JOC The Journal of Organic Chemistry
Cite This: J. Org. Chem. XXXX, XXX, XXX−XXX
Article
pubs.acs.org/joc

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

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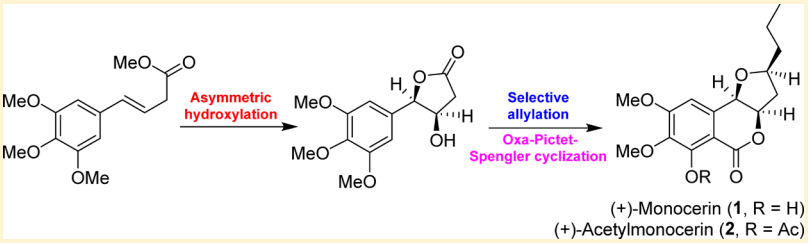
Supporting Information



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 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. We investigated this reaction with a variety of Lewis acids. A selective CrO_3-mediated oxidation of isochroman provided the corresponding lactone derivative. The synthesis is quite efficient and may be useful for the preparation of derivatives.

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.[3−5] Monocerin (**1**, Figure 1), which was first isolated by Aldridge and Turner from *Exserohilum monoceras* (Drechsler), is a dihydroisocoumarin natural product that protects wheat against the powdery mildew *Erysiphe graminis*.[6] Aldridge and Turner also demonstrated monocerin's antifungal properties. Subsequently, Grove and Pople identified monocerin as a constituent of the entomogenous fungus *Fusarium larvarum* Fuckel and showed its insecticidal properties.[7] The assignment of absolute configuration of monocerin was addressed by Grove and Pople as well as by Scott and co-workers.[7,8] Subsequently, the synthesis and biosynthesis of the first polyketide synthase-free intermediate in monocerin was reported by Axford and co-workers.[9] Since then, there have been many reports concerning the phytotoxic properties of monocerin and its derivatives **2**−**4**.[8,10−13] In 2008, Sappapan and co-workers reported potent antimalarial properties of monocerin against the multidrug-resistant strain of *Plasmodium falcifarum* with an IC_{50} value of 680 nM.[14] Its acetate derivative **2** also showed good antimalarial activity (IC_{50} = 820 nM).[14] Lasionectrin (**5**), a dihydronaphthopyrone natural product, was isolated from fermentations of the fungus *Lasionectria* (F-176,994).[15] Like monocerin, lasionectrin also exhibited antimalarial activity, although subsequently weaker than that of monocerin.[15] Monocerin features a 4-oxyisochroman-1-one structural unit and 2,3,5-trisubstituted tetrahydrofuran ring containing all-*cis* stereochemistry.

Structural features and broad-spectrum biological properties of monocerin led to considerable synthetic attention over the years. Mori and Takaishi 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 potential. A number of

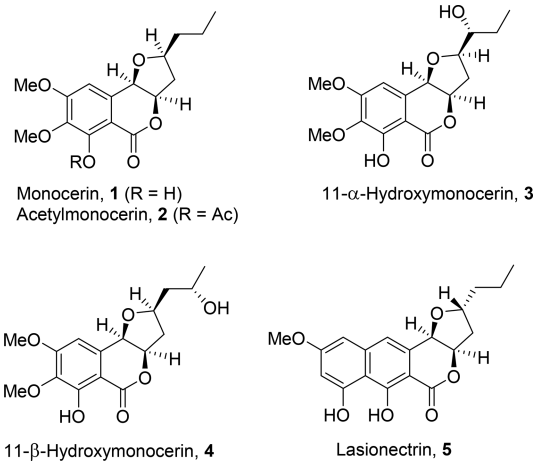


Figure 1. Structures of dihydroisocoumarin natural products **1**−**5**.

Received: February 11, 2019

DOI: 10.1021/acs.joc.9b00414
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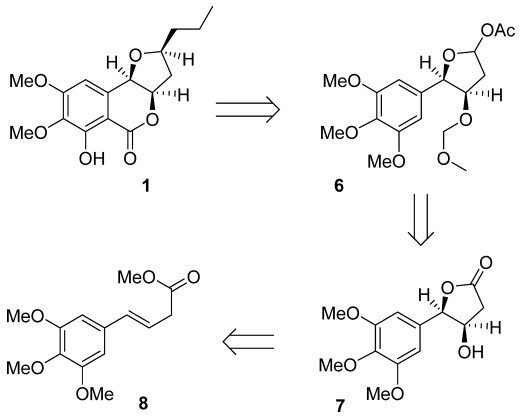
total syntheses of monocerin have been reported.[18−23] Recently, an enantioselective total synthesis of lasionectrin has also been reported.[24] Herein, we report a short and practical synthesis of monocerin and its acetate derivative in optically active form. The synthesis features Sharpless asymmetric dihydroxylation, Lewis acid-catalyzed, oxocarbenium ion-mediated stereoselective allylation, formulation reaction, and CrO_3-mediated oxidation of the benzopyran to a dihydroisocoumarin derivative. The synthesis is potentially amenable toward 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

