After addition, the mixture was stirred at –78 °C for 1 h and was then warmed to 23 °C overnight. The resulting suspension was concentrated under reduced pressure, H₂O (100 mL) was added, and the mixture was washed with CH₂Cl₂. The aqueous phase was acidified to pH = 1 with a 1 M solution of HCl and extracted with Et₂O (3x). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure.

The crude β,γ-unsaturated carboxylic acid above was then dissolved in distilled MeOH (20 mL) and TMSCl (0.97 mL, 1.26 equiv) was dropwise added at 0 °C under argon atmosphere. The mixture was stirred at 23 °C overnight then concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (10% EtOAc in hexanes) to yield **8** (746 mg, 49% over two steps) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 6.58 (s, 2H), 6.41 (d, *J* = 15.8, 1H), 6.20 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.86 (s, 6H), 3.83 (s, 3H), 3.71 (s, 3H), 3.24 (dd, *J* = 7.1, 1.5 Hz, 2H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 171.9, 153.2, 137.7, 133.3, 132.5, 121.0, 103.3, 60.8, 56.0, 51.9, 38.0. LRMS (ESI) 267.0 ([M+H]⁺); HRMS (ESI-Orbitrap) *m/z*: [M+Na]⁺ calcd for C₁₄H₁₈O₅Na; [M+Na]⁺: 289.1046, found 289.1049.

(4R,5R)-4-Hydroxy-5-(3,4,5-Trimethoxyphenyl)Dihydrofuran-2(3H)-one (7).—AD-mix-β (3.926 g), NaHCO₃ (706 mg, 8.4 mmol), and methanesulfonamide (267 mg, 2.8 mmol) were dissolved in *t*-BuOH (7 mL) and water (14 mL). After the mixture was cooled to 0 °C, methyl ester **8** (746 mg, 2.8 mmol) in *t*-BuOH (7 mL) was added. The mixture was stirred at 0 °C for 22 h. After this period, sodium sulfite (5.0 g) was added. The mixture was stirred for 1 h at 23 °C and extracted with EtOAc (3x). The combined organic layer was dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was then purified by column chromatography on silica gel (50–80% EtOAc in hexanes) to afford lactone **7** (700 mg, 90 %) as a white amorphous solid. [α]_D²⁰ – 23.9 (*c* 0.41, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ: 6.54 (s, 2H), 5.38 (d, *J* = 3.3 Hz, 1H), 4.62 – 4.56 (m, 1H),

3.82 (s, 6H), 3.78 (s, 3H), 2.85 (ddd, $J = 17.5, 5.0, 1.5$ Hz, 1H), 2.71 (d, $J = 17.5$ Hz, 1H), 2.06 (m, 1H; OH); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ : 175.4, 153.6, 137.9, 128.5, 103.0, 85.1, 70.1, 60.7, 56.1, 38.4. LRMS (ESI) 269.0 $[M+H]^+$; HRMS (ESI-Orbitrap) m/z : $[M+H]^+$ calcd for $C_{13}H_{16}O_6 + H$ 269.1020, found 269.1024.

(4R,5R)-4-(Methoxymethoxy)-5-(3,4,5-Trimethoxyphenyl)Dihydrofuran-2(3H)-one (10a).—To a stirred solution of lactone **7** (272 mg, 1.02 mmol) in distilled THF (4 mL) at 0 °C under argon atmosphere were consecutively added DIPEA (1.77 mL, 10.2 mmol), TBAI (75 mg, 0.20 mmol), and MOM-Cl (0.44 mL, 5.80 mmol). The reaction mixture was then stirred at 50 °C for 24 h. After dilution with CH_2Cl_2 , the mixture was washed with water, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (60% EtOAc in hexane) to give MOM protected lactone **10a** (300 mg, 95%) as a yellow amorphous solid. $[\alpha]_D^{20} - 46.1$ (c 0.79, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ : 6.58 (d, $J = 0.6$ Hz, 2H), 5.43 (d, $J = 3.8$ Hz, 1H), 4.56 (ddd, $J = 5.1, 3.8, 0.9$ Hz, 1H), 4.32 (d, $J = 7.1$ Hz, 1H), 4.14 (d, $J = 7.1$ Hz, 1H), 3.85 (s, 6H), 3.83 (s, 3H), 3.06 (s, 3H), 2.88 (dd, $J = 17.5, 5.3$ Hz, 1H), 2.73 (dd, $J = 17.5, 0.9$ Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ : 174.9, 153.2, 137.9, 129.3, 103.6, 95.1, 84.6, 74.1, 60.8, 56.1, 55.4, 37.5. LRMS (ESI) 647.2 $[2M+Na]^+$; HRMS (ESI-Orbitrap) m/z : $[M+Na]^+$ calcd for $C_{15}H_{20}O_7Na$ 335.1101, found 335.1103.

