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Asymmetric synthesis of 3-substituted 8-hydroxy-3,4-dihydroisocoumarins from (S)-4-isopropyl-2-(2-methoxy-6-methylphenyl)oxazoline

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Abstract- Reaction of the laterally lithiated (S)-4-isopropyl-2-(2-methoxy-6-methylphenyl)oxazoline with p-tolualdehyde gave an inseparable mixture of the addition products in low diastereoselectivity. However, the (S,S)-product cyclized to the corresponding 3,4-dihydroisocoumarin faster than the (S,R)-product on silica gel, which allowed to be produced both enantiomers of 8-methoxy-3-(p-tolyl)-3,4-dihydroisocoumarin in moderate to good optical purity [S-enantiomer: 75% ee; R-enantiomer: 96% ee]. This procedure was applied to the short-step synthesis of optically active 3,4-dihydroisocoumarin natural products such as (R)-8-hydroxy-3-(1-tridecyl)-3,4-dihydroisocoumarin and (R)-phyllodulcin.

Keywords: Asymmetric synthesis; 3,4-Dihydroisocoumarin; oxazoline; Lateral lithiation; Diastereomer-selective lactonization; Silica gel.

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1. Introduction

The 3,4-dihydroisocoumarins constitute a class of natural products, which exhibit a wide range of biological activities such as antifungal, antiulcer, antileukemic, antiallergic, differentiation-inducing, and antimalarial activities. Structurally, these natural products generally possess an aryl or alkyl substituent at C-3 and a
hydroxy group at C-8 of the dihydroisocoumarin core. In addition, most of them are optically active due to the stereocenter at C-3.

\[
\begin{align*}
&\text{Figure 1. Common scaffold of 3,4-dihydroisocoumarin natural products.} \\
\end{align*}
\]

Although a variety of synthetic approaches to this class of compounds have been developed\textsuperscript{2}, the most straightforward route may be the reaction of laterally lithiated \textit{o}-toluic acid derivatives with aldehydes\textsuperscript{3}. In 2002, we reported unprecedented reagent-controlled optional \textit{ortho}- and lateral lithiations of 4,4-dimethyl-2-(\textit{o}-tolyl)oxazolines\textsuperscript{4}. This unique reaction has been successfully applied to the short-step synthesis of 3-substituted 8-hydroxy-3,4-dihydroisocoumarins, including (±)-hydrangenol and (±)-phyllodulcin\textsuperscript{5}. Recently, we also investigated an asymmetric synthesis of 3-substituted 3,4-dihydroisocoumarins via stereoselective addition of laterally lithiated chiral 2-(\textit{o}-tolyl)oxazoline 1 to aldehydes\textsuperscript{6}. In the research, we disclosed the addition reactions proceeded in good stereoselectivities (up to 84\% de) in diethyl ether in the presence of TMEDA. In addition, we found the major diastereomers 2 lactonized to 3,4-dihydroisocoumarins 3 faster than the minor diastereomers under acidic conditions. By combination of these matched stereoselective reactions, we obtained 3-substituted 3,4-dihydroisocoumarins 3 in good optical purity (up to 97\% ee) (Scheme 1).

\[
\begin{align*}
&\text{Scheme 1} \\
\end{align*}
\]

Herein, we report an application of this method for asymmetric synthesis of
3-substituted 8-hydroxy-3,4-dihydroisocoumarins including natural products by using 2-(2-methoxy-6-methylphenyl)oxazoline 4 as the starting material.

2. Results and discussion

2.1. Addition of the laterally lithiated oxazoline 4 to p-tolualdehyde

Treatment of the oxazoline 4 with sec-BuLi in diethyl ether or THF at -78 °C resulted in the corresponding lateral lithio species as a characteristic burgundy red solution, which upon treatment with p-tolualdehyde afforded the addition product 5 after chromatographic purification over Chromatorex NH-DM1020 silica gel. Purification over normal silica gel caused considerable decomposition of 5 to the corresponding 3,4-dihydroisocoumarin (vide infra). The diastereomer ratio 5a:5b was determined by HPLC analysis. As shown in Table 1, the stereoselectivities of this reaction are disappointingly low even in the presence of Lewis basic ligands including TMEDA. This is in sharp contrast to the results observed in a similar reaction of the parental oxazoline 1. Although the reason for the low selectivity is not clear, it is reasonable to assume that the methoxy group adjacent to the oxazoline ring in the lithiated 4 interferes to keep 4 from taking the rigid eight-membered ring transition state for the stereoselective addition proposed by us.

<table>
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<tr>
<th>entry</th>
<th>solvent</th>
<th>additive</th>
<th>yield (%)</th>
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<tr>
<td>1</td>
<td>Et₂O</td>
<td>none</td>
<td>80</td>
<td>1 : 1.3</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>none</td>
<td>78</td>
<td>1 : 1</td>
</tr>
<tr>
<td>3</td>
<td>Et₂O</td>
<td>TMEDA</td>
<td>70</td>
<td>1 : 1.1</td>
</tr>
<tr>
<td>4</td>
<td>Et₂O</td>
<td>PMDTA</td>
<td>56</td>
<td>1 : 1.2</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>tert-BuOK</td>
<td>75</td>
<td>1 : 1</td>
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</table>
2.2. Diastereomer-selective lactonization of the addition product 5

In order to produce an enantiomerically enriched 8-methoxy-3,4-dihydroisocoumarin 6, we next pursued the diastereomer-selective lactonization of the addition product 5. Thus, 5 was treated with trifluoroacetic acid in aqueous THF at 0 °C for 24 h to effect lactonization. Under these previously established conditions, the cyclization was extremely slow and the unreacted starting material 5 was recovered. The slow cyclization may be accounted for by stabilization of the N-protonated oxazoline through intramolecular hydrogen bonding to the ortho-methoxy group. As mentioned briefly in the previous section, we observed considerable lactonization took place during the chromatographic purification of 5 on silica gel. Thus, we examined the silica gel-catalyzed cyclization of 5. The mixture of 5 (5a:5b=1:1.3) and silica gel (Merck Silica gel 60) in dichloromethane was stirred at 0 °C and the reaction was monitored by HPLC analysis of the supernatant. It was found that (S,S)-diastereomer 5a cyclized to the corresponding 3,4-dihydroisocoumarin 6a faster than (S,R)-diastereomer 5b. The time-dependence of ee of the cyclized 6a and that of de of the unreacted 5b is shown in Figure 2. The ee of 6a was quite high at the initial stage of the reaction such as 90% ee after 9 h. On the other hand, de of 5b increased up to 100% after 36 h. These results suggested both enantiomers of 3-substituted 8-methoxy-3,4-dihydroisocoumarins could be produced in good optical purity by means of this diastereomer-selective lactonization technique even if the diastereomer ratio of the starting adduct is low. The selectivity can be accounted for by the gauche interaction between two aromatic rings in the transition state of the cyclization. A similar rationale has been proposed in the previous paper.
In practice, both enantiomers of the 3,4-dihydroisocoumarins 6a and 6b were prepared as follows (Scheme 2). The addition product 5 was treated with silica gel in dichloromethane at 0 °C for 30 h. After column chromatography, (S)-3,4-dihydroisocoumarin 6a (75% ee) and unreacted (S,R)-adduct 5b (98% de) were isolated in 43% and 42% yields, respectively. The recovered 5b was converted to the corresponding (R)-3,4-dihydroisocoumarin 6b (96% ee) by treatment with silica gel in dichloromethane at room temperature for 4 days in 93% yield.

