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Electochemical asymmetric dimerization of cinnamic acid derivatives and application to the enantioselective syntheses of furofuran lignans

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ABSTRACT

A new electrochemical method for the asymmetric oxidative dimerization of cinnamic acid derivatives has been developed. This method enabled the enantioselective syntheses of furofuran lignans, yangambin, sesamin and eudesmin.

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1. Introduction

There are a number of lignans[1] in plants and furofuran lignans, one of the largest subclass of them, have various biological activities such as antitumor, antimitotic, antiviral and antimicrobial activities. The diversity of their bioactivities has attracted the attention of chemists, and the stereocontrolled synthesis of the substituted 3,7-dioxabicyclo[3,3,0]octane skeleton has also been a challenging target to synthetic chemists.[2] Furofuran lignans in our research interests are shown in Fig. 1. Yangambin was first obtained as a dimethylated derivative of lirioresinol-B[3] isolated from tulip tree, *Liriodendron tulipifera* L., and then isolated from Chinese medicinal plant, *Magnolia fargesii*.[4] Yangambin displays selective inhibition against platelet activating factor,[5] protective effects against cardiovascular collapse and anaphylactic shock, anti-allergic properties, analgesic activity, depressant effect in the central nervous system[6] and apoptosis induction.[7] Sesamin,[8] which is a major constituent of sesame seed, is very famous of its antihypertensive,[9] anticancer[10] and antioxidant[9d] properties. Eudesmine has been isolated from *Araucaria angustifolia*,[11] *Humbertia madagascariensis*[12] and the bark of *Mangnolia kubus*[13] up to the present. It shows selective inhibition against platelet activating factor,[14] T-cell proliferation,[15] antioxidant[16] and neuritogenic[17] activities. Concise enantioselective syntheses of yangambin, sesamin and eudesmin have been reported by several research groups.[18]

We have previously developed an asymmetric oxidative dimerization of 3,4,5-trimethoxycinnamic acid derivative **1a** by using Yuzikhin's condition[19] (PbO_2, TFA, CH_2Cl_2) (Scheme 1) and applied it to the efficient syntheses of furofuran lignans, yangambin (5 steps, 30% yield, 100% e.e.) and caruilignan A (6 steps, 30% yield, 100% e.e.).[20] Although other substrates (**1b** ~ **d**) with less oxygen atom on the benzene ring were subjected to the same condition, it was found that a trace amount of the desired bislactones (**2b** ~ **d**) was obtained along with an innegligible amount of aldehyde **3**, which was produced by oxidative cleavage of the double bond. Therefore, we proposed electrochemical oxidation[21] as an alternative method to suppress the generation of **3** by setting factors such as solvent, supporting electrolyte, volumes of electric current and voltage suitable for each substrate. Herein, we report a new electrochemical method for the asymmetric oxidative dimerization of cinnamic acid derivatives and the enantioselective syntheses of furofuran lignans, yangambin, sesamin and eudesmin.

2. Results and discussion

Four substrates (**1a** ~ **d**) for electrochemical oxidation were

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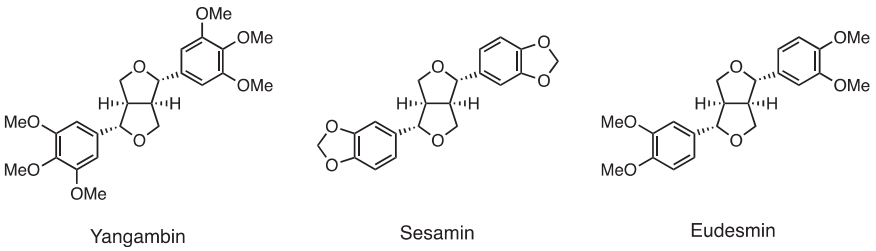
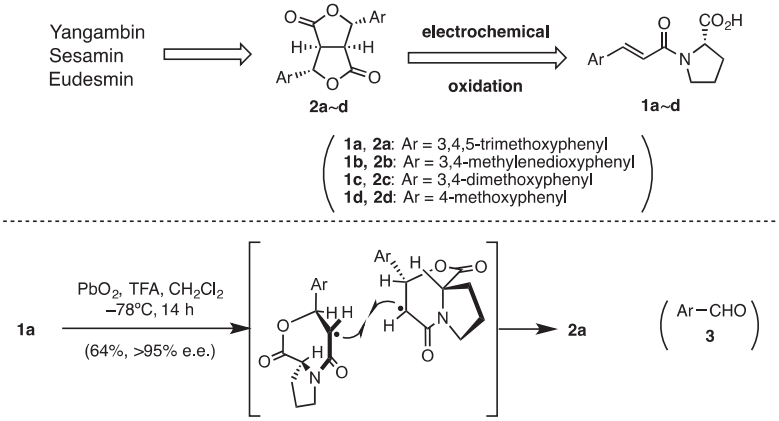


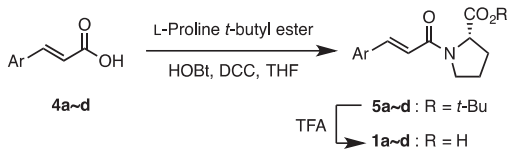
Fig. 1. Structures of furofuran lignans.



Scheme 1. Synthetic strategies for furofuran lignans.

prepared by the same method reported previously[20] (Scheme 2). Cinnamic acid derivatives (**4a** ~ **d**) were condensed with L-proline *t*-butyl ester followed by treatment with TFA to give desired carboxylic acids (**1a** ~ **d**).