(4R,5R)-4-(Methoxymethoxy)-5-(3,4,5-Trimethoxyphenyl)Tetrahydrofuran-2-ol (6).—To a stirred solution of lactone **10a** (240 mg, 0.77 mmol) in CH_2Cl_2 (6 mL) at -78 °C under argon atmosphere was added DIBAL-H (0.92 mL, 0.92 mmol) and the resulting mixture was stirred at the same temperature for 2 h. After this period, the reaction mixture was quenched by the addition of MeOH (3 mL) and warmed to 23 °C. Then, saturated aqueous solution of sodium potassium tartarate was added and stirred vigorously at 23 °C for 2 h until it forms white suspension. The suspension was filtered through a plug of Celite and solvents were removed under reduced pressure.

To a crude lactol, DMAP (17 mg, 0.14 mmol), Et_3N (0.50 mL, 3.59 mmol) and Ac_2O (0.17 mL, 1.80 mmol) were added at 0 °C under argon atmosphere and the resulting mixture was stirred for 2 h. Upon completion, solvents were removed under reduced pressure and the crude product was purified by column chromatography over silica gel (50 % EtOAc in hexanes) to give acetate **6** (240 mg) as the major isomer and the corresponding minor anomer (16 mg) as colorless oils in 88 % over two steps. Acetate **6**: 1H NMR (400 MHz, $CDCl_3$) δ : 6.61 (s, 1H), 6.59 (dd, $J = 6.1, 3.3$ Hz, 1H), 5.09 (d, $J = 3.8$ Hz, 1H), 4.45 (ddd, $J = 5.8, 3.8, 1.9$ Hz, 1H), 4.30 (d, $J = 7.0$ Hz, 1H), 4.12 (d, $J = 6.9$ Hz, 1H), 3.84 (s, 6H), 3.81 (s, 3H), 3.06 (s, 3H), 2.53 (ddd, $J = 14.7, 6.1, 1.9$ Hz, 1H), 2.37 (ddd, $J = 14.7, 6.1, 3.3$ Hz, 1H), 2.06 (s, 3H); $^{13}C\{^1H\}$ NMR (Major anomer, 101 MHz, $CDCl_3$) δ : 170.2, 152.9, 137.5, 131.1, 104.2, 97.4, 95.1, 83.7, 76.6, 60.8, 56.1, 55.2, 40.4, 21.2; LRMS (ESI) 735.2 ($[2M+Na]^+$); HRMS (ESI-Orbitrap) m/z : $[M+Na]^+$ calcd for $C_{17}H_{24}O_8Na$ 379.1363, found 379.1360; Minor Isomer: 1H NMR (400 MHz, $CDCl_3$) δ : 6.63 (s, 2H), 6.42 (d, $J = 5.8$ Hz, 1H), 5.08 (d, $J = 4.5$ Hz, 1H), 4.42 – 4.35 (m, 2H), 4.23 – 4.17 (m, 1H), 3.88 – 3.85 (s, 6H), 3.83 (s, $J = 0.9$ Hz, 3H), 3.11 (s, 3H), 2.50 – 2.42 (m, 1H), 2.40 – 2.34 (m, 1H), 2.13 (s, 3H);

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ : 170.4, 152.8, 132.14, 129.8, 104.4, 98.0, 95.2, 86.4, 75.4, 60.8, 56.0, 55.2, 39.3, 21.4; LRMS (ESI) 357.1 $[\text{M}+\text{H}]^+$.

(4R,5R)-4-(Methoxymethoxy)-5-(3,4,5-Trimethoxyphenyl)Tetrahydrofuran-2-yl Acetate (11).—To a stirred solution of lactone **7** (95 mg, 0.354 mmol) in CH_2Cl_2 (3 mL) at 0 °C under argon atmosphere were added 2,6-lutidine (0.12 mL, 1.06 mmol) and TBSOTf (0.12 mL, 0.53 mmol). The reaction mixture was warmed to 23 °C and stirred for 3h. When the reaction was finished, the mixture was quenched by the addition of saturated aqueous NaHCO_3 and extracted with dichloromethane. The extracts were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (40 % EtOAc in hexanes) to give silyl ether derivative (69 mg, 51 %) as an orange amorphous solid. $[\alpha]_{\text{D}}^{20}$ – 34.7 (*c* 0.29, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ : 6.54 (s, 2H), 5.37 (d, *J* = 3.5 Hz, 1H), 4.55 (ddd, *J* = 4.8, 3.5, 0.7 Hz, 1H), 3.85 (s, 6H), 3.82 (s, 3H), 2.87 (dd, *J* = 17.1, 4.8 Hz, 1H), 2.59 (dd, *J* = 17.1, 0.7 Hz, 1H), 0.67 (s, 9H), –0.13 (s, 3H), –0.34 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ : 175.5, 153.1, 138.0, 129.9, 103.8, 86.0, 71.5, 60.8, 56.1, 40.2, 25.3, 17.7, –5.4, –5.6; LRMS (ESI) 405.2 $[\text{M}+\text{Na}]^+$.