**Scheme 2.** Diastereomer-selective lactonization of 5.

2.3. Determination of the absolute configuration of 3,4-dihydroisocoumarin 6b

The absolute configuration of 3,4-dihydroisocoumarin 6b was determined by the sequence shown in Scheme 3. The compound 6b was treated with 1 equiv. of BBr₃ to
give demethylated compound 7 in 87% yield. The hydroxy group of 7 was trifluoromethanesulfonated with Tf₂O in pyridine to generate 8. Finally, the trifluoromethanesulfonyloxy group of 8 was removed by hydrogenolysis using Et₃SiH in the presence of Pd(OAc)₂ and 1,1’-bis(diphenylphosphino)ferrocene (dpdf)⁷ to give 9. The absolute configuration of 9 was found to be R by chiroptical comparison with previously reported data.⁶ Thus, the absolute configuration of 6b was determined to be R.

![Scheme 3](image)

**Scheme 3.** Reagents and conditions: (a) BBr₃ (1.0 equiv.), CH₂Cl₂, -78 °C, 3 h then 0 °C, 1 h (87%, 96% ee); (b) (1) Tf₂O (1.5 equiv.), pyridine, 0 °C, 1 h then r.t., 19 h, (2) Tf₂O (1.5 equiv.), r.t., 24 h (77%, 96% ee); (c) Pd(OAc)₂ (5 mol%), dpf (5 mol%), Et₃SiH (2.5 equiv.), DMF, 60 °C, 30 min (97%, 96% ee)

2.4. Asymmetric synthesis of the natural products 12 and 16

Next, we applied the aforementioned method for asymmetric synthesis of 3,4-dihydroisocoumarins natural products having an alkyl or aryl substituent at C-3. At first, 8-hydroxy-3-(1-tridecyl)-3,4-dihydroisocoumarin (12), which was isolated from *Ginkgo biloba* L., was selected as a target.⁸ The synthesis of both enantiomers of 12 is shown in Scheme 4. Lateral lithiation of oxazoline 4 using sec-BuLi at −78 °C in diethyl ether followed by quenching with 1-tetradecanal produced the addition product 10 in 65% yield. The diastereomer ratio was determined to be 1:1:1 by HPLC analysis. The addition product 10 was treated with silica gel in dichloromethane at 0 °C for 30 h to give 11a (64% ee) and 10b (99% de) in 64% and 34%, respectively. Further treatment of 10b with silica gel in dichloromethane at 30 °C for 4 days afforded 11b (98% ee) in 98% yield. Final demethylation of 11a and 11b with BBr₃ gave the desired products 12a and 12b, respectively, without loss of optical purity. The absolute configurations of these products were determined by chiroptical comparison with previously established data.⁸
Phyllodulcin (16) is a sweet component of Amacha (Hydrangea Dulcis Folium), a natural medicine indigenous to Japan, produced from the leaves of Hydrangea macrophylla Seringe var. thumbergii Makino. It has been reported that (R)-enantiomer 16b exhibits an intensely sweet taste, while the (S)-enantiomer 16a is completely tasteless. In spite of its simple structure, asymmetric synthesis of phyllodulcin is rather problematic due to easy epimerization at C-3. The first enantioselective synthesis was reported by Napolitano in 1996. Our synthesis of optically active phyllodulcin is shown in Scheme 5. The laterally lithiated 4 was reacted with O-methoxymethylisovanillin in a similar manner as described above to give 13 in 78% yield as a 1:1.2 diastereomeric mixture. Treatment of 13 with silica gel in dichloromethane at 0 °C for 30 h produced (S)-3,4-dihydroisocoumarin 14a (49% ee) and unreacted (S,R)-adduct 13b (97% de) in 57% and 31% yields, respectively. Treatment of 13b with silica gel in dichloromethane at 30 °C for 4 days gave (R)-3,4-dihydroisocoumarin 14b (91% ee) in 73% yield. An attempted simultaneous deprotection of methyl and methoxymethyl groups of 14b with BBr3 afforded only completely racemized (±)-phyllodulcin even at -78 °C. After an extensive survey for deprotection conditions (BCl3, TMSI, TMSBr, Me2NCH2CH3SNa/DMF12), we found that the methyl group of 14b could be removed by heating with lithium chloride in dry DMF13 with minimum racemization to produce 15b (83% ee). Final deprotection of the methoxymethyl group with HCl in methanol produced (R)-phyllodulcin (16b) (83% ee) in quantitative yield. The (S)-phyllodulcin 16a was also prepared in a similar manner from 14a albeit in low optical purity.14
3. Conclusion

The addition of the laterally lithiated 2-(2-methoxy-6-methylphenyl)oxazoline 4 to aldehydes proceeded non-stereoselectively. However, lactonization of the addition products over silica gel proceeded diastereomer-selectively. The combination of these reactions allowed both enantiomers of 3-substituted 8-hydroxy-3,4-dihydroisocoumarins to be produced including natural products in modest to good optical purity.

4. Experimental

4.1. General

Melting points were determined with a Yanagimoto micro melting points apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer System 2000 instrument. NMR spectra were recorded on a JEOL JNM-AL400 instrument (400 MHz for $^1$H and 100 MHz for $^{13}$C) using tetramethylsilane as an internal standard. High resolution mass spectra were recorded on a JEOL JMS-700N spectrometer.
HPLC analyses were performed on a Shimadzu LC-6A apparatus. Optical rotations were measured on a JASCO DPI-1000 digital polarimeter at ambient temperature. Column chromatography was conducted on Silica Gel 60N, 63-210 µm (Kanto Chemical Co., Inc.) or Chromatorex NH-DM1020 silica gel (Fuji Silysia Chemical Ltd.). sec-Butyllithium was purchased from Kanto Chemical Co., Inc. and used after titration with 2,5-dimethoxybenzyl alcohol. Dry diethyl ether and THF were distilled from Na-benzophenone ketyl under argon immediately before use.