After screening suitable reaction conditions, oxidative dimerization of each substrate was found to proceed under Ronlan's electrochemical conditions[22] (Pt anode, *n*-Bu_4NBF_4, CH_2Cl_2/TFA) without the formation of aldehyde **3**. So we examined chemical yield and enantiomeric excess of bislactones (**2a** ~ **d**), which could be obtained under Ronlan's conditions (Table 1). Since chemical yield of **2a** was almost the same between CH_2Cl_2/TFA = 5:1 and 2:1 at 0 °C, solvent ratio was set to CH_2Cl_2/TFA = 5:1 to avoid crystallization of TFA at lower temperature, and same volumes (1.8 mA/cm^3) of electric current flowed. Enantiomeric excess was determined by chiral HPLC analysis of **7a** ~ **d** (**7a**: yangambin, **7b**: sesamin, **7c**: eudesmin), which were obtained from **2a** ~ **d** by reduction with $Ca(BH_4)_2$ and subsequent ether formation. At first, the reaction of 3,4,5-trimethoxycinnamic acid derivative **1a** was performed at various temperatures (r.t., 0 °C, −20 °C, −40 °C), and it became clear that chemical yield as well as enantiomeric excess were higher at lower temperature. Since electric current was sometimes hard to be kept the same flow at −40 °C in spite of getting the best result (52% yield, 91% e.e.), reactions of other substrates were carried out at 0 °C or −20 °C. On 3,4-methylenedioxycinnamic acid derivative **1b**, chemical yield decreased compared to those of 3,4,5-trimethoxycinnamic acid derivative **1a**, but was better (24%) than that of Yuzikhin's racemic synthesis[19] (15%). On the other hand, bislactones **2c** and **2d** were obtained in low chemical yield (8−10%), while enantiomeric excess of 3,4-dimethoxycinnamic acid derivative **2c** was tolerable (85−87% e.e.). The low chemical yields of **2c** and **2d** were due to decompositions of the starting materials **1c** and **1d** during the reactions. Interestingly, in our experiments, chemical yields were better in the case of the substrates with more oxygenated benzene ring, which was opposite to the results of Yuzikhin's racemic synthesis.[19]



Scheme 2. Preparation of the substrates.

Next, we searched for more effective supporting electrolytes and protonic acids in the reaction of 3,4-dimethoxycinnamic acid derivative **1c**. Seven supporting electrolytes were tested and the results were summarized in Table 2. Although the desired bislactone **2c** was obtained with the use of Et_4NClO_4, Et_4NOTFA, *n*-Bu_4NPF_6 or *n*-Bu_4NHSO_4, chemical yield could not be improved dramatically (entry 1−4). Tetraalkylammonium salts with halide ion were not effective to this reaction (entry 5−7). Furthermore, other protonic acids (TfOH, HSO_3F, MsOH, $HClO_4$, $HBF_4 \cdot Et_2O$) were also tested, but a trace amount of desired bislactone **2c** was obtained only when TfOH was used.

In summary, we have developed a new electrochemical method for the asymmetric oxidative dimerization of cinnamic acid derivatives. Three natural furofuran lignans, yangambin, sesamin and eudesmin could be synthesized with high enantiomeric excess by this electrochemical method.

3. Experimental

3.1. General

Optical rotations were recorded with a JASCO DIP-1000 polarimeter. IR spectra were measured with a JASCO FT/IR-230

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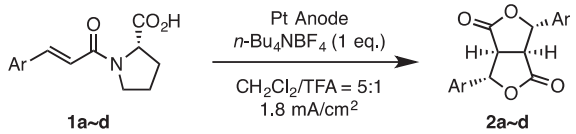
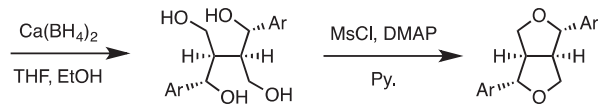
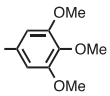
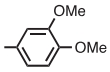
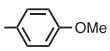
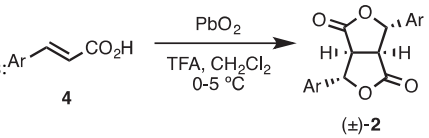
Table 1
Electochemical asymmetric dimerization of **1a** ~ **d** and synthesis of furofuran lignans **7a** ~ **d**.





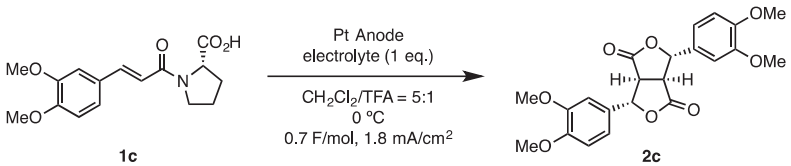
Substrate	Temp. (°C)	F/mol	Yield of **2** (%)	e.e. of **7** (%)	Yield of (±)-**2** (%)[d]
	r.t.	1.4	38	70	
	0	1.4	42	73	14
	−20	1.6	47	82	
	−40[c]	1.4	52	91	
	0	0.7[b]	16 (26)[a]	72	15
	−20	1.3	24 (32)[a]	83	
	0	0.7[b]	10 (22)[a]	85	28
	−20	1.3	8 (9)[a]	87	
	0	0.7[b]	8 (9)[a]	40	53
	−20	1.3	8 (9)[a]	39	

[a] (): based on recovery.
[b] Decomposition of the product was observed when more than 0.7 F/mol passed.
[c] 6 equiv. of *n*-Bu_4NBF_4 were added.
[d] Yuzikhin's racemic synthesis:



spectrophotometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (125 MHz) data were recorded by JEOL JNM AL300 or JEOL JNM LA 500. Chemical shifts (δ) were referenced to the residual solvent peak as the internal standard ($CDCl_3$: $\delta_H = 7.26$, $\delta_C = 77.0$; CD_3OD: $\delta_H = 3.30$, $\delta_C = 49.0$). Mass spectra were recorded on JEOL JMS T100LC. HPLC was performed using a HITACHI UV Detector L-2400 and HITACHI Pump L-2130. Electrochemical oxidation reaction was performed on POTENTIOSTAT/GALVANOSTAT HA-151A. Melting points were measured with a Yanaco micro meltingpoint apparatus and are uncorrected. Column chromatography was performed on Kanto silica gel 60N (0.060−0.200 mm) and TLC was carried out on Merck glass plates precoated with silica gel 60 F254 (0.25 mm).

