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Tetrahedron
Tetrahedron 63 (2007) 7178–7186

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

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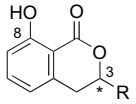
Received 13 March 2007; revised 25 April 2007; accepted 26 April 2007
Available online 3 May 2007

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.

1. Introduction

The 3,4-dihydroisocoumarins constitute a class of natural products, which exhibit a wide range of biological activities such as antifungal,[1a] antiulcer,[1b] antileukemic,[1c] antiallergic,[1d] differentiation-inducing,[1e] and antimalarial[1f] 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 (Fig. 1).

Although a variety of synthetic approaches to this class of compounds have been developed,[2] the most straightforward route may be the reaction of laterally lithiated *o*-toluic acid derivatives with aldehydes.[3] In 2002, we reported unprecedented reagent-controlled optional *ortho*- and lateral lithiations of 4,4-dimethyl-2-(*o*-tolyl)oxazolines.[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.[5] Recently, we also investigated an asymmetric synthesis of 3-substituted 3,4-dihydroisocoumarins via stereoselective addition of laterally lithiated chiral 2-(*o*-tolyl)oxazoline **1** to aldehydes.[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).



R = aryl or alkyl

Figure 1. Common scaffold of 3,4-dihydroisocoumarin natural products.

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

Keywords: Asymmetric synthesis; 3,4-Dihydroisocoumarin; Oxazoline; Lateral lithiation; Diastereomer-selective lactonization; Silica gel.
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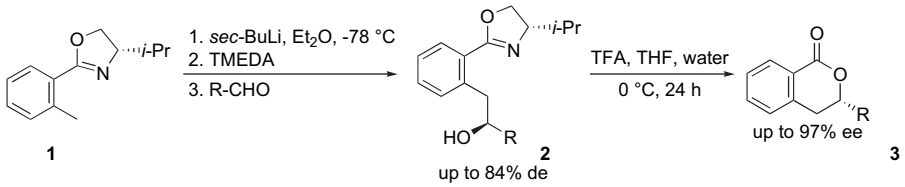
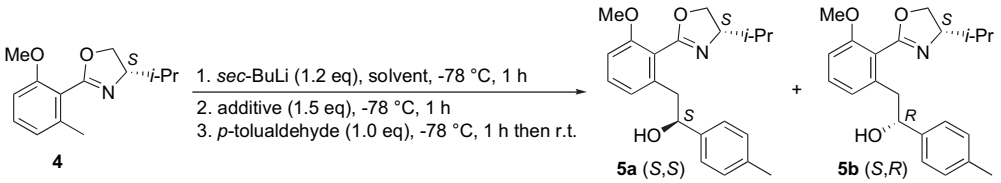
doi:10.1016/j.tet.2007.04.092



Scheme 1.

Table 1. Addition of laterally lithiated oxazoline **4** to *p*-tolualdehyde



Entry	Solvent	Additive	Yield[a] (%)	dr (**5a**/**5b**)[b]
1	Et_2O	None	80	1:1.3
2	THF	None	78	1.1:1
3	Et_2O	TMEDA	70	1:1.1
4	Et_2O	PMDTA[c]	56	1:1.2
5	THF	*tert*-BuOK	75	1:1

[a] Isolated yield.
[b] Determined by HPLC analysis (Daicel Chiralpak AD-H).
[c] *N*,*N*,*N*′,*N*″,*N*″-Pentamethyldiethylenetriamine.

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.[6]

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,[6] 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 Section 2.1, 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.[6]

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 30 °C for 4 days in 93% yield.

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 BBr_3 to give demethylated compound **7** in 87% yield. The hydroxy group

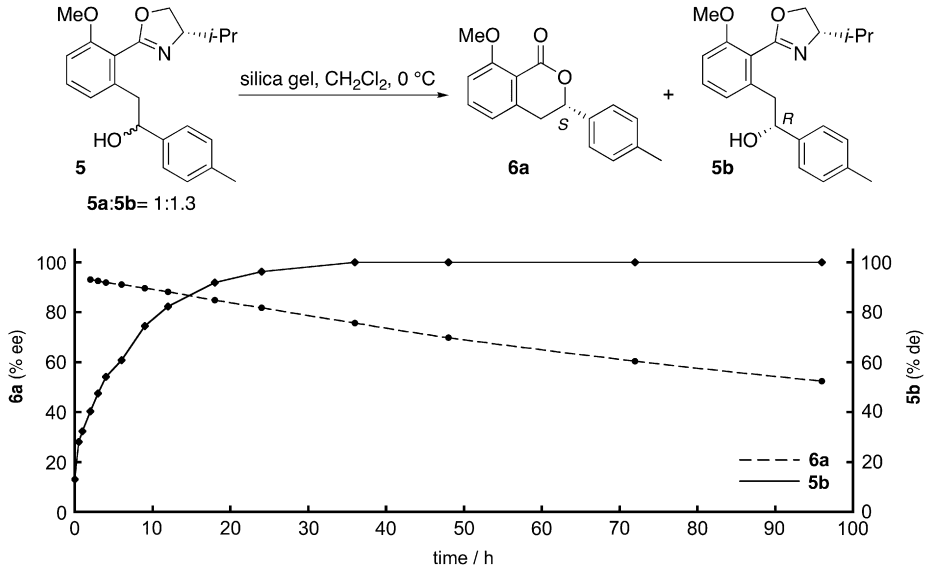
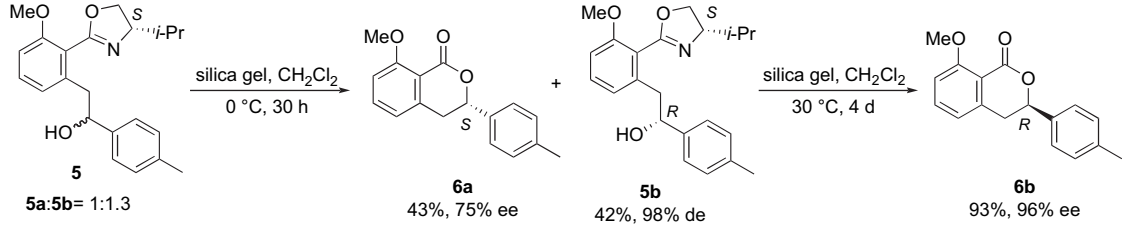