4.1.1. (S)-4-Isopropyl-2-(2-methoxy-6-methylphenyl)-4,5-dihydrooxazole (4). Thionyl chloride (9.2 mL, ca. 126 mmol) was added as a neat liquid to 2-methoxy-6-methylbenzoic acid\textsuperscript{15} (3.00 g, 18.1 mmol) at 0 °C. After being stirred for 10 min, the mixture was allowed to warm to room temperature, stirred for 8 h, and evaporated. The residual thionyl chloride was removed by azeotropic treatment with toluene to give 2-methoxy-6-methylbenzoyl chloride. The crude acid chloride was dissolved in dichloromethane (10 mL) and the solution was added dropwise to a mixture of (S)-valinol (1.86 g, 18.1 mmol) and triethylamine (8.81 mL, 63.2 mmol) in dichloromethane (80 mL) at 0 °C. After being stirred for 2 h, the mixture was allowed to warm to room temperature, stirred for 1 h, and cooled to 0 °C again. Methanesulfonyl chloride (1.54 mL, 19.9 mmol) was added as a neat liquid to the reaction mixture. After being stirred for 1 h, the mixture was allowed to warm to room temperature and stirred for 15 h. The mixture was quenched with 10% aqueous NaOH and the product was extracted with dichloromethane. The extract was washed successively with 10% aqueous NaOH and brine, dried over Na\textsubscript{2}SO\textsubscript{4}, and evaporated. The residue was purified by bulb-to-bulb distillation (115-120 °C/ 0.6 mmHg) to give 4 as colorless oil (3.80 g, 90%). IR (neat): 1671, 1586, 1472, 1270, 1087, 1052, 954 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 1.00 (d, \( J= 6.8 \) Hz, 3H), 1.05 (d, \( J= 6.8 \) Hz, 3H), 1.84-1.96 (m, 1H), 2.32 (s, 3H), 3.79 (s, 3H), 4.10-4.20 (m, 2H), 4.41 (dd, \( J= 7.4 \) and 8.9 Hz, 1H), 6.73 (d, \( J= 8.0 \) Hz, 1H), 6.80 (d, \( J= 8.0 \) Hz, 1H), 7.22 (t, \( J= 8.0 \) Hz, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \( \delta \) 18.35, 18.83, 19.39, 32.61, 55.81, 69.76, 72.82, 108.18, 118.78, 122.11, 130.14, 138.51, 157.68, 161.58; \([\alpha]_{D}^{26} = -64.3 \) (c 1.00, MeOH). HREIMS \textit{m/z}. Calcd for C\textsubscript{14}H\textsubscript{19}NO\textsubscript{2} (M\textsuperscript{+}): 233.1416. Found: 233.1399.
4.2. Addition of the laterally lithiated oxazoline 4 to p-tolualdehyde

The reactions summarized in Table were conducted in a similar manner as described in the previous paper. Preparation of 5 is shown below.

4.2.1 2-{2-[(S)-4-Isopropyl-4,5-dihydrooxazol-2-yl]-3-methoxyphenyl}-1-(p-tolyl)ethanol (5). Under an argon atmosphere, a hexane-cyclohexane solution of sec-butyllithium (4.8 mmol) was added dropwise to a solution of the oxazoline 4 (933 mg, 4.0 mmol) in diethyl ether (20 mL) at –78 °C. After being stirred for 1 h, a solution of p-tolualdehyde (481 mg, 4.0 mmol) in diethyl ether (10 mL) was added and the mixture was stirred for an additional 1 h at –78 °C. The reaction mixture was allowed to warm to room temperature and quenched with water. The products were extracted with diethyl ether and the extract was washed successively with water and brine, dried over Na₂SO₄, and evaporated. The residue was purified by flash chromatography over Chromatorex NH-DM1020 silica gel (hexane-ethyl acetate=3:1) to give 1.13 g (80%) of 5 (5a:5b=1:1.3). The diastereomer ratio was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane-i-PrOH=8:2). IR (KBr): 3222, 1655, 1583, 1467, 1268, 1081 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.00 (d, J= 6.7 Hz, 1.31H, (S,S)-isomer), 1.01 (d, J= 6.6 Hz, 1.69H, (S,R)-isomer), 1.12 (d, J= 6.6 Hz, 1.69H, (S,R)-isomer), 1.13 (d, J= 6.7 Hz, 1.31H, (S,S)-isomer), 1.83-1.97 (m, 1H, both isomers), 2.34 (s, 3H, both isomers), 2.92-3.10 (m, 2H, both isomers), 3.83 (s, 3H, both isomers), 4.08-4.22 (m, 2H, both isomers), 4.46-4.56 (m, 1H, both isomers), 4.83 (dd, J= 3.6 and 9.0 Hz, 0.56H, (S,R)-isomer), 4.90 (dd, J= 4.3 and 8.1 Hz, 0.44H, (S,S)-isomer), 6.02 (br s, 0.44H, (S,S)-isomer), 6.62 (br s, 0.56H, (S,R)-isomer), 6.77 (d, J= 7.7 Hz, 0.44H, (S,S)-isomer), 6.81 (d, J= 8.3 Hz, 0.44H, (S,S)-isomer), 6.87 (d, J= 7.7 Hz, 0.56H, (S,R)-isomer), 7.14 (d, J= 7.4 Hz, 0.87H, (S,S)-isomer), 7.16 (d, J= 7.4 Hz, 1.13H, (S,R)-isomer), 7.26-7.36 (m, 3H, both isomers). HREIMS m/z. Calcd for C₂₂H₂₇NO₃ (M⁺): 353.1991. Found: 353.1972.

4.3. Silica gel-catalyzed lactonization of 5. HPLC analysis.
The results shown in Figure were obtained as follows. The addition product 5 (5a:5b=1:1.3) (50 mg, 0.141 mmol) and 2,3-dimethylnapthalene (20.0 mg, 0.128 mmol; an internal standard) were dissolved in dichloromethane (5.0 mL) and the mixture was cooled to 0 °C. Silica gel (Merck Silica gel 60) (200 mg) was added portionwise to this mixture and the progress of the lactonization was monitored by HPLC (Daicel Chiralpak AD-H, hexane-i-PrOH=8:2). An aliquot of 1 µL of the supernatant was used for each analysis. Retention times of the reactants and the products are as follows, 5a: 8.7 min; 5b: 19.8 min; 6a: 18.2 min; 6b: 22.5 min. The absolute yields could not be estimated because considerable amounts of these compounds were absorbed on silica gel. Figure shows only de of 5 and ee of 6 dissolved in supernatant.

4.4. Diastereomer-selective lactonization of 5

The addition product 5 (5a:5b=1:1.3) (342 mg, 0.967 mmol) was dissolved in dichloromethane (35 mL) and the mixture was cooled to 0 °C. Silica gel (Merck Silica gel 60) (1.40 g) was added portionwise to this mixture. After being stirred for 30 h at 0 °C, the reaction mixture was quenched with triethylamine (3.5 mL). Silica gel was removed by filtration over a pad of Celite and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography over silica gel 60N (dichloromethane-ethyl acetate=20:1~ethyl acetate containing 1% triethylamine) to give 3,4-dihydroisocoumarin 6a (111 mg, 43%) and uncyclized 5b (143 mg, 42%).