Table 2
Screening of supporting electrolytes.



Entry	Electrolyte	Yield (%)
1	Et_4NClO_4	12 (21)[a]
2	Et_4NOTFA	12 (24)[a]
3	*n*-Bu_4NPF_6	11 (21)[a]
4	*n*-Bu_4NHSO_4	6 (14)[a]
5	*n*-Bu_4NCl	3
6	*n*-Bu_4NI	0
7	Et_4NBr	0

[a] (): based on recovery.

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3.2. tert-Butyl (S)-1-[(E)-3-(3,4,5-trimethoxyphenyl)propenoyl] pyrrolidine-2-carboxylate (**5a**)

To a solution of HOBt (2.56 g, 19.0 mmol), L-proline *tert*-butyl ester (2.50 g, 14.6 mmol), 3,4,5-trimethoxycinnamic acid (3.48 g, 14.6 mmol) in THF (50 mL) was added DCC (3.92 g, 19.0 mmol) at 0 °C. After stirring at room temperature for 3 h, the reaction mixture was filtered through Celite®. The filtrate was poured into sat. $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with sat. NH_4Cl solution and brine, dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–EtOAc (3:1–1:1) gave **5a** (4.56 g, 80%) as colorless crystals; mp 44–46 °C; $[\alpha]_D^{17}$ −61 (c = 0.90, $CHCl_3$). IR (KBr): 2975, 1736, 1652, 1582, 1506, 1413, 1331, 1153, 1126, 1005 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, several peaks appeared separately as amide rotamers): δ = 1.44 (3H, s), 1.48 (6H, s), 1.86–2.20 (4H, m), 3.72 (1H, m), 3.86 (1H, m), 3.87 (3H, s), 3.89 (2H, s), 3.90 (4H, s), 4.48 (1H, m), 6.47 (1/3H, d, J = 15.3 Hz), 6.63 (2/3H, d, J = 15.3 Hz), 6.71 (2/3H, s), 6.71 (4/3H, s), 7.61 (1/3H, d, J = 15.3 Hz), 7.63 (2/3H, d, J = 15.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.7, 24.6, 27.6, 27.8, 29.1, 31.4, 46.8, 47.0, 55.8, 55.9, 56.2, 56.3, 59.7, 59.8, 81.2, 82.1, 104.8, 104.9, 117.4, 117.5, 130.6, 130.8, 139.4, 142.3, 142.6, 153.3, 164.6, 165.1, 171.4, 171.7. Anal. Calcd for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.16; H, 7.46; N, 3.48.

3.3. (S)-1-[(E)-3-(3,4,5-Trimethoxyphenyl)propenoyl]pyrrolidine-2-carboxylic acid (**1a**)

A solution of **5a** (769 mg, 1.97 mmol) in TFA (8 mL) was stirred at 0 °C for 4 h. The reaction mixture was concentrated in vacuo and the residue was chromatographed over silica gel. Elution with EtOAc gave **1a** (543 mg, 82%) as colorless crystals; mp 100–102 °C; $[\alpha]_D^{17}$ −216 (c = 1.0, $CHCl_3$). IR (KBr): 2941, 1735, 1646, 1583, 1505, 1455, 1333, 1243, 1125, 1002 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.97 (1H, m), 2.07–2.13 (2H, m), 2.64 (1H, br d, J = 12.3 Hz), 3.70 (1H, m), 3.80 (1H, m), 3.89 (3H, s), 3.90 (6 H, s), 4.76 (1H, d, J = 8.1 Hz), 6.58 (1H, d, J = 15.3 Hz), 6.77 (2H, s), 7.76 (1H, d, J = 15.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.7, 27.4, 47.8, 55.9, 56.4, 60.6, 105.4, 115.5, 129.9, 140.1, 145.1, 153.4, 167.6, 172.4. Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.42; H, 6.58; N, 4.24.

3.4. (1S,4S,5S,8S)-4,8-Bis(3,4,5-trimethoxyphenyl)-3,7-dioxabicyclo[3.3.0]octane-2,6-dione (**2a**)

To a 100 mL vial container were added **1a** (101 mg, 0.301 mmol), CH_2Cl_2 (5 mL), n-Bu_4NBF_4 (596 mg, 1.81 mmol) and TFA (1 mL). The reaction vial container was then fitted with a Pt anode (ca. 1.7 cm^2) and a Pt cathode (ca. 1.7 cm^2). A constant current of 3 mA was applied to the solution at −40 °C for 226 min until a total of 1.4 F/mol of charge had been passed. The reaction mixture was concentrated in vacuo. The residue was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–EtOAc (1:1) gave **2a** (36.8 mg, 52%) as colorless crystals; mp 179–181 °C; $[\alpha]_D^{18}$ +31 (c = 0.70, $CHCl_3$). IR (KBr): 2946, 2831, 1768, 1595, 1509, 1456, 1418, 1360, 1327, 1236, 1124, 1009 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.54 (2H, s), 3.82 (6H, s), 3.87 (12H, s), 5.88 (2H, s), 6.49 (4H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 48.4, 56.3, 60.8, 81.5, 101.3, 133.6, 138.3, 153.9, 174.9. Anal. Calcd for $C_{24}H_{26}O_{10}$: C, 60.76; H, 5.52. Found: C, 60.46; H, 5.64.