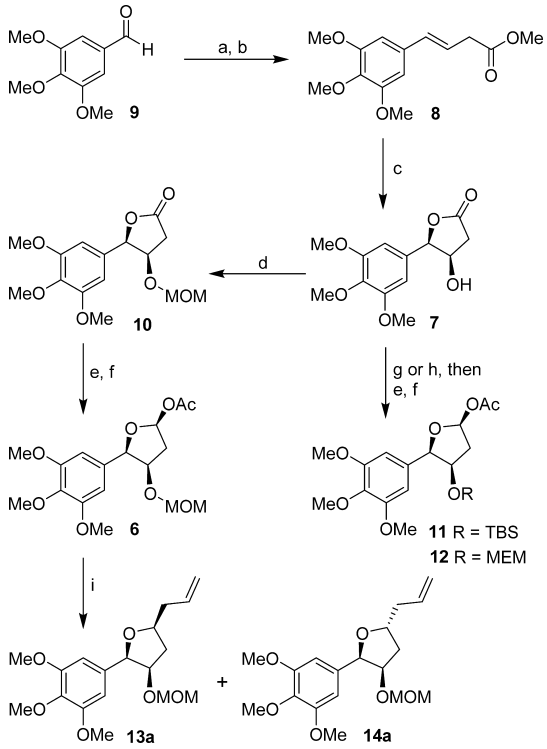
Scheme 1. Retrosynthetic Analysis of (+)-Monocerin



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 are 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 to 23 °C for 18 h.[29,31] The resulting β,γ-unsaturated acid was esterified by exposure to TMSCl in MeOH at 0 to 23 °C for 12 h to provide methyl ester **8** in 49% yield over two 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 a chiralpak IC column. Protection of the hydroxyl group as a MOM ether was

Scheme 2. Synthesis of Allyl Derivatives 13a and 14a[a]



[a]Reagents and conditions: (a) $Ph_3P^+CH_2CO_2HBr^-$, *t*-BuOK, THF, −78 to 23 °C, 18 h, (65%); (b) TMSCl, dry MeOH, 0 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 to 23 °C, 1.5 h (88%); (g) TBSOTf, 2,6-lutidine, DCM, 0 to 23 °C, 3 h (51%); (h) MEMCl, DIPEA, TBAI, THF, 0 to 55 °C, 72 h (79%); (i) allyltrimethylsilane, $SnBr_4$, DCM, −78 °C, 3 h, (84%).

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 the other 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 an acetate group for **6**, **11**, and **12** was assigned by using ^{1}H NMR nuclear Overhauser enhancement spectroscopy (NOESY) experiments (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 equiv of $SnBr_4$ and 4 equiv 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 ^{1}H NMR analysis of diastereomeric protons. We then investigated other Lewis acids under various conditions, and the results are

DOI: 10.1021/acs.joc.9b00414
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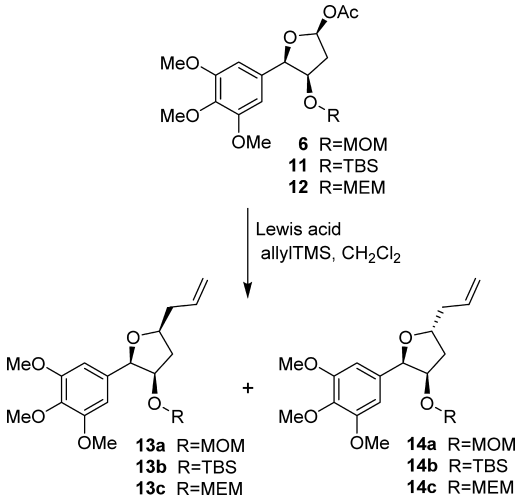
shown in Table 1. The use of 2 equiv of $SnBr_4$ did not improve diastereoselectivity, and the reaction yield was reduced (entry 2). The use of 1.1 equiv of $TiCl_4$ resulted in 69% yield of a mixture of diastereomers (60:40) similar to $SnBr_4$ reaction (entry 3). An increase of Lewis acid to 2 equiv 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 $BF_3{\cdot}OEt_2$ 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 equiv of $SnBr_4$ and 4 equiv of allyltrimethylsilane in CH_2Cl_2 at −78 °C for 3 h. This has resulted in a slight improvement in the diastereomeric ratio (70:30) of allyl derivatives **13b** and **14b** in 81% yield (entry 7). The use of 1.1 equiv of $TiCl_4$ also provided comparable diastereoselectivity and yield (entry 8). Interestingly, allylation of MEM-protected acetate derivative **12** with 1.1 equiv of $SnBr_4$ and 4 equiv 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 equiv of $BF_3{\cdot}OEt_2$ and 1.5 equiv 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 (see the Supporting Information for details).