The title compound was prepared from above lactone (55 mg) was reduced and protected as acetate derivatives following the procedure described for the preparation of acetate **6**. The compound was purified by flash column chromatography over silica gel (20% EtOAc in hexanes) to give acetate **11** (50 mg, 81% over two steps) as a white amorphous solid. $[\alpha]_{\text{D}}^{20}$ – 13.6 (*c* 0.5, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ : 6.60 (dd, *J* = 5.9, 3.8 Hz, 1H), 6.56 (d, *J* = 0.5 Hz, 2H), 5.03 (d, *J* = 3.6 Hz, 1H), 4.43 (ddd, *J* = 5.4, 3.6, 1.9 Hz, 1H), 3.83 (s, 6H), 3.78 (s, 3H), 2.44 – 2.27 (m, 2H), 2.05 (s, 3H), 0.67 (s, 9H), –0.17 (s, 3H), –0.35 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ : 170.3, 152.7, 137.5, 131.7, 104.6, 97.9, 85.2, 73.7, 60.7, 56.0, 43.1, 25.4, 21.2, 17.8, –5.4, –5.5. LRMS (ESI) 449.2 $[\text{M}+\text{Na}]^+$; HRMS (ESI-Orbitrap) *m/z*: $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{34}\text{O}_7\text{SiNa}$ 449.1966, found 449.1969.

(4R,5R)-4-((2-Methoxyethoxy)Methoxy)-5-(3,4,5-Trimethoxyphenyl)Tetrahydrofuran-2-yl Acetate (12).—To a stirred solution of lactone **7** (125 mg, 0.47 mmol) in distilled THF (2 mL) at 0 °C under argon atmosphere were consecutively added DIPEA (0.81 mL, 4.7 mmol), TBAI (43 mg, 0.12 mmol) and MEM-Cl (0.27 mL, 2.33 mmol). The resulting reaction mixture was stirred at 55 °C for 72 h. Upon completion, the mixture was diluted with EtOAc and washed with water. The organic phase was dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (80% EtOAc in hexanes) to give MEM protected lactone (131 mg, 79%) as a yellow amorphous solid. $[\alpha]_{\text{D}}^{20}$ – 25.5 (*c* 0.29, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ : 6.57 (s, 2H), 5.43 (d, *J* = 3.8 Hz, 1H), 4.62 (ddd, *J* = 5.0, 3.8, 1.0 Hz, 1H), 4.42 (d, *J* = 7.3 Hz, 1H), 4.23 (d, *J* = 7.3 Hz, 1H), 3.85 (s, 6H), 3.83 (s, 3H), 3.45 (ddd, *J* = 10.6, 5.6, 3.3 Hz, 1H), 3.41 – 3.36 (m, 2H), 3.32 (s, 3H), 3.22 (ddd, *J* = 10.6, 5.3, 3.4 Hz, 1H), 2.87 (dd, *J* = 17.6, 5.2 Hz, 1H), 2.74 (dd, *J* = 17.5, 1.0 Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ : 175.0, 153.2, 137.9, 129.3, 103.5, 93.9, 84.6, 74.0, 71.4, 67.0, 60.8, 58.9, 56.1, 37.4; LRMS (ESI) 379.4 $[\text{M}+\text{Na}]^+$.

The title compound was prepared from above lactone (111 mg) following the procedure described for the preparation of acetate **6**. The compound was purified by flash column chromatography (20% EtOAc in hexane) to give acetate **12** (50 mg, 72 % over two steps) as a white amorphous solid. $[\alpha]_D^{20} + 4.1$ (*c* 0.69, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ: 6.58 (s, 2H), 6.55 (dd, *J* = 6.1, 3.3 Hz, 1H), 5.07 (d, *J* = 3.8 Hz, 1H), 4.48 (ddd, *J* = 5.8, 3.8, 1.7 Hz, 1H), 4.37 (d, *J* = 7.2 Hz, 1H), 4.19 (d, *J* = 7.1 Hz, 1H), 3.81 (s, 6H), 3.78 (s, 3H), 3.41 (ddd, *J* = 10.4, 5.8, 3.3 Hz, 1H), 3.37 – 3.32 (m, 2H), 3.29 (s, 3H), 3.17 (ddd, *J* = 10.4, 5.2, 3.3 Hz, 1H), 2.50 (ddd, *J* = 14.7, 6.1, 1.8 Hz, 1H), 2.34 (ddd, *J* = 14.7, 6.0, 3.3 Hz, 1H), 2.03 (s, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ: 170.2, 152.8, 137.3, 131.1, 104.1, 97.4, 93.9, 83.7, 76.5, 71.4, 66.7, 60.8, 58.8, 56.0, 40.3, 21.2; LRMS (ESI) 423.2 [M+Na]⁺; HRMS (ESI-Orbitrap) *m/z*: [M+Na]⁺ calcd for C₁₉H₂₈O₉Na 423.1626, found 423.1623.