3.5. (1S,2R,3R,4S)-2,3-Bis(hydroxymethyl)-1,4-bis(3,4,5-trimethoxyphenyl)butane-1,4-diol (**6a**)

$CaCl_2$ (119 mg, 1.07 mmol) and $NaBH_4$ (81.3 mg, 2.15 mmol) were added to EtOH (1.9 mL). After stirring at room temperature for 15 min, **2a** (72.8 mg, 0.153 mmol) in EtOH (0.5 mL) and THF (1.5 mL) was added to the mixture. After stirring at room temperature overnight, the reaction mixture was poured into diluted HCl and extracted with $CHCl_3$. The organic layer was washed with sat. $(NH_4)_2SO_4$ solution, dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with toluene–acetone (1:1–0:1) gave **6a** (33.3 mg, 45%) as colorless crystals; mp 202–204 °C; $[\alpha]_D^{21}$ −29 (c = 0.51, MeOH). IR (KBr): 3306, 2940, 1594, 1508, 1458, 1418, 1332, 1235, 1127, 922 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ = 2.19–2.25 (2H, m), 3.72 (18H, s), 3.75–3.88 (4H, m), 4.81 (2H, d, J = 4.0 Hz), 6.37 (4H, s). ^{13}C NMR (125 MHz, CD_3OD): δ = 46.1, 56.2, 61.0, 61.8, 74.2, 103.9, 137.2, 141.3, 153.9. Anal. Calcd for $C_{24}H_{34}O_{10}$: C, 59.74; H, 7.10. Found: C, 59.28; H, 7.20.

3.6. (1S,3aR,4S,6aR)-1,3a,4,6a-Tetrahydro-1,4-bis(3,4,5-trimethoxyphenyl)-3H,6H-furo[3,4-c]furan (**7a**, yangambin)

To a solution of **6a** (32.3 mg, 66.9 μmol) in pyridine (0.6 mL) were added DMAP (2.5 mg, 20.5 μmol) and MsCl (16.0 mL, 207 mmol) at 0 °C. After stirring at 0 °C for 6 h, the mixture was warmed to room temperature and stirring was continued for 62 h. The reaction mixture was poured into H_2O and extracted with EtOAc. The organic layer was dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–EtOAc (1:1) gave **7a** (19.5 mg, 69%, 91% e.e.). Recrystallization from EtOAc gave colorless crystals (9.1 mg, 47%, 98% e.e.); mp 125–126 °C; $[\alpha]_D^{19}$ +43 (c = 0.38, $CHCl_3$) {Lit.[23] $[\alpha]_D^{29}$ +46 (c = 0.4, $CHCl_3$)}. Enantiomeric excess was determined by HPLC with a CHIRALCEL® OD column (EtOH), 1.0 mL/min; major enantiomer tr = 5.63 min, minor enantiomer tr = 8.62 min. IR (KBr): 2952, 2825, 1589, 1509, 1463, 1421, 1329, 1237, 1129, 998 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.09–3.12 (2H, m), 3.84 (6H, s), 3.88 (12H, s), 3.94 (2H, dd, J = 9.2, 3.7 Hz), 4.31 (2H, dd, J = 9.2, 7.0 Hz), 4.75 (2H, d, J = 3.7 Hz), 6.57 (4H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.3, 56.1, 60.8, 71.9, 85.9, 102.7, 136.7, 137.4, 153.4. Anal. Calcd for $C_{24}H_{30}O_8$: C, 64.56; H, 6.77. Found: C, 64.56; H, 6.81.

3.7. tert-Butyl (S)-1-[(E)-3-(3,4-methylenedioxyphenyl)propenoyl] pyrrolidine-2-carboxylate (**5b**)

To a solution of HOBt (3.08 g, 22.8 mmol), L-proline *tert*-butyl ester (2.99 g, 17.7 mmol), 3,4-methylenedioxycinnamic acid (3.37 g, 17.5 mmol) in THF (60 mL) was added DCC (4.71 g, 22.8 mmol) at 0 °C. After stirring at room temperature for 3 h, the reaction mixture was filtered through Celite®. The filtrate was poured into sat. $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with sat. NH_4Cl solution and brine, dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–EtOAc (2:1–1:2) gave **5b** (4.88 g, 81%) as pale yellow crystals; mp 106–107 °C; $[\alpha]_D^{21}$ −66 (c = 1.0, $CHCl_3$). IR (KBr): 3009, 2975, 2929, 2877, 1736, 1650, 1599, 1501, 1490, 1446, 1421, 1351, 1256, 1166, 1039, 924, 810 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, several peaks appeared separately as amide rotamers): δ = 1.44 (3H, s), 1.48 (6H, s), 1.94–2.23 (4H, m), 3.66–3.82 (2H, m), 4.48 (1H, m), 6.00 (2H, s), 6.41 (1/3H, d, J = 15.3 Hz), 6.57 (2/3H, d, J = 15.3 Hz), 6.80 (1H, d, J = 7.8 Hz), 6.98–7.04 (2H, m), 7.61 (1/3H, d, J = 15.3 Hz), 7.62 (2/3H, d, J = 15.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.7, 24.7, 27.9, 28.0,

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29.2, 31.4, 46.7, 46.9, 59.7, 60.3, 81.1, 82.1, 101.4, 106.4, 108.5, 116.2, 123.9, 129.6, 142.0, 142.2, 148.1, 149.0, 164.8, 165.3, 171.5, 171.7. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.06; H, 6.76; N, 4.17.