Table 1. Allylation of Acetate Derivatives with Various Lewis Acids[a]



entry	compd.	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**	$BF_3{\cdot}OEt_2$ (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**	$BF_3{\cdot}OEt_2$ (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 equiv of allyl trimethylsilane was added instead of 4 equiv.

The observed *cis*-diastereoselectivity is consistent with C3-alkoxy-substituted tetrahydrofuranyl substrates examined by Woerpel 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

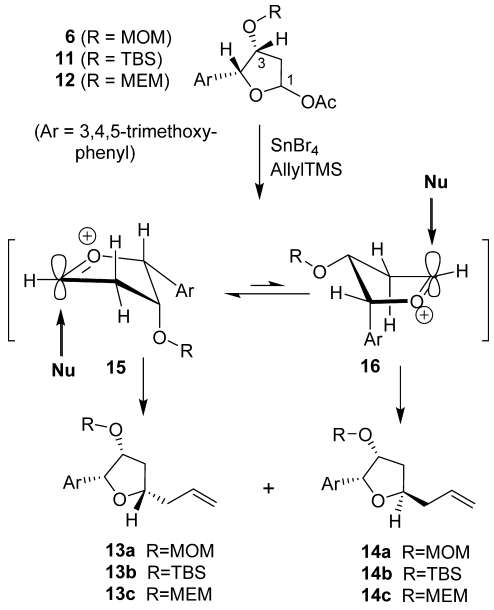


Figure 2. Stereochemical analysis of *cis*-allylation reaction.

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 the 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 to 23 °C in an effort to promote selective allylation, as well as to carry out Friedel−Crafts alkylation through the MOM or MEM groups onto 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 equiv of $SnBr_4$ in the presence of allyltrimethylsilane at −78 to 23 °C for 4 h provided a diastereomic 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, the reaction of MOM derivative **6** was carried out with 1.6 equiv of $SnBr_4$ in the presence of allyltrimethylsilane at −78 to 23 °C for 4 h. Reaction was monitored by TLC and showed complete consumption of the starting acetate derivatives. After this

DOI: 10.1021/acs.joc.9b00414
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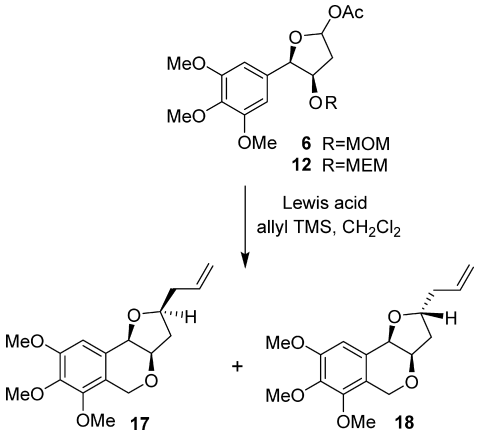
Table 2. Lewis Acid-Catalyzed Tandem Allylation and Oxa-Pictet–Spengler Cyclization of Acetate Derivative 6 and 12[a]