4.4.1. (S)-8-Methoxy-3-(p-tolyl)-3,4-dihydroisocoumarin (6a). Colorless solid. HPLC (Daicel Chiralpak AD-H, hexane-i-PrOH=8:2): 75% ee. Mp 116.0-119.0 °C; IR (KBr): 1732, 1596, 1477, 1239, 1075, 1056 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.36 (s, 3H), 3.03 (dd, J= 2.8 and 16.2 Hz, 1H), 3.25 (dd, J= 12.0 and 16.2 Hz, 1H), 3.96 (s, 3H), 5.38 (dd, J= 2.8 and 12.0 Hz, 1H), 6.83 (d, J= 7.5 Hz, 1H), 6.94 (d, J= 8.5 Hz, 1H), 7.19 (d, J= 8.0 Hz, 2H), 7.35 (d, J= 8.0 Hz, 2H), 7.47 (dd, J= 7.5 and 8.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 21.17, 36.72, 56.21, 79.02, 111.09, 113.90, 119.22,
(R)-2-[2-[(S)-4-Isopropyl-4,5-dihydrooxazol-2-yl]-3-methoxyphenyl]-1-(p-tolyl)ethanol (5b). Colorless solid. HPLC (Daicel Chiralpak AD-H, hexane-\(i\)-PrOH=8:2): 98% de. Mp 118.0-122.0 °C; IR (KBr): 3129, 1651, 1583, 1470, 1269, 1087 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.01 (d, \(J=6.7\) Hz, 3H), 1.12 (d, \(J=6.7\) Hz, 3H), 1.83-1.95 (m, 1H), 2.34 (s, 3H), 2.95 (dd, \(J=9.3\) and 13.7 Hz, 1H), 3.02 (dd, \(J=3.9\) and 13.7 Hz, 1H), 3.83 (s, 3H), 4.12 (dd, \(J=6.7, 9.0\) and 9.0 Hz, 1H), 4.19 (dd, \(J=8.0\) and 9.0 Hz, 1H), 4.49 (dd, \(J=8.0\) and 9.0 Hz, 1H), 6.62 (br s, 1H), 6.81 (d, \(J=8.4\) Hz, 1H), 6.87 (d, \(J=7.7\) Hz, 1H), 7.16 (d, \(J=7.9\) Hz, 2H), 7.28 (d, \(J=7.9\) Hz, 2H), 7.33 (dd, \(J=7.7\) and 8.4 Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 18.72, 19.07, 21.11, 32.89, 43.82, 56.05, 71.38, 72.03, 75.19, 90.28, 118.46, 122.50, 125.44, 128.92, 131.19, 136.38, 140.44, 143.33, 158.35, 164.03; [\(\alpha\)]\(_D\)\(^{25}\) +57.7 (c 1.00, MeOH). HREIMS m/z. Calcd for C\(_{22}\)H\(_{27}\)NO\(_3\) (M\(^+\)): 353.1991. Found: 353.1980.

4.4.3. (R)-8-Methoxy-3-(p-tolyl)-3,4-dihydroisocoumarin (6b). A mixture of the 98% de sample of 5b (120 mg, 0.340 mmol), silica gel (Merck Silica gel 60) (982 mg) and dichloromethane (12.3 mL) was stirred for 4 days at room temperature. Silica gel was removed by filtration over a pad of Celite and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography over silica gel 60N (dichloromethane-ethyl acetate=20:1) to give 3,4-dihydroisocoumarin 6b (85.0 mg, 93%) as colorless solid. HPLC (Daicel Chiralpak AD-H, hexane-\(i\)-PrOH=8:2): 96% ee. Mp 126.0-128.0 °C; [\(\alpha\)]\(_D\)\(^{25}\) +185 (c 1.00, MeOH). HREIMS m/z. Calcd for C\(_{17}\)H\(_{16}\)O\(_3\) (M\(^+\)): 268.1099. Found: 268.1091.

4.5. Determination of the absolute configuration of 6b.

4.5.1. (R)-8-Hydroxy-3-(p-tolyl)-3,4-dihydroisocoumarin (7). Under an argon atmosphere, a dichloromethane solution of BBr\(_3\) (1.0 M, 186 µL, 0.186 mmol) was added dropwise to a solution of 6b (50.0 mg, 0.186 mmol) in dichloromethane (10 mL) at −78 °C. After being stirred for 3 h at this temperature, the reaction mixture was...
allowed to warm to 0 °C and stirred for an additional 1 h. The mixture was quenched with saturated aqueous NaHCO₃ and extracted with dichloromethane. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane-ethyl acetate=3:1~1:1) to give 7 as colorless solid (41.0 mg, 87%). HPLC (Daicel Chiralcel OD-H, hexane-i-PrOH=9:1): 96% ee. Mp 104.0-106.0 °C; IR (KBr): 3123, 1671, 1620, 1463, 1226, 1208, 1115, 1036 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.37 (s, 3H), 3.10 (dd, J= 3.2 and 16.5 Hz, 1H), 3.30 (dd, J= 12.1 and 16.5 Hz, 1H), 5.55 (dd, J= 3.2 and 12.1 Hz, 1H), 6.73 (d, J= 7.4 Hz, 1H), 6.92 (d, J= 8.3 Hz, 1H), 7.22 (d, J= 8.1 Hz, 2H), 7.34 (d, J= 8.1 Hz, 2H), 7.43 (dd, J= 7.4 and 8.3 Hz, 1H), 11.01 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 21.20, 35.2, 80.8, 108.5, 116.4, 117.9, 126.1, 129.4, 134.9, 136.3, 138.8, 139.3, 162.3, 169.8; $\left[\alpha\right]_{D}^{24} +95.0$ (c 0.730, MeOH).


4.5.2. (R)-3-(p-Tolyl)-8-trifluoromethanesulfonyloxy-3,4-dihydroisocoumarin (8).
Under an argon atmosphere, trifluoromethanesulfonic anhydride (37.7 µL, 0.224 mmol) was added as a neat liquid to a solution of 7 (38.0 mg, 0.149 mmol) in pyridine (3.0 mL) at 0 °C. After being stirred for 1 h, the reaction mixture was allowed to warm to room temperature and stirred for 19 h. Additional trifluoromethanesulfonic anhydride (37.7 µL, 0.224 mmol) was added and the mixture was stirred for further 24 h at room temperature. The mixture was quenched with 2 M aqueous HCl and the product was extracted with ethyl acetate. The extract was washed successively with 2 M aqueous HCl, water, and brine, and dried over Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (toluene-toluene-ethyl acetate=20:1) to give 8 as colorless solid (44.7 mg, 77%). HPLC (Daicel Chiralpak AD-H, hexane-i-PrOH=8:2): 96% ee. Mp 159.5-161.0 °C; IR (KBr): 1723, 1614, 1431, 1267, 1224, 1141, 1012 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.37 (s, 3H), 3.18 (dd, J= 3.0 and 16.6 Hz, 1H), 3.35 (dd, J= 11.7 and 16.6 Hz, 1H), 5.51 (dd, J= 3.0 and 11.7 Hz, 1H), 7.21 (d, J= 8.1 Hz, 2H), 7.29 (d, J= 7.9 Hz, 1H), 7.33 (d, J= 8.1 Hz, 2H), 7.35 (d, J= 7.9 Hz, 1H), 7.63 (t, J= 7.9 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 21.19, 35.98, 79.54, 118.80 (q, J= 321 Hz), 119.11, 122.24, 126.08, 127.79, 129.45, 134.65, 134.72, 138.84, 142.25, 149.42, 160.75; $\left[\alpha\right]_{D}^{23} +144$ (c 0.500, CHCl₃).