3.8. (S)-1-[(E)-3-(3,4-methylenedioxyphenyl)propenoyl] pyrrolidine-2-carboxylic acid (**1b**)

A solution of **5b** (4.67 g, 13.5 mmol) in TFA (45 mL) was stirred at 0 °C for 5 h. The reaction mixture was concentrated in vacuo and the residue was chromatographed over silica gel. Elution with hexane-EtOAc (2:3–0:1) gave **1b** (3.52 g, 90%) as colorless crystals; mp 175–177 °C; $[\alpha]_D^{22}$ −275 (c = 1.0, $CHCl_3$). IR (KBr): 2966, 2891, 2584, 1941, 1714, 1643, 1604, 1556, 1501, 1446, 1362, 1327, 1256, 1104, 1033, 976, 925, 810, 755, 614 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.95 (1H, m), 2.03–2.18 (2H, m), 2.64 (1H, br d, J = 11.0 Hz), 3.53–3.83 (2H, m), 4.75 (1H, dd, J = 8.1, 1.5 Hz), 6.03 (2H, s), 6.53 (1H, d, J = 15.4 Hz), 6.83 (1H, d, J = 8.4 Hz), 7.02–7.12 (2H, m), 7.75 (1H, d, J = 15.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.0, 27.2, 48.1, 60.9, 101.9, 106.7, 108.9, 114.2, 125.2, 129.0, 145.3, 148.6, 150.1, 168.5, 171.9. Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.22; H, 5.27; N, 4.85.

3.9. (1S,4S,5S,8S)-4,8-Bis(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane-2,6-dione (**2b**)

To a 100 mL vial container were added **1b** (300 mg, 1.04 mmol), CH_2Cl_2 (15 mL), n-Bu_4NBF_4 (346 mg, 1.05 mmol) and TFA (3 mL). The reaction vial container was then fitted with a Pt anode (ca. 5 cm^2) and a Pt cathode (ca. 5 cm^2). A constant current of 9 mA was applied to the solution at −20 °C for 241 min until a total of 1.3 F/mol of charge had been passed. The reaction mixture was concentrated in vacuo. The residue was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–EtOAc (1:1–0:1) gave **2b** (48.2 mg, 24%) as colorless crystals, together with the recovered starting material (72.0 mg, 24%); mp 192–194 °C, $[\alpha]_D^{23}$ +44 (c = 0.52, $CHCl_3$). IR (KBr): 2990, 2908, 1767, 1503, 1448, 1351, 1319, 1258, 1171, 1034, 1014, 923, 809, 795 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.53 (2H, s), 5.82 (2H, s), 5.99 (4H, s), 6.84–6.73 (6H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 48.2, 81.8, 101.6, 105.2, 108.7, 118.5, 131.7, 148.3, 148.5, 174.6. Anal. Calcd for $C_{20}H_{14}O_8$: C, 62.83; H, 3.69. Found: C, 62.66; H, 3.53.

3.10. (1S,2R,3R,4S)-2,3-Bis(hydroxymethyl)-1,4-bis(3,4-methylenedioxyphenyl)butane-1,4-diol (**6b**)

$CaCl_2$ (156 mg, 1.41 mmol) and $NaBH_4$ (114 mg, 1.91 mmol) were added to EtOH (2.5 mL). After stirring at room temperature for 15 min, **2b** (76.9 mg, 0.201 mmol) in EtOH (1 mL) and THF (1 mL) was added to the mixture. After stirring at room temperature for 23 h, the reaction mixture was poured into diluted HCl and extracted with $CHCl_3$. The organic layer was washed with sat. $(NH_4)_2SO_4$ solution, dried with anhyd Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with benzene–acetone (1:1–0:1) gave **6b** (48.1 mg, 61%) as colorless crystals; mp 202–204 °C, $[\alpha]_D^{26}$ −21 (c = 0.11, MeOH). IR (KBr): 3217, 2878, 1504, 1442, 1329, 1248, 1116, 1029, 929, 898, 827, 813, 790, 723, 679, 639 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ = 2.12–2.21 (2H, m), 3.67–3.83 (4H, m), 4.75 (2H, d, J = 3.7 Hz), 5.88 (1H, s), 5.92 (1H, s), 6.40–6.62 (6H, m). ^{13}C NMR (125 MHz, CD_3OD): δ = 45.9, 61.9, 73.9, 102.1, 107.3, 108.3, 120.0, 139.0, 147.6, 148.7. Anal. Calcd for $C_{20}H_{22}O_8$: C, 61.53; H, 5.68. Found: C, 61.22; H, 5.72.

3.11. (1S,3aR,4S,6aR)-1,3a,4,6a-Tetrahydro-1,4-bis(3,4-methylenedioxyphenyl)-3H,6H-furo[3,4-c]furan (**7b**, sesamin)

To a solution of **6b** (27.3 mg, 69.9 μmol) in pyridine (0.6 mL) were added DMAP (2.6 mg, 21.3 μmol) and MsCl (17.0 μL, 220 μmol) at 0 °C. After stirring at 0 °C for 6 h, the mixture was warmed to room temperature and stirring was continued for 33 h. The reaction mixture was poured into H_2O and extracted with EtOAc. The organic layer was dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–EtOAc (2:1) gave **7b** (17.3 mg, 70%, 83% e.e.) as colorless crystals; mp 121–122 °C; $[\alpha]_D^{18}$ +49 (c = 0.26, $CHCl_3$) {Lit.[2e] (1*R*,3a*S*,4*R*,6a*S*)-**7b** (98% e.e.): $[\alpha]_D^{26}$ −66.8 (c = 0.30, $CHCl_3$)}. Enantiomeric excess was determined by HPLC with a CHIRALCEL® OD column (EtOH), 1.0 mL/min; major enantiomer tr = 6.66 min, minor enantiomer tr = 14.2 min. IR (KBr): 2968, 2902, 2850, 2782, 1500, 1442, 1365, 1250, 1194, 1095, 1058, 1036, 969, 927, 857, 803, 782 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.04–3.06 (2H, m), 3.87 (2H, dd, J = 9.2, 3.7 Hz), 4.23 (2H, dd, J = 9.2, 6.6 Hz), 4.71 (2H, d, J = 4.4 Hz), 5.95 (4H, s), 6.86–6.75 (6H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.3, 85.8, 101.1, 106.5, 108.2, 119.4, 135.0, 147.1, 147.9. Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.67; H, 5.23.