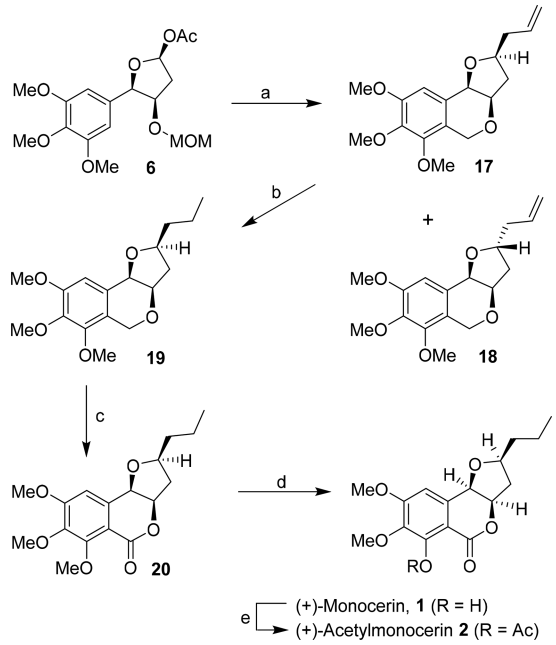
entry	compd.	Lewis acid (equiv, time)	yield % (13/14)	yield % (17/18 and ratio)
1	6	$SnBr_4$ (1.6, 4 h)	54	22 (3:1)
2[b]	6	$SnBr_4$ (1.6, 4 h), then (2, 12 h)		52 (4:1)
3[c]	6	$SnBr_4$ (1.1, 3 h), then (2, 12 h)	-	35 (3.2:1)
4[b,d]	6	$SnBr_4$ (1.1, 3 h), then (2, 12 h)		42 (3:1)
5[c]	6	$TiCl_4$ (1, 4 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 CH_2Cl_2 with 4 equiv of allyltrimethylsilane at −78 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 equiv of Lewis acid, the reaction mixture was stirred at −78 °C for 3 h.

period, the reaction was cooled to 0 °C, 2 equiv of $SnBr_4$ was added, and the resulting mixture was warmed to 23 °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 equivalents of Lewis acid was then investigated at lower temperature. Acetate **6** was treated with 1.1 equiv of $SnBr_4$ at −78 to 23 °C for 3 h, and 2 equiv of $SnBr_4$ was added at −78 °C. The resulting mixture was allowed to warm from −78 to 23 °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 equiv of $SnBr_4$ at −78 °C for 3 h, then 2 equiv of $SnBr_4$ was added at −78 °C, and the reaction was warmed to 23 °C for 12 h. This has resulted to products **17** and **18** as a 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 a 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

Scheme 3. Synthesis of (+)-Monocerin[a]



[a]Reagents and conditions: (a) $SnBr_4$, allyltrimethylsilane, CH_2Cl_2, −78 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 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%).

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 ^{13}C NMR spectra of our synthetic bicyclic ether **19** showed excellent agreement with the reported derivative.[18] Furthermore, NOESY correlation of *cis*-hydrogens in compound **17** supported stereochemistry of **17** and **19** (see the Supporting Information for details). Oxidation of the isochroman ring was carried out with CrO_3 and pyridine in CH_2Cl_2 at 0 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 BCl_3 in CH_2Cl_2 at −10 °C for 2 h to provide synthetic (+)-monocerin **1** in 41% yield (88% brsm). The ^1H NMR and ^{13}C NMR spectra of synthetic (+)-monocerin $\{[\alpha]_D^{23}$ + 57.8 (*c* 0.29, $CHCl_3)\}$ are in complete agreement with spectra reported for the natural (+)-monocerin $\{[\alpha]_D^{24}$ + 53 (*c* 0.85, $CHCl_3)\}$.[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 to 23 °C for 5 h to furnish acetate derivative **2** in 96% yield. $\{[\alpha]_D^{23}$ + 3.6 (*c* 0.29, $CHCl_3)\}$. 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 framework in a one-pot operation. The allylation reaction was investigated with various Lewis acids and by varying protecting groups at

DOI: 10.1021/acs.joc.9b00414
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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 selectivity 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: CH_2Cl_2 from calcium hydride, diethyl ether and tetrahydrofuran from Na/benzophenone, and 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 in thickness, F-254 indicator). Column chromatography was performed using 230−400 mesh silica gel (pore diameter, 60 Å). ^{1}H NMR spectra were recorded at room temperature on a 400 MHz spectrometer. ^{13}C NMR spectra were recorded on 100 and 200 MHz spectrometers. Chemical shifts (δ values) were reported in parts per million and are referenced to the deuterated residual solvent peak. NMR data are reported as follows: 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. Low-resolution mass spectrometry (LRMS) and high-resolution mass spectrometry (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 M 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, H_2O (100 mL) was added, and the mixture was washed with CH_2Cl_2. The aqueous phase was acidified to pH = 1 with a 1 M solution of HCl and extracted with Et_2O (3×). The combined organic extracts were dried over $MgSO_4$, 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 and 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 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 $C_{14}H_{18}O_5Na$, 289.1046; found, 289.1049.

(4*R*,5*R*)-4-Hydroxy-5-(3,4,5-trimethoxyphenyl)-dihydrofuran-2(3*H*)-one (7). AD-mix-β (3.926 g), $NaHCO_3$ (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 (3×). The combined organic layer was dried with Na_2SO_4, 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. $[\alpha]_D^{20}$ − 23.9 (*c* 0.41, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 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, O*H*); ^{13}C{^{1}H} 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.