General procedure for the allylation of tetrahydrofuranyl acetate

A solution of tetrahydrofuranyl acetate in distilled CH₂Cl₂ at –78 °C under argon atmosphere was treated with allyltrimethylsilane (4.0 equiv) and Lewis acid. The resulting reaction mixture was stirred at –78 °C for 3 h. After this period, the reaction mixture was treated with saturated aqueous Na₂HPO₄ (1 mL per mmol of acetate). The aqueous layer was then extracted three times with CH₂Cl₂, and the collected organic phases were dried (Na₂SO₄), filtered, and concentrated under reduced pressure.

Preparation of (2R,3R,5S)-5-Allyl-3-(Methoxymethoxy)-2-(3,4,5-Trimethoxyphenyl) Tetrahydrofuran (**13a**) and (2R,3R,5R)-5-Allyl-3-(Methoxymethoxy)-2-(3,4,5-Trimethoxyphenyl) Tetrahydrofuran (**14a**) mixture.—

Following the general procedure described above and starting from acetate **6** (18 mg, 0.05 mmol) in CH₂Cl₂ (1 mL), compounds **13a** and **14a** (14.4 mg, 84% yield) were obtained as a colorless oil after the crude residue was purified by column chromatography over silica gel (5–20% EtOAc in hexanes). The results are summarized in Table S1. ¹H NMR (mixture, 400 MHz, CDCl₃) δ: 6.64 (s, 3.2H), 6.61 (s, 2H), 6.00 – 5.74 (m, 2.6H), 5.18 – 5.04 (m, 5.2H), 4.93 (d, *J* = 3.3 Hz, 1H), 4.73 (d, *J* = 4.1 Hz, 1.6H), 4.58 – 4.44 (m, 1H), 4.41 – 4.25 (m, 5.3H), 4.18 – 4.01 (m, 4.8H), 3.85 (s, 15.2H), 3.81 (s, 4.6H), 3.81 (s, 3H), 3.07 (s, 4.8H), 3.04 (s, 3H), 2.70 – 2.57 (m, 1.7H), 2.52 – 2.29 (m, 5.8H), 2.19 (ddd, 1H), 1.91 (ddd, *J* = 13.2 Hz, 1H), 1.85 (ddd, *J* = 11.4, 6.0 Hz, 1.7H); ¹³C {¹H} NMR (mixture, 100 MHz, CDCl₃) δ: 152.8, 134.8, 134.1, 133.6, 133.1, 117.4, 116.9, 104.2, 104.0, 95.0, 84.30, 83.7, 78.7, 77.8, 77.6, 77.1, 60.8, 56.0, 55.1, 40.4, 40.2, 38.8, 38.3; LRMS (ESI) *m/z*: 361.2 [M+Na]⁺; HRMS (ESI-Orbitrap) *m/z*: [M+Na]⁺ calcd for C₁₈H₂₆O₆Na 361.1622, found 361.1624.

Preparation of (((2R,3R,5S)-5-Allyl-2-(3,4,5-Trimethoxyphenyl)Tetrahydrofuran-3-yl)oxy)(tert-butyl)Dimethylsilane (**13b**).—

Following the general procedure described above and starting from acetate **11** (21.7 mg, 0.05 mmol) in CH₂Cl₂ (1 mL), the title compound **13b** (16.8 mg, 81% yield) was prepared as a colorless oil after the crude residue was purified by column chromatography over silica gel (5–20% EtOAc in hexanes). The results are summarized in Table S1. $[\alpha]_D^{20} - 62.0$ (*c* 0.79, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ: 6.59 (s, 2H), 5.99 – 5.85 (m, 1H), 5.18 – 5.04 (m, 2H), 4.73 (d, *J* = 3.7 Hz, 1H), 4.30 (td, *J* = 3.7, 1.8 Hz, 1H), 4.22 – 4.13 (m, 1H), 3.84 (s,

6H), 3.79 (s, 3H), 2.67 (dt, $J = 13.6, 6.7$ Hz, 1H), 2.48 (dt, $J = 13.8, 6.9$ Hz, 1H), 2.35 (ddd, $J = 13.6, 8.5, 5.4$ Hz, 1H), 1.80 (ddd, $J = 13.2, 4.4, 1.7$ Hz, 1H), 0.68 (s, 9H), -0.13 (s, 3H), -0.37 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ : 152.6, 135.3, 133.9, 116.6, 104.6, 85.9, 77.4, 74.6, 60.7, 55.9, 41.0, 40.6, 25.5, 17.7, -5.3 , -5.6 ; LRMS (ESI) 431.2 $[\text{M}+\text{Na}]^+$; HRMS (ESI-Orbitrap) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{37}\text{O}_5\text{Si}$ 409.2405, found 409.2401.