HREIMS m/z. Calcd for C₁₇H₁₄F₃O₅S (M⁺): 386.0436. Found: 386.0429.
4.5.3. (R)-3-[(p-Tolyl)-3,4-dihydroisocoumarin (9). Under an argon atmosphere, triethylsilane (40.3 µL, 0.252 mmol) was added as a neat liquid to a solution of 8 (39.0 mg, 0.100 mmol), Pd(OAc)$_2$ (1.1 mg, 5.1 µmol), and 1,1’-bis(diphenylphosphino)ferrocene (2.8 mg, 5.1 µmol) in DMF (2.0 mL) at 60 °C. After being stirred for 30 min, the reaction mixture was cooled to room temperature and diluted with diethyl ether. The product was washed successively with water, saturated aqueous NaHCO$_3$, and brine, dried over Na$_2$SO$_4$, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane-ethyl acetate=3:1) to give 9 as colorless solid (23.0 mg, 97%). HPLC (Daicel Chiralpak AD-H, hexane-i-PrOH=7:3): 96% ee. Mp 93.5-94.5 °C; IR (KBr): 1720, 1605, 1463, 1275, 1066, 1006 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 2.37 (s, 3H), 3.11 (dd, $J$= 3.1 and 16.4 Hz, 1H), 3.33 (dd, $J$= 12.0 and 16.4 Hz, 1H), 5.52 (dd, $J$= 3.1 and 12.0 Hz, 1H), 7.21 (d, $J$= 8.1 Hz, 2H), 7.28 (d, $J$= 7.6 Hz, 1H), 7.36 (d, $J$= 8.1 Hz, 2H), 7.42 (t, $J$= 7.6 Hz, 1H), 7.56 (dt, $J$= 1.3 and 7.6 Hz, 1H), 8.15 (d, $J$= 7.6 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 21.19, 35.55, 79.93, 125.22, 126.11, 127.36, 127.83, 129.33, 130.41, 133.85, 135.64, 138.49, 139.05, 165.42; $\alpha$$_D^{23}$ +124 (c 1.15, MeOH) {lit.$^6$ $\alpha$$_D^{26}$ -132 (c 1.02, MeOH, >99% ee, (S)-isomer). HREIMS m/z. Calcd for C$_{16}$H$_{14}$O$_2$ (M$^+$): 238.0994. Found: 238.0972.

4.6. Synthesis of (R)- and (S)-8-hydroxy-3-(1-tridecyl)-3,4-dihydroisocoumarins (12a, b)

4.6.1 1-{2-[[(S)-4-Isopropyl-4,5-dihydrooxazol-2-yl]-3-methoxyphenyl]-2-pentadecanol (10). This compound was prepared from 4 (700 mg, 3.0 mmol) and 1-tetradecanal$^{16}$ (637 mg, 3.0 mmol) in a similar manner as described for 5 in 4.2.1. After chromatographic purification over Chromatorex NH-DM1020 silica gel (hexane-ethyl acetate=5:1~3:1), 10 was obtained as colorless semisolid (871 mg, 65%). HPLC (Daicel Chiralpak AD-H, hexane-i-PrOH=30:1): (S,R):(S,S)=1:1:1. IR (KBr): 3344, 1669, 1582, 1467, 1273, 1088 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 0.88 (t, $J$= 6.8 Hz, 3H, both isomers), 0.97 (d, $J$= 6.7 Hz, 1.44H, (S,S)-isomer), 1.00 (d, $J$= 6.7 Hz, 1.56H, (S,R)-isomer), 1.06 (d, $J$= 6.7 Hz, 1.44H, (S,S)-isomer), 1.10 (d, $J$= 6.7 Hz, 1.56H,
(S,R)-isomer), 1.20-1.60 (m, 24H, both isomers), 1.79-1.91 (m, 1H, both isomers), 2.68 (dd, J= 8.9 and 13.4 Hz, 0.48H, (S,S)-isomer), 2.73 (dd, J= 8.6 and 13.4 Hz, 0.52H, (S,R)-isomer), 2.83 (dd, J= 3.6 and 13.4 Hz, 0.48H, (S,S)-isomer), 2.86 (dd, J= 3.8 and 13.4 Hz, 0.52H, (S,R)-isomer), 3.70-3.80 (m, 1H, both isomers), 3.81 (s, 3H, both isomers), 4.05-4.19 (m, 2H, both isomers), 4.47 (dd, J= 8.1 and 9.3 Hz, 0.48H, (S,S)-isomer), 4.49 (dd, J= 7.8 and 9.2 Hz, 0.52H, (S,R)-isomer), 5.08 (br s, 0.52H, (S,R)-isomer), 5.16 (br s, 0.48H, (S,S)-isomer), 6.79 (d, J= 8.4 Hz, 1H, both isomers), 6.86 (d, J= 7.8 Hz, 0.48H, (S,S)-isomer), 6.87 (d, J= 7.8 Hz, 0.52H, (S,R)-isomer), 7.32 (dd, J= 7.8 and 8.4 Hz, 1H, both isomers). HREIMS m/z. Calcd for C_{23}H_{24}NO_{3} (M^+): 445.3556. Found: 445.3547.

4.6.2. Diastereomer-selective lactonization of 10. A mixture of 10 (504 mg, 1.13 mmol), silica gel (Merck Silica gel 60) (1.60 g), dichloromethane (40 mL) were stirred for 30 h at 0 °C and worked up in a similar manner as described in 4.4. After chromatographic purification over Silica Gel 60N (toluene-ethyl acetate=5:1–ethyl acetate containing 1% triethylamine), 11a (261 mg, 64%) and 10b (173 mg, 34%) were isolated.