(4*R*,5*R*)-4-(Methoxymethoxy)-5-(3,4,5-trimethoxyphenyl)-dihydrofuran-2(3*H*)-one (10). 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 **10** (300 mg, 95%) as a yellow amorphous solid. $[\alpha]_D^{20}$ − 46.1 (*c* 0.79, $CHCl_3$). ^{1}H 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{^{1}H} 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.

(4*R*,5*R*)-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 into a 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**: ^{1}H 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{^{1}H} 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: ^{1}H 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}C{^{1}H} NMR (100 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 ([M + H]$^+$).

(4*R*,5*R*)-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

DOI: 10.1021/acs.joc.9b00414
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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. $[\alpha]_D^{20}$ − 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). $^{13}C\{^1H\}$ 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 $[M + Na]^+$.

The title compound was prepared from above lactone (55 mg), 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. $[\alpha]_D^{20}$ − 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). $^{13}C\{^1H\}$ 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 $[M + Na]^+$. HRMS (ESI-Orbitrap) *m*/*z*: $[M + Na]^+$ calcd for $C_{21}H_{34}O_7SiNa$, 449.1966; found, 449.1969.

(4*R*,5*R*)-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. $[\alpha]_D^{20}$ − 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). $^{13}C\{^1H\}$ 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 $[M + Na]^+$.

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, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): 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).$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 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 $C_{19}H_{28}O_9Na$, 423.1626; found, 423.1623.

General Procedure for the Allylation of Tetrahydrofuranyl Acetate. A solution of tetrahydrofuranyl acetate in distilled CH_2Cl_2 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 Na_2HPO_4 (1 mL per mmol of acetate). The aqueous layer was then extracted three times with CH_2Cl_2, and the collected organic phases were dried (Na_2SO_4), 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 CH_2Cl_2 (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, $CDCl_3$): 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). $^{13}C\{^1H\}$ NMR (mixture, 100 MHz, $CDCl_3$): 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 $C_{18}H_{26}O_6Na$, 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 CH_2Cl_2 (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, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): 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). $^{13}C\{^1H\}$ 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 $[M + Na]^+$. HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{37}O_5Si$, 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. $[\alpha]_D^{20}$ − 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). $^{13}C\{^1H\}$ 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 $[M + Na]^+$. HRMS (ESI-Orbitrap) *m*/*z*: $[M + Na]^+$ calcd for $C_{20}H_{30}O_7Na$, 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

DOI: 10.1021/acs.joc.9b00414
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with dichloromethane (2×). 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. $[\alpha]_D^{20}$ + 25.6 (*c* 0.67, $CHCl_3$). *cis*-Isomer **17** (major): ^{1}H 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}C{^{1}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 $[M + H]^+$. HRMS (ESI-Orbitrap) *m*/*z*: $[M + Na]^+$ calcd for $C_{17}H_{22}O_5$, 329.1359; found, 329.1357. *trans*-Isomer **18** (minor): ^{1}H 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}C{^{1}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 $[M + H]^+$.

*(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%). $[\alpha]_D^{20}$ + 15.3 (*c* 0.40, $CHCl_3$); reported $[\alpha]_D^{26}$ + 16.5 (*c* 1.02, $CHCl_3$).[17] ^{1}H 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}C{^{1}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 $[M + H]^+$.

*(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 aqueous $CuSO_4$ 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). $[\alpha]_D^{20}$ + 20.4 (*c* 0.31, $CHCl_3$); reported $[\alpha]_D^{26}$ + 21.5 (*c* 0.50, $CHCl_3$).[18] ^{1}H 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}C{^{1}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 $[M + H]^+$. HRMS (ESI-Orbitrap) *m*/*z*: $[M + Na]^+$ calcd for $C_{17}H_{22}O_6Na$, 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). $[\alpha]_D^{20}$ + 57.8 (*c* 0.29, $CHCl_3$); reported $[\alpha]_D^{24}$ + 53.0 (*c* 0.85, MeOH).[6] ^{1}H 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}C{^{1}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 $[M + H]^+$. HRMS (ESI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{21}O_6$, 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. $[\alpha]_D^{25}$ + 3.6 (*c* 0.29, $CHCl_3$); reported $[\alpha]_D^{24}$ − 3.0 (*c* 0.1, EtOH) for enantiomer of compound **2**.[19] ^{1}H 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}C{^{1}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 $[M + Na]^+$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b00414.

Full spectroscopic data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support of this work was provided by the National Institutes of Health (GM122279) and Purdue University.

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