Preparation of (((2R,3R,5S)-5-Allyl-2-(3,4,5-Trimethoxyphenyl)Tetrahydrofuran-3-yl)oxy)(tert-butyl)Dimethylsilane (13c).—

Following the general procedure described above and starting from acetate **12** (20 mg, 0.05 mmol) in CH_2Cl_2 (1 mL), the title compound **13c** (6.3 mg, 33% yield) was prepared as a colorless oil after the crude residue was purified by column chromatography over silica gel (40% EtOAc in hexanes). The results are summarized in Table S1. $[\alpha]_{\text{D}}^{20} -85.0$ (c 0.12, CHCl_3); ^1H NMR (800 MHz, CDCl_3) δ : 6.63 (s, 2H), 5.91 – 5.86 (m, 1H), 5.15 (dd, $J = 35.1, 13.7$ Hz, 2H), 4.96 (d, $J = 3.2$ Hz, 1H), 4.53 (dq, $J = 12.2, 6.1$ Hz, 1H), 4.49 (d, $J = 7.2$ Hz, 1H), 4.43 (t, $J = 3.7$ Hz, 1H), 4.28 (d, $J = 7.2$ Hz, 1H), 3.88 (s, 6H), 3.84 (s, 3H), 3.44 (ddd, $J = 10.7, 6.2, 3.2$ Hz, 1H), 3.41 – 3.36 (m, 2H), 3.35 (s, 3H), 3.19 (ddd, $J = 10.7, 5.5, 3.2$ Hz, 1H), 2.51 (dt, $J = 13.2, 6.3$ Hz, 1H), 2.41 (dt, $J = 14.0, 6.9$ Hz, 1H), 2.25 (dd, $J = 13.3, 5.9$ Hz, 1H), 1.93 (ddd, $J = 13.6, 9.6, 4.5$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (200 MHz, CDCl_3) δ : 152.9, 137.2, 134.2, 133.8, 117.5, 104.1, 94.0, 83.8, 78.7, 77.8, 71.6, 66.6, 60.9, 59.0, 56.1, 40.3, 38.8; LRMS (ESI) 405.1 $[\text{M}+\text{Na}]^+$; HRMS (ESI-Orbitrap) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{30}\text{O}_7\text{Na}$ 405.1884, found 405.1882.

(2S,3aR,9bR)-2-Allyl-6,7,8-Trimethoxy-3,3a,5,9b-Tetrahydro-2H-furo[3,2-c]isochromene (17).—To a stirred solution of acetate **6** (13.2 mg, 0.037 mmol) in CH_2Cl_2 (2.4 mL) at -78°C under argon atmosphere were added allyltrimethylsilane (24 μL , 0.148 mmol) and SnBr_4 (26 mg, 0.059 mmol, 1.6 equiv). The reaction mixture was stirred for 3 h at the same temperature and the reaction progress was monitored by TLC. When the starting material was completely consumed, additional portion of SnBr_4 (33 mg, 0.075 mmol, 2.0 equiv) was added at 0°C and the resulting mixture was warmed to 23°C overnight. After this period, the reaction mixture was quenched by the addition of saturated aqueous Na_2HPO_4 (0.4 mL) and extracted with dichloromethane (2x). The extracts were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. NMR analysis of the unpurified crude product showed a pair of diastereomers in a 4:1 ratio (*cis:trans* diastereomers). The crude product was purified by column chromatography over silica gel (10% EtOAc in hexanes) to give **17** and **18** (5.9 mg, 52%) as a colorless oil. $[\alpha]_{\text{D}}^{20} +25.6$ (c 0.67, CHCl_3); *cis*-isomer **17** (major): ^1H NMR (400 MHz, CDCl_3) δ : 6.79 (s, 1H), 5.96 – 5.64 (m, 1H), 5.21 – 4.97 (m, 2H), 4.90 (d, $J = 15.1$ Hz, 1H), 4.42 (d, $J = 15.1$ Hz, 1H), 4.30 (d, $J = 3.3$ Hz, 1H), 4.16 (ddd, $J = 6.8, 3.3, 1.7$ Hz, 1H), 4.02 (qd, $J = 7.4, 5.8$ Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 2.65 – 2.44 (m, 2H), 2.43 – 2.29 (m, 1H), 1.81 (ddd, $J = 14.0, 7.2, 1.7$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ : 152.9, 149.0, 141.7, 134.7, 126.5, 121.8, 117.1, 108.7, 78.1, 75.4, 63.3, 60.9, 60.7, 56.1, 40.3, 39.0; LRMS (ESI) 307.1 $[\text{M}+\text{H}]^+$; HRMS (ESI-Orbitrap) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{22}\text{O}_5$ 329.1359, found 329.1357; *Trans*-isomer **18** (minor): ^1H NMR (400 MHz, CDCl_3) δ : 6.79 (s, 1H), 5.92 – 5.76 (m, 1H), 5.18 – 5.04 (m, 2H), 4.91 (d, $J = 15.0$ Hz, 1H), 4.61 (d, $J = 3.0$ Hz, 1H), 4.45 – 4.32 (m, 2H), 4.26 – 4.18 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 2.48 (dt, $J = 12.6,$