4.6.2.1. (R)-8-Methoxy-3-(1-tridecyl)-3,4-dihydroisocoumarin (11a) Colorless solid. HPLC (Daicel Chiralpak AD-H, hexane-i-PrOH=9:1): 64% ee. Mp 73.0-75.0 °C; IR (KBr): 1733, 1596, 1484, 1220, 1091 cm^{-1}; ^1H NMR (400 MHz, CDCl_{3}): δ 0.88 (t, J= 6.7 Hz, 3H), 1.23-1.37 (m, 20H), 1.37-1.48 (m, 1H), 1.48-1.60 (m, 1H), 1.60-1.71 (m, 1H), 1.71-1.89 (m, 1H), 2.83 (dd, J= 3.5 and 16.0 Hz, 1H), 2.90 (dd, J= 10.7 and 16.0 Hz, 1H), 3.94 (s, 3H), 4.33-4.41 (m, 1H), 6.79 (d, J= 7.6 Hz, 1H), 6.90 (d, J= 8.3 Hz, 1H), 7.43 (dd, J= 7.6 and 8.3 Hz, 1H); ^13C NMR (100 MHz, CDCl_{3}): δ 14.09, 22.66, 24.94, 29.32, 29.37, 29.48, 29.54, 29.60, 29.62, 29.62, 29.65, 31.89, 34.44, 34.68, 56.10, 77.73, 110.74, 113.90, 119.08, 134.13, 141.92, 160.94, 162.51; [α]_{D}^{26} -55.0 (c 1.00, MeOH). HREIMS m/z. Calcd for C_{23}H_{36}O_{3} (M^+): 360.2664. Found: 360.2664.

4.6.2.2. (S)-1-{2-[(S)-4-Isopropyl-4,5-dihydrooxazol-2-yl]-3-methoxyphenyl}-2-pentadecanoic acid (10b). Colorless oil. HPLC (Daicel Chiralpak AD-H, hexane-i-PrOH=30:1): 99% ee. IR (KBr): 3277, 1655, 1584, 1467, 1268, 1086 cm^{-1}; ^1H NMR (400 MHz, CDCl_{3}):
δ 0.88 (t, J = 6.7 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H), 1.22-1.60 (m, 24H), 1.79-1.91 (m, 1H), 2.68 (dd, J = 8.9 and 13.5 Hz, 1H), 2.83 (dd, J = 3.5 and 13.5 Hz, 1H), 3.71-3.81 (m, 1H), 3.81 (s, 3H), 4.09 (ddd, J = 6.7, 8.0 and 9.0 Hz, 1H), 4.16 (t, J = 8.0 Hz, 1H), 4.46 (dd, J = 8.0 and 9.0 Hz, 1H), 5.17 (br s, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 7.7 Hz, 1H), 7.32 (dd, J = 7.7 and 8.4 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 14.12, 18.52, 19.02, 22.70, 25.60, 29.37, 29.67, 29.71, 29.73, 29.83, 31.94, 32.78, 38.47, 40.69, 55.99, 70.93, 72.11, 72.74, 109.00, 118.57, 122.52, 130.97, 140.93, 158.23, 163.45; [α]D25 +14.5 (c 1.00, MeOH). HREIMS m/z. Calcd for C28H47NO3 (M+): 445.3556. Found: 445.3549.

4.6.3. (S)-8-Methoxy-3-(1-tridecyl)-3,4-dihydroisocoumarin (11b). This compound was prepared from 10b (91.2 mg, 0.205 mmol) in a similar manner as described for 6b in 4.4.3. After chromatographic purification over Silica Gel 60N (hexane-ethyl acetate=3:1), 11b was obtained as colorless solid (72.2 mg, 98%). HPLC (Daicel Chiralpak AD-H, hexane-i-PrOH=9:1): 98% ee. Mp 78.0-79.0 °C; [α]D25 +87.2 (c 1.00, MeOH). HREIMS m/z. Calcd for C23H36O3 (M+): 360.2664. Found: 360.2661.

4.6.4. (R)-8-Hydroxy-3-(1-tridecyl)-3,4-dihydroisocoumarin (12a). Under an argon atmosphere, a dichloromethane solution of BBr3 (1.0 M, 624 µL, 0.624 mmol) was added dropwise to a solution of 11a (150 mg, 0.416 mmol) in dichloromethane (10 mL) at −78 °C. After being stirred for 10 min at this temperature, the reaction mixture was allowed to warm to 0 °C and stirred for an additional 15 min. The mixture was quenched with water and extracted with dichloromethane. The extract was washed with brine, dried over Na2SO4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane-ethyl acetate=3:1) to give 12a as colorless solid (126 mg, 87%). HPLC (Daicel Chiralcel OD-H, hexane-i-PrOH=200:1): 64% ee. Recrystallization from diethyl ether-hexane gave an optically pure sample as colorless needles. Mp 91.0-92.0 °C; IR (KBr): 1655, 1618, 1465, 1242 cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 0.88 (t, J = 6.8 Hz, 3H), 1.21-1.39 (m, 20H), 1.39-1.60 (m, 2H), 1.66-1.77 (m, 1H), 1.83-1.93 (m, 1H), 2.88-2.99 (m, 2H), 4.53-4.61 (m, 1H), 6.69 (d, J = 7.4 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 7.40 (dd, J = 7.4 and 8.4 Hz, 1H), 11.04 (s, 1H); 13C NMR (100 MHz, CDCl3): δ 14.12, 22.70, 24.84, 29.36, 29.47, 29.55, 29.64, 29.66, 29.69, 31.93, 32.95, 34.81, 79.77, 108.55,
116.17, 117.92, 136.07, 139.55, 162.18, 170.00; [α]D25 -34.4 (c 1.00, CHCl₃, >99% ee) {lit.8 [α]D23 -31 (c 1, CHCl₃): (R)-isomer}. HREIMS m/z. Caled for C₂₅H₃₄O₃ (M⁺): 346.2508. Found: 346.2494.

4.6.5. (S)-8-Hydroxy-3-(1-tridecyl)-3,4-dihydroisocoumarin (12b). This compound was prepared from 11b (50 mg, 0.139 mmol) in a similar manner as described for 12a. After chromatographic purification over Silica Gel 60N (hexane-ethyl acetate=3:1), 12b was obtained as colorless solid (45.6 mg, 95%). HPLC (Daicel Chiralcel OD-H, hexane-i-PrOH=200:1): 98% ee. Recrystallization from diethyl ether-hexane gave an optically pure sample as colorless needles. Mp 91.0-92.0 °C; [α]D25 +34.7 (c 0.705, CHCl₃, >99% ee) {lit.8 [α]D23 +32 (c 1, CHCl₃): (S)-isomer}. HREIMS m/z. Caled for C₂₂H₃₄O₃ (M⁺): 346.2508. Found: 346.2496.