3.12. tert-Butyl (S)-1-[(E)-3-(3,4-dimethoxyphenyl)propenoyl] pyrrolidine-2-carboxylate (**5c**)

To a solution of HOBt (5.47 g, 40.5 mmol), L-proline *tert*-butyl ester (5.32 g, 31.1 mmol), 3,4-dimethoxycinnamic acid (6.48 g, 31.1 mmol) in THF (100 mL) was added DCC (8.34 g, 40.4 mmol) at 0 °C. After stirring at room temperature for 5 h, the reaction mixture was filtered through Celite®. The filtrate was poured into sat. $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with sat. NH_4Cl solution and brine, dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–EtOAc (1:1–1:6) gave **5c** (8.56 g, 76%) as a colorless oil; $[\alpha]_D^{22}$ −61 (c = 0.73, $CHCl_3$). IR (neat): 2969, 1737, 1650, 1597, 1514, 1422, 1265, 1154, 1024 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, several peaks appeared separately as amide rotamers): δ = 1.43 (3H, s), 1.47 (6H, s), 1.89–2.36 (4H, m), 3.62–3.88 (2H, m), 3.90 (4H, s), 3.91 (2H, s), 4.50 (1H, m), 6.44 (1/3H, d, J = 15.4 Hz), 6.60 (2/3H, d, J = 15.4 Hz), 6.85 (1H, d, J = 8.1 Hz), 6.98–7.14 (2H, m), 7.63 (1/3H, d, J = 15.4 Hz), 7.65 (2/3H, d, J = 15.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.8, 24.7, 27.9, 28.0, 29.2, 31.4, 46.7, 47.0, 55.9, 59.8, 60.3, 81.1, 82.0, 109.8, 110.0, 111.0, 116.0, 121.9, 128.2, 142.2, 142.5, 149.0, 150.5, 164.9, 165.4, 171.5, 171.8 cm^{-1}. HRMS (EI) $[M+Na]^+$ calcd for $C_{20}H_{27}NNaO_5$: 384.1787; found: 384.1739.

3.13. (S)-1-[(E)-3-(3,4-Dimethoxyphenyl)propenoyl]pyrrolidine-2-carboxylic acid (**1c**)

A solution of **5c** (8.56 g, 23.7 mmol) in TFA (96 mL) was stirred at 0 °C for 5 h. The reaction mixture was concentrated in vacuo. Recrystallization from CH_2Cl_2 gave **1c** (4.81 g, 67%) as colorless crystals; mp 190–191 °C; $[\alpha]_D^{22}$ −309 (c = 0.50, $CHCl_3$). IR (KBr): 2964, 1723, 1644, 1569, 1516, 1442, 1264, 1139, 1020, 764 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.94 (1H, m), 2.06–2.17 (2H, m), 2.66 (1H, br d, J = 12.0 Hz), 3.63–3.81 (2H, m), 3.93 (6H, s), 4.76 (1H, dd, J = 8.1, 1.8 Hz), 6.55 (1H, d, J = 15.4 Hz), 6.89 (1H, d, J = 8.4 Hz), 7.04 (1H, d, J = 1.8 Hz), 7.17 (1H, dd, J = 8.4, 1.8 Hz), 7.80 (1H, d, J = 15.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.8, 26.9, 47.9, 56.0, 60.7, 110.2, 111.1, 113.8, 122.7, 127.3, 145.4, 149.2, 151.4, 168.4, 171.7. Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.02; H, 6.27; N, 4.61.

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3.14. (1S,4S,5S,8S)-4,8-Bis(3,4-dimethoxyphenyl)-3,7-dioxabicyclo[3.3.0]octane-2,6-dione (**2c**)

To a 100 mL vial container were added **1c** (300 mg, 0.985 mmol), CH_2Cl_2 (15 mL), *n*-Bu_4NBF_4 (340 mg, 1.03 mmol) and TFA (3 mL). The reaction vial container was then fitted with a Pt anode (ca. 5 cm^2) and a Pt cathode (ca. 5 cm^2). A constant current of 9 mA was applied to the solution at −20 °C for 229 min until a total of 1.3 F/mol of charge had been passed. The reaction mixture was concentrated in vacuo. The residue was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane−EtOAc (1:1−0:1) gave **2c** (16.1 mg, 8%) as colorless crystals, together with the recovered starting material (45.7 mg, 15%); mp 209−210 °C; $[\alpha]_D$ +45 (c = 1.0, $CHCl_3$). IR (KBr): 3014, 2967, 2843, 1784, 1593, 1522, 1459, 1428, 1384, 1341, 1321, 1265, 1231, 1201, 1167, 1146, 1035, 1020, 997, 960, 868, 823, 806, 763, 717, 616 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.57 (2H, s), 3.88 (6H, s), 3.89 (6H, s), 5.89 (2H, s), 6.77−6.88 (6H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 48.4, 56.1, 81.8, 107.9, 111.4, 116.7, 130.4, 149.6, 174.9. Anal. Calcd for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.51; H, 5.34.