6.2 Hz, 1H), 2.34 (dt, $J = 14.0, 7.0$ Hz, 1H), 2.26 (dd, $J = 13.5, 5.7$ Hz, 1H), 1.94 (ddd, $J = 13.6, 9.8, 4.8$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ : 152.8, 148.8, 141.4, 134.2, 127.2, 121.0, 117.3, 108.4, 77.6, 77.4, 74.5, 62.8, 60.7, 60.6, 56.0, 39.9, 39.4; LRMS (ESI) 307.1 $[\text{M}+\text{H}]^+$.

(2S,3aR,9bR)-6,7,8-Trimethoxy-2-Propyl-3,3a,5,9b-Tetrahydro-2H-furo[3,2-c]isochromene (19).—To a stirred of isochromene **17** (47.4 mg, 0.156 mmol) in EtOAc (2 mL) at 23 °C was added 10 % Pd/C (10 mg). The resulting solution was stirred at 23 °C under a hydrogen filled balloon over 12 h. Upon completion, the mixture was filtered through a plug of Celite and solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography (20 % EtOAc in hexane) to give propyl derivative **19** (42.2 mg, 88 %). $[\alpha]_{\text{D}}^{20} +15.3$ (c 0.40, CHCl_3); reported $[\alpha]_{\text{D}}^{26} +16.5$ (c 1.02, CHCl_3)¹⁷; ^1H NMR (400 MHz, CDCl_3) δ : 6.80 (s, 1H), 4.89 (d, $J = 15.0$ Hz, 1H), 4.41 (d, $J = 15.1$ Hz, 1H), 4.26 (d, $J = 3.3$ Hz, 1H), 4.20 – 4.09 (m, 1H), 3.93 (q, $J = 7.1$ Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 2.52 (dt, $J = 14.3, 7.3$ Hz, 1H), 1.80 – 1.69 (m, 2H), 1.61–1.52 (m, 1H), 1.47 – 1.36 (m, 2H), 0.92 (t, $J = 7.3$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ : 152.8, 148.9, 141.6, 126.6, 121.8, 108.7, 78.6, 77.4, 75.2, 63.3, 60.9, 60.7, 56.1, 39.6, 38.1, 19.6, 14.1; LRMS (ESI) 309.1 $[\text{M}+\text{H}]^+$.

(2S,3aR,9bR)-6,7,8-Trimethoxy-2-Propyl-2,3,3a,9b-Tetrahydro-5H-furo[3,2-c]isochromen-5-one (20).—To a solution of propyl derivative **19** (41.2 mg, 0.135 mmol) in CH_2Cl_2 (4 mL), pyridine (54 μL , 0.67 mmol) and CrO_3 (40 mg, 0.40 mmol) were added and stirred for 36 h at 23 °C. After this period, the reaction mixture was concentrated under reduced pressure and ethyl acetate (10 mL) was added and filtered. The filtrate was washed with aq. CuSO_4 solution followed by water. The organic phase was dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. Flash chromatography over silica gel (30% EtOAc in hexanes) provided δ -valerolactone **20** (17.2 mg, 40%; 60% brsm) as a pale-yellow oil with the recovered starting material **19** (13.7 mg). $[\alpha]_{\text{D}}^{20} +20.4$ (c 0.31, CHCl_3); reported¹⁸ $[\alpha]_{\text{D}}^{26} + 21.5$ (c 0.50, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ : 6.78 (s, 1H), 4.94 (ddd, $J = 5.8, 2.9, 1.0$ Hz, 1H), 4.51 (d, $J = 2.9$ Hz, 1H), 4.25 – 4.06 (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), 2.16 (ddd, $J = 14.3, 5.5, 1.1$ Hz, 1H), 1.76 – 1.69 (m, 1H), 1.66 – 1.58 (m, 1H), 1.45 – 1.31 (m, 2H), 0.91 (t, $J = 7.4$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ : 159.8, 157.9, 156.4, 144.2, 132.5, 111.2, 108.0, 79.4, 78.9, 75.0, 61.7, 61.0, 56.1, 39.0, 38.0, 19.1, 13.9; LRMS (ESI) 323.0 $[\text{M}+\text{H}]^+$; HRMS (ESI-Orbitrap) m/z : $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{17}\text{H}_{22}\text{O}_6\text{Na}$ 345.1309, found 345.1306.