4.7. Synthesis of (S)- and (R)-phyllo dulcins (16a, b)

4.7.1. 2-{2-[(S)-4-Isopropyl-4,5-dihydrooxazol-2-yl]-3-methoxyphenyl}-1-(4-methoxy-3-methoxymethoxyphenyl)ethanol (13). This compound was prepared from 4 (933 mg, 4.0 mmol) and O-methoxymethylisovanillin¹⁷ (785 mg, 4.0 mmol) in a similar manner as described for 5 in 4.2.1. After chromatographic purification over Chromatorex NH-DM1020 silica gel (hexane-ethyl acetate=1:1), 13 was obtained as colorless semisolid (1.35 g, 78%). HPLC (Daicel Chiralpak AD-H, hexane-i-PrOH=1:1): (S,S):(S,R)=1:1.2. IR (KBr): 3172, 1649, 1583, 1515, 1475, 1270, 1083 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.00 (d, J= 6.7 Hz, 1.33H, (S,S)-isomer), 1.02 (d, J= 6.5 Hz, 1.67H, (S,R)-isomer), 1.13 (d, J= 6.5 Hz, 1.67H, (S,R)-isomer), 1.14 (d, J= 6.7 Hz, 1.33H, (S,S)-isomer), 1.84-1.98 (m, 1H, both isomers), 2.93-3.10 (m, 2H, both isomers), 3.52 (s, 1.33H, (S,S)-isomer), 3.53 (s, 1.67H, (S,R)-isomer), 3.84 (s, 3H, both isomers), 3.88 (s, 3H, both isomers), 4.12-4.24 (m, 2H, both isomers), 4.48-4.58 (m, 1H, both isomers), 4.80 (dd, J= 4.9 and 8.6 Hz, 0.56H, (S,R)-isomer), 4.88 (dd, J= 4.1 and 8.3 Hz, 0.44H, (S,S)-isomer), 5.21 (d, J= 6.7 Hz, 0.44H, (S,S)-isomer), 5.23 (d, J= 6.8 Hz, 0.56H, (S,R)-isomer), 5.24 (d, J= 6.7 Hz, 0.44H, (S,S)-isomer), 5.28 (d, J= 6.8 Hz, 0.56H, (S,R)-isomer), 6.15 (br s, 1H, both isomers), 6.76 (d, J= 7.7 Hz, 0.44H, (S,S)-isomer), 6.81 (d, J= 8.4 Hz, 0.44H, (S,S)-isomer), 6.82 (d, J= 8.4 Hz, 0.56H,
(S,R)-isomer), 6.87 (d, J = 8.2 Hz, 0.56H, (S,R)-isomer), 6.88 (d, J = 8.2 Hz, 1H, both isomers), 7.00 (dd, J = 2.0 and 8.2 Hz, 0.56H, (S,R)-isomer), 7.02 (dd, J = 2.0 and 8.2 Hz, 0.44H, (S,S)-isomer), 7.18 (d, J = 2.0 Hz, 0.44H, (S,S)-isomer), 7.21 (d, J = 2.0 Hz, 0.56H, (S,R)-isomer), 7.30 (dd, J = 7.7 and 8.4 Hz, 0.44H, (S,S)-isomer), 7.34 (dd, J = 7.7 and 8.4 Hz, 0.56H, (S,R)-isomer). HREIMS m/z. Calcd for C_{24}H_{31}NO_6 (M^+): 429.2151. Found: 429.2136.

4.7.2. Diastereomer-selective lactonization of 13. A mixture of 13 (950 mg, 2.21 mmol), silica gel (Merck Silica gel 60) (3.20 g), dichloromethane (80 mL) were stirred for 30 h at 0 °C and worked up in a similar manner as described in 4.4. After chromatographic purification over Silica Gel 60N (dichloromethane-ethyl acetate=10:1 containing 1% triethylamine), 14a (436 mg, 57%) and 13b (293 mg, 31%) were isolated.

4.7.2.1. (S)-8-Methoxy-3-(4-methoxy-3-methoxymethoxyphenyl)-3,4-dihydroisocoumarin (14a). Colorless solid. HPLC (Daicel Chiralcel OD-H, hexane-EtOH=7:3): 49% ee. Mp 97.5-99.0 °C; IR (KBr): 1719, 1596, 1521, 1476, 1237, 1082, 997 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.04 (dd, J = 2.7 and 16.2 Hz, 1H), 3.30 (dd, J = 12.0 and 16.2 Hz, 1H), 3.53 (s, 3H), 3.90 (s, 3H), 3.97 (s, 3H), 5.24 (d, J = 6.8 Hz, 1H), 5.27 (d, J = 6.8 Hz, 1H), 5.35 (dd, J = 2.7 and 12.0 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 6.96 (d, J = 8.6 Hz, 1H), 7.11 (dd, J = 2.1 and 8.3 Hz, 1H), 7.25 (d, J = 2.1 Hz, 1H), 7.47 (dd, J = 7.5 and 8.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 36.58, 56.00, 56.21, 56.31, 78.94, 95.66, 111.08, 111.66, 113.83, 114.81, 119.23, 120.64, 131.14, 134.62, 141.81, 146.55, 150.03, 161.30, 162.39; [α]_D^{26} -68.8 (c 1.00, MeOH). HREIMS m/z. Calcd for C_{19}H_{20}O_6 (M⁺): 344.1260. Found: 344.1257.

4.7.2.2. (R)-2-[((S)-4-Isopropyl-4,5-dihydrooxazol-2-yl)-3-methoxyphenyl]-1-(4-methoxy-3-methoxymethoxyphenyl)ethanol (13b). Colorless semisolid. HPLC (Daicel Chiralpak AD-H, hexane-i-PrOH=1:1): 97% de. IR (KBr): 3387, 1655, 1584, 1509, 1467, 1265, 1080, 1010 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.01 (d, J = 6.7 Hz, 3H), 1.12 (d, J = 6.7 Hz, 3H), 1.83-1.94 (m, 1H), 2.93-3.04 (m, 2H), 3.53 (s, 3H), 3.83 (s, 3H),
3.87 (s, 3H), 4.13-4.23 (m, 2H), 4.47-4.57 (m, 1H), 4.80 (dd, J= 4.7 and 9.0 Hz, 1H), 5.22 (d, J= 6.7 Hz, 1H), 5.27 (d, J= 6.7 Hz, 1H), 6.80 (br s, 1H), 6.82 (d, J= 8.4 Hz, 1H), 6.87 (d, J= 7.7 Hz, 1H), 6.87 (d, J= 8.3 Hz, 1H), 7.00 (dd, J= 1.9 and 8.3 Hz, 1H), 7.20 (d, J= 1.9 Hz, 1H), 7.33 (dd, J= 7.7 and 8.4 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 18.73, 18.99, 32.96, 43.75, 56.02, 56.05, 56.20, 71.48, 71.88, 74.97, 95.61, 109.29, 111.54, 113.88, 118.43, 119.38, 122.50, 131.19, 139.24, 140.26, 146.57, 148.68, 158.34, 164.05; [α]D 25 +32.1 (c 1.00, MeOH). HREIMS m/z. Calcd for C24H31NO6 (M+): 429.2151. Found: 429.2144.