3.15. (1S,2R,3R,4S)-2,3-Bis(hydroxymethyl)-1,4-bis(3,4-dimethoxyphenyl)butane-1,4-diol (**6c**)

$CaCl_2$ (178 mg, 1.60 mmol) and $NaBH_4$ (124 mg, 3.28 mmol) were added to EtOH (2.8 mL). After stirring at r.t. for 25 min, **2c** (94.3 mg, 0.228 mmol) was added to the mixture in one portion. After stirring at room temperature for 17 h, the reaction mixture was poured into diluted HCl and extracted with $CHCl_3$. The organic layer was washed with sat. $(NH_4)_2SO_4$ solution, dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with toluene−acetone (1:1−0:1) gave **6c** (73.6 mg, 76%) as colorless crystals; mp 139−141 °C; $[\alpha]_D$ −33 (c = 0.38, MeOH). IR (KBr): 3469, 3339, 2907, 2870, 1598, 1518, 1466, 1256, 1136, 1025, 896, 843, 802, 765, 664 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ = 2.14−2.24 (2H, m), 3.67 (6H, s), 3.69−3.86 (4H, m), 3.81 (6H, s), 4.77 (2H, d, J = 3.3 Hz), 6.49−6.59 (4H, m), 6.69 (2H, d, J = 8.1 Hz). ^{13}C NMR (125 MHz, CD_3OD): δ = 45.9, 55.9, 56.2, 62.0, 74.0, 110.3, 111.9, 119.1, 137.7, 148.8, 149.8. Anal. Calcd for $C_{22}H_{30}O_8$: C, 62.55; H, 7.16. Found: C, 62.22; H, 7.10.

3.16. (1S,3aR,4S,6aR)-1,3a,4,6a-Tetrahydro-1,4-bis(3,4-dimethoxyphenyl)-3H,6H-furo[3,4-c]furan (**7c**, eudesmin)

To a solution of **6c** (46.2 mg, 109 μmol) in pyridine (0.9 mL) were added DMAP (4.4 mg, 36.0 μmol) and MsCl (25.0 μL, 328 μmol) at 0 °C. After stirring at 0 °C for 6 h, the mixture was warmed to room temperature and stirring was continued for 34 h. The reaction mixture was poured into H_2O and extracted with EtOAc. The organic layer was dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane−EtOAc (1:1) gave **7c** (24.2 mg, 57%, 87% e.e.) as colorless crystals; mp 96−97 °C; $[\alpha]_D^{27}$ +62 (c = 0.67, $CHCl_3$) {Lit.[2a] (1*R*,3a*S*,4*R*,6a*S*)-**7c** (99% e.e.): $[\alpha]_D^{23}$ −64 (c = 1.1, $CHCl_3$)}. Enantiomeric excess was determined by HPLC with a CHIRALCEL® OD column (EtOH), 1.0 mL/min; major enantiomer tr = 7.38 min, minor enantiomer tr = 8.75 min. IR (KBr): 2963, 2937, 2839, 1590, 1519, 1467, 1448, 1264, 1142, 1025, 815, 744 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.10−3.14 (2H, m), 3.85−3.95 (2H, m), 3.88 (6H, s), 3.90 (6H, s), 4.26 (2H, dd, J = 9.2, 7.0 Hz), 4.76 (2H, d, J = 4.4 Hz), 6.81−6.94 (6H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.1, 55.9, 71.7, 85.8, 109.1, 111.0, 118.2, 133.5, 148.6, 149.2. Anal. Calcd for $C_{22}H_{22}O_8$: C, 68.38; H, 6.78. Found: C, 68.16; H, 6.82.

3.17. tert-Butyl (S)-1-[(E)-3-(4-methoxyphenyl)propenoyl]pyrrolidine-2-carboxylate (**5d**)

To a solution of HOBt (3.10 g, 22.9 mmol), L-proline *tert*-butyl ester (3.00 g, 17.5 mmol), 4-methoxycinnamic acid (3.13 g, 17.6 mmol) in THF (60 mL) was added DCC (4.71 g, 22.8 mmol) at 0 °C. After stirring at room temperature for 6 h, the reaction mixture was filtered through Celite®. The filtrate was poured into sat. $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with sat. NH_4Cl solution and brine, dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane−EtOAc (2:1−1:1) gave **5d** (5.10 g, 88%) as a pale yellow solid; mp 83−85 °C; $[\alpha]_D^{23}$ −75 (c = 1.0, $CHCl_3$). IR (KBr): 3008, 2964, 2931, 2881, 2834, 1734, 1651, 1603, 1513, 1429, 1249, 1166, 1033, 981, 827 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, several peaks appeared separately as amide rotamers): δ = 1.43 (3H, s), 1.48 (6H, s), 1.89−2.23 (4H, m), 3.62−3.91 (2H, m), 3.83 (3H, s), 4.48 (1H, m), 6.46 (1/3H, d, J = 15.4 Hz), 6.62 (2/3H, d, J = 15.4 Hz), 6.89 (2H, d, J = 8.8 Hz), 7.44 (2/3H, d, J = 8.8 Hz), 7.47 (4/3H, d, J = 8.8 Hz), 7.66 (1/3H, d, J = 15.4 Hz), 7.67 (2/3H, d, J = 15.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.5, 24.4, 27.6, 27.7, 28.9, 31.1, 46.5, 46.7, 55.0, 59.5, 60.0, 80.8, 81.8, 113.9, 115.6, 127.6, 129.1, 129.2, 141.6, 141.8, 160.6, 164.7, 165.2, 171.3, 171.5. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.94; H, 7.61; N, 4.26.