(+)-Monocerin (1).—To a solution of δ -valerolactone **20** (13.4 mg, 0.042 mmol) in dry CH_2Cl_2 (1 mL) at -10 °C under argon atmosphere was added BCl_3 (1.0 M in DCM, 50 μL , 0.11 mmol). The mixture was stirred at -10 °C for 2 h and the reaction was quenched by the addition of saturated aqueous NaHCO_3 (1 mL). The mixture was extracted with ethyl acetate and the organic layer was washed with brine, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. Purification by column chromatography over silica gel (20% EtOAc in hexanes) gave (+)-monocerin (**1**) (4.9 mg, 41% yield; 88% yield brsm) as a colorless oil with the recovered starting material **20** (7.6 mg). $[\alpha]_{\text{D}}^{20} +57.8$ (c 0.29, CHCl_3); reported⁶ $[\alpha]_{\text{D}}^{24} + 53.0$ (c 0.85, MeOH); ^1H NMR (400 MHz, CDCl_3) δ : 11.28 (s, 1H), 6.59 (s, 1H),

5.05 (ddd, $J = 6.3, 3.2, 1.2$ Hz, 1H), 4.54 (d, $J = 3.1$ Hz, 1H), 4.12 (dq, $J = 8.6, 6.3$ Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.59 (ddd, $J = 14.6, 8.6, 6.2$ Hz, 1H), 2.16 (ddd, $J = 14.5, 5.9, 1.2$ Hz, 1H), 1.74–1.65 (m, 1H), 1.62–1.52 (m, 1H), 1.49–1.29 (m, 2H), 0.91 (t, $J = 7.3$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ : 167.9, 158.8, 156.4, 137.5, 131.3, 104.5, 102.2, 81.4, 78.9, 74.6, 60.9, 56.4, 39.2, 38.2, 19.3, 14.1; LRMS (ESI) 309.1 $[\text{M}+\text{H}]^+$ HRMS (ESI-Orbitrap) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{21}\text{O}_6$ 309.1333, found 309.1335.

(+)-Acetylmonocerin (2).—Acetic anhydride (75 μL , 0.8 mmol) and DMAP (catalytic amount) were added to a solution of (+)-monocerin (**1**) (2.2 mg, 0.007 mmol) in 0.2 mL of distilled pyridine at 0 °C under argon atmosphere, and the mixture was stirred at 23 °C for 5 h. After removing the solvent under reduced pressure, the crude product was purified by flash column chromatography on silica gel (33% EtOAc in hexanes) to give (+)-acetylmonocerin (**2**) (2.4 mg, 96% yield) as a white amorphous solid. $[\alpha]_{\text{D}}^{25} +3.6$ (c 0.29, CHCl_3); reported¹⁹ $[\alpha]_{\text{D}}^{24} - 3.0$ (c 0.1, EtOH) for enantiomer of compound **2**; ^1H NMR (800 MHz, CDCl_3) δ : 6.90 (s, 1H), 4.99 (m, 1H), 4.55 (d, $J = 3.1$ Hz, 1H), 4.14 (m, 1H), 3.97 (s, 3H), 3.85 (s, 3H), 2.53 (ddd, $J = 14.5, 8.7, 5.9$ Hz, 1H), 2.42 (s, 3H), 2.13 (dd, $J = 14.3, 5.5$ Hz, 1H), 1.71–1.64 (m, 1H), 1.58–1.54 (m, 1H), 1.44–1.39 (m, 1H), 1.35–1.32 (m, 1H), 0.90 (t, $J = 7.3$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (200 MHz, CDCl_3) δ : 169.3, 159.9, 158.0, 146.1, 143.3, 132.7, 110.4, 109.9, 79.9, 79.0, 74.6, 61.2, 56.3, 39.0, 38.2, 21.0, 19.1, 14.0; LRMS (ESI) 373.1 $[\text{M}+\text{Na}]^+$.

Supplementary Material

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Monocerin, **1** (R = H)
Acetoxy Monocerin **2** (R = Ac)

11- α -Hydroxy Monocerin, **3**

11- β -Hydroxy Monocerin, **4**

Lasionectrin, **5**

Figure 1.
Structures of dihydroisocoumarin natural products **1–5**.