4.7.3.

(R)-8-Methoxy-3-(4-methoxy-3-methoxymethoxyphenyl)-3,4-dihydroisocoumarin (14b). This compound was prepared from 13b (238 mg, 0.553 mmol) in a similar manner as described for 6b in 4.4.3. After chromatographic purification over Silica Gel 60N (hexane-ethyl acetate=1:1), 14b was obtained as colorless solid (139 mg, 73%). HPLC (Daicel Chiralcel OD-H, hexane-EtOH=7:3): 91% ee. Mp 98.5-101.0 °C; [α]D 25 +122 (c 1.00, MeOH). HREIMS m/z. Calcd for C19H20O6 (M+): 344.1260. Found: 344.1247.

4.7.4.

(S)-8-Hydroxy-3-(4-methoxy-3-methoxymethoxyphenyl)-3,4-dihydroisocoumarin (15a). Under an argon atmosphere, a solution of 14a (50 mg, 0.145 mmol) and LiCl (18.5 mg, 0.435 mmol) in DMF (4.0 mL) was heated at 150 °C for 17 h. The reaction mixture was allowed to cool to room temperature and quenched with saturated aqueous NH4Cl. The product was extracted with ethyl acetate and the extract was washed successively with water and brine, dried over Na2SO4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (toluene-ethyl acetate=20:1) to give 15a as colorless solid (19.8 mg, 41%). HPLC (Daicel Chiralpak AS, hexane-i-PrOH=1:1): 43% ee. Mp 93.0-95.0 °C; IR (KBr): 3431, 1671, 1615, 1514, 1463, 1235, 1159, 1000 cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 3.10 (dd, J= 3.2 and 16.5 Hz, 1H), 3.33 (dd, J= 12.2 and 16.5 Hz, 1H), 3.52 (s, 3H), 3.90 (s, 3H), 5.24 (d, J= 6.8 Hz, 1H), 5.26 (d, J= 6.8 Hz, 1H), 5.52 (dd, J= 3.2 and 12.2 Hz, 1H), 6.74 (d, J= 7.4 Hz, 1H), 6.92 (d, J= 8.4 Hz, 2H), 7.09 (dd, J= 2.1 and 8.4 Hz, 1H), 7.25 (d, J= 2.1 Hz, 1H), 7.44 (dd, J= 7.4 and 8.4 Hz, 1H), 11.00 (s, 1H); 13C NMR
(100 MHz, CDCl$_3$): $\delta$ 35.03, 56.02, 56.32, 80.74, 95.69, 108.47, 111.73, 114.76, 116.41, 117.94, 120.59, 130.51, 136.32, 139.39, 146.74, 150.30, 162.31, 169.82; $[\alpha]_D^{25}$ -30.8 (c 0.980, MeOH). HREIMS $m/z$. Calcd for C$_{18}$H$_{18}$O$_6$ (M$^+$): 330.1103. Found: 330.1103.

4.7.5. (R)-8-Hydroxy-3-(4-methoxy-3-methoxymethoxyphenyl)-3,4-dihydroisocoumarin (15b). This compound was prepared from 14b (50.0 mg, 0.145 mmol) in a similar manner as described for 15a. After chromatographic purification over Silica Gel 60N (toluene-ethyl acetate=20:1), 15b was obtained as colorless solid (18.6 mg, 39%). HPLC (Daicel Chiralpak AS, hexane-PrOH=1:1): 83% ee. Mp 92.0-94.0 °C; $[\alpha]_D$ +56.8 (c 0.835, MeOH). HREIMS $m/z$. Calcd for C$_{18}$H$_{18}$O$_6$ (M$^+$): 330.1103. Found: 330.1105.

4.7.6. (S)-Phyllodulcin (16a). To a solution of 15a (17.1 mg, 51.7 µmol) in methanol (3.0 mL) was added catalytic amount of concd. HCl (2 drops). After being stirred for 3 h at room temperature, the mixture was evaporated under reduced pressure. The product was dissolved in dichloromethane and the solution was washed with brine, dried over Na$_2$SO$_4$, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane-ethyl acetate=1:1) to give 16a as colorless solid (14.5 mg, 98%). HPLC (Daicel Chiralpak AD, hexane-EtOH=1:1): 42% ee. Mp 103.0-107.0 °C; IR (KBr): 3346, 1675, 1622, 1587, 1520, 1467, 1282, 1231, 1208, 1113 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.09 (d$d$, $J$= 3.2 and 16.5 Hz, 1H), 3.30 (d$d$, $J$= 12.1 and 16.5 Hz, 1H), 3.91 (s, 3H), 5.50 (d$d$, $J$= 3.2 and 12.1 Hz, 1H), 5.70 (br s, 1H), 6.73 (d, $J$= 7.4 Hz, 1H), 6.87 (d, $J$= 8.3 Hz, 1H), 6.92 (d, $J$= 8.4 Hz, 1H), 6.95 (d$d$, $J$= 2.1 and 8.3 Hz, 1H), 7.02 (d, $J$= 2.1 Hz, 1H), 7.43 (dd, $J$= 7.4 and 8.4 Hz, 1H), 11.01 (br s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 35.02, 56.05, 80.66, 108.49, 110.62, 112.63, 116.40, 117.95, 118.23, 131.13, 136.31, 139.38, 145.85, 147.00, 162.30, 169.79; $[\alpha]_D^{25}$ -29.8 (c 0.725, acetone) {lit.$^{10}$ $[\alpha]_D^{20}$ -77.6 (c 1.02, acetone): (S)-isomer}. HREIMS $m/z$. Calcd for C$_{16}$H$_{14}$O$_5$ (M$^+$): 286.0841. Found: 286.0825.

4.7.7. (R)-Phyllodulcin (16b). This compound was prepared from 15b (13.6 mg, 41.2 µmol) in a similar manner as described for 16a. After chromatographic purification over Silica Gel 60N (hexane-ethyl acetate=1:1), 16b was obtained as colorless solid
HPLC (Daicel Chiralpak AD, hexane-EtOH=1:1): 83% ee. Mp 110.0-112.0 °C; [α]23D +56.1 (c 0.585, acetone) \{\text{lit.}^{10} [α]20D +78.8 (c 1.01, acetone): (R)-isomer\}. HREIMS m/z. Calcd for C_{16}H_{14}O_{5} (M^+): 286.0841. Found: 286.0819.

Acknowledgments

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References


14. Recrystallization of 16a from two different solvent systems (diethyl ether-hexane or ethanol) has been attempted. Unfortunately, however, the enantiomeric purity of 16a was not improved.
Graphical abstract

1. lateral lithiation
2. R-CHO

MeO
H
\[
\text{silica gel diastereomer-selective lactonization}
\]

MeO
H
\[
\text{silica gel}
\]

1. lat. lithation
2. R-CHO

MeO
H

H

MeO
H

H