3.18. (S)-1-[(E)-3-(4-Methoxyphenyl)propenoyl]pyrrolidine-2-carboxylic acid (**1d**)

A solution of **5d** (3.54 g, 10.7 mmol) in TFA (36 mL) was stirred at 0 °C for 5 h. The reaction mixture was concentrated in vacuo. Recrystallization from CH_2Cl_2 gave **1d** (1.85 g, 63%) as colorless crystals; mp 195−197 °C; $[\alpha]_D$ −301 (c = 0.30, $CHCl_3$). IR (KBr): 2973, 1717, 1639, 1603, 1512, 1446, 1259, 1175, 1021, 1004, 828 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.93 (1H, m), 2.04−2.14 (2H, m), 2.66 (1H, br d, J = 12.0 Hz), 3.60−3.80 (2H, m), 3.85 (3H, s), 4.76 (1H, dd, J = 8.1, 1.5 Hz), 6.57 (1H, d, J = 15.4 Hz), 6.92 (2H, d, J = 8.8 Hz), 7.52 (2H, d, J = 8.8 Hz), 7.81 (1H, d, J = 15.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.9, 26.6, 48.0, 55.4, 60.8, 113.3, 114.4, 127.0, 130.1, 145.3, 161.7, 168.9, 171.2. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.45; H, 6.32; N, 5.08.

3.19. (1S,4S,5S,8S)-4,8-Bis(4-methoxyphenyl)-3,7-dioxabicyclo[3.3.0]octane-2,6-dione (**2d**)

To a 100 mL vial container were added **1d** (500 mg, 1.82 mmol), CH_2Cl_2 (25 mL), *n*-Bu_4NBF_4 (597 mg, 1.81 mmol) and TFA (5 mL). The reaction vial container was then fitted with a Pt anode (ca. 8 cm^2) and a Pt cathode (ca. 8 cm^2). A constant current of 15 mA was applied to the solution at −20 °C for 255 min until a total of 1.3 F/mol of charge had been passed. The reaction mixture was concentrated in vacuo. The residue was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane−EtOAc (1:1−0:1) gave **2d** (25.8 mg, 8%) as colorless crystals, together with the recovered starting material (76.0 mg, 15%); mp 155−156 °C; $[\alpha]_D^{21}$ +28 (c = 0.43, $CHCl_3$). IR (KBr): 3057, 2967, 2842, 1784, 1615, 1518, 1361, 1254, 1173, 1044, 1017, 817 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.56 (2H, s), 3.81 (6H, s), 5.89 (2H, s), 6.92 (4H, d, J = 7.0 Hz), 7.23 (4H, d, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 48.2, 55.4, 81.8, 114.5, 126.2, 129.9, 160.1, 174.9. Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.77; H, 5.20.

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3.20. (1S,2R,3R,4S)-2,3-Bis(hydroxymethyl)-1,4-bis(4-methoxyphenyl)-butane-1,4-diol (**6d**)

$CaCl_2$ (80.7 mg, 0.727 mmol) and $NaBH_4$ (55.0 mg, 1.45 mmol) were added to EtOH (2 mL). After stirring at r.t. for 15 min, **2d** (36.8 mg, 0.104 mmol) in THF (1.5 mL) was added to the mixture. After stirring at room temperature for 27 h, the reaction mixture was poured into diluted HCl and extracted with $CHCl_3$. The organic layer was washed with sat. $(NH_4)_2SO_4$ solution, dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with toluene–acetone (1:1–0:1) gave **6d** (16.6 mg, 44%) as colorless crystals; mp 188–190 °C; $[\alpha]_D^{27}$ −7.4 (c = 0.14, MeOH). IR (KBr): 3227, 2906, 1613, 1517, 1255, 1178, 1024, 999, 835, 737, 692 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ = 2.18–2.29 (2H, m), 3.62–3.70 (4H, m), 3.78 (6H, s), 4.78 (2H, d, J = 4.8 Hz), 6.71 (4H, d, J = 8.8 Hz), 6.97 (4H, d, J = 8.8 Hz). ^{13}C NMR (125 MHz, CD_3OD): δ = 46.3, 55.6, 61.5, 73.8, 114.4, 128.1, 137.0, 159.9. Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.14; H, 7.20.

3.21. (1S,3aR,4S,6aR)-1,3a,4,6a-Tetrahydro-1,4-bis(4-methoxyphenyl)-3H,6H-furo[3,4-c]furan (**7d**)

To a solution of **6d** (17.0 mg, 46.0 μmol) in pyridine (0.4 mL) were added DMAP (1.7 mg, 13.9 μmol) and MsCl (11.0 μL, 140 μmol) at 0 °C. After stirring at 0 °C for 6 h, the mixture was warmed to room temperature and stirring was continued for 22 h. The reaction mixture was poured into H_2O and extracted with EtOAc. The organic layer was dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–EtOAc (2:1) gave **7d** (9.8 mg, 55%) as colorless crystals; mp 98–100 °C; 39% e.e., $[\alpha]_D^{27}$ +18 (c = 0.25, $CHCl_3$). Enantiomeric excess was determined by HPLC with a CHIRALCEL® OD column (EtOH), 1.0 mL/min; major enantiomer tr = 6.74 min, minor enantiomer tr = 10.2 min. IR (KBr): 2963, 2851, 1612, 1517, 1459, 1307, 1247, 1174, 1043, 1027, 957, 817 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.04–3.16 (2H, m), 3.81 (6H, s), 3.87 (2H, dd, J = 9.2, 3.7 Hz), 4.24 (2H, dd, J = 9.2, 7.0 Hz), 4.76 (2H, d, J = 4.4 Hz), 6.89 (4H, d, J = 8.8 Hz), 7.28 (4H, d, J = 8.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.1, 55.2, 71.6, 85.6, 113.9, 127.3, 133.0, 159.1. Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.51; H, 6.82.

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