Figure 2.
 Stereochemical analysis of *cis*-allylation reaction.

Scheme 1.
Retrosynthetic analysis of (+)-monocerin

Scheme 2.

Synthesis of allyl derivatives **13a** and **14a**. Reagents and Conditions: (a) $\text{Ph}_3\text{P}^+\text{CH}_2\text{CO}_2\text{HBr}^-$, *t*-BuOK, THF, -78°C to 23°C , 18 h, (65%); (b) TMSCl, dry MeOH, 0°C to 23°C , 18 h (76%); (c) AD-mix- β , NaHCO_3 , MeSO_2NH_2 , *t*-BuOH/ H_2O = 1.1, 0°C , 24 h (90%); (d) DIPEA, MOMCl, TBAI (cat.), THF, 50°C , 24 h (95%); (e) DIBAL-H, Toluene, -78°C ; (f) Et_3N , DMAP, Ac_2O , DCM, 0°C to 23°C , 1.5 h (88%); (g) TBSOTf, 2,6-lutidine, DCM, 0°C to 23°C , 3 h (51%); (h) MEMCl, DIPEA, TBAI, THF, 0°C to 55°C , 72 h (79%); (i) allyltrimethylsilane, SnBr_4 , DCM, -78°C , 3 h, (84%).

Scheme 3.

Synthesis of (+)-monocerin. Reagents and Conditions: (a) SnBr_4 , allyltrimethylsilane, CH_2Cl_2 , -78°C to 23°C , 18 h (52%); (b) H_2 , 10%, Pd-C, EtOAc, 23°C , 12 h (88%); (c) CrO_3 , Pyridine, CH_2Cl_2 , 0°C to 23°C , 36 h (40%, 60% brsm); (d) BCl_3 , CH_2Cl_2 , -10°C , 2 h (41%, 88% brsm); (e) Ac_2O , Pyridine, CH_2Cl_2 , 23°C , 5 h (96%).

Table 1.Allylation of acetate derivatives with various Lewis acids ^a

Entry	Comp.	Lewis Acid (equiv)	Time	Yield (%)	dr (13:14 Ratio)
1	6	SnBr_4 [1.1]	3 h	83.9	62 : 38
2	6	SnBr_4 [2.0]	3 h	75.1	63 : 37
3	6	TiCl_4 [1.1]	3 h	69.4	60 : 40
4	6	TiCl_4 [2.0]	4 h	38.2	58 : 42
5	6	$\text{BF}_3 \cdot \text{OEt}_2$ [1.1]	3 h	52.1	63 : 37
6	6	TMSOTf [1.0]	3 h	57.1	58 : 42
7	11	SnBr_4 [1.1]	3 h	80.7	70 : 30
8	11	TiCl_4 [1.1]	3 h	76	72 : 28
9	12	SnBr_4 [1.1]	3 h	32.7	51 : 49
10 ^b	12	$\text{BF}_3 \cdot \text{OEt}_2$ [1.1]	3 h	36.4	63 : 37

^a All reactions were carried out in CH_2Cl_2 at -78°C and allyltrimethylsilane (4.0 equiv). Ratios were determined by ^1H -NMR analysis;^b 1.5 equivalents of allyl trimethylsilane was added instead of 4 equivalents.

Table 2.

Lewis acids-catalyzed tandem allylation and Oxa-Pictet-Spengler cyclization of acetate derivative **6** and **12**^a

Entry	Comp.	Lewis Acid (equiv, time)	Yield% (13/14)	Yield % (17/18 and ratio)
1	6	SnBr ₄ (1.6, 4 h)	54	22 (3:1)
2 ^b	6	SnBr ₄ (1.6, 4 h) then (2, 12 h)	---	52 (4:1)
3 ^c	6	SnBr ₄ (1.1, 3 h) then (2, 12 h)	---	35 (3.2:1)
4 ^{d,b}	6	SnBr ₄ (1.1, 3 h) then (2, 12 h)	---	42 (3:1)
5 ^c	6	TiCl ₄ (1, 4 h) then (1.5, 12 h)	trace	trace
6 ^b	12	SnBr ₄ (1.6, 3 h), then (2, 12 h)	---	21 (1.7:1)

^a All reactions were carried out in CH₂Cl₂ with 4 equiv of allyltrimethylsilane at -78 °C to 23 °C;^b Additional Lewis acid was added at 0 °C and the reaction mixture was slowly warmed to 23 °C;^c Additional Lewis acid was added at -78 °C and the reaction mixture was warmed to 23 °C;^d After adding 1.1 equivalents of Lewis acid, the reaction mixture was stirred at -78 °C for 3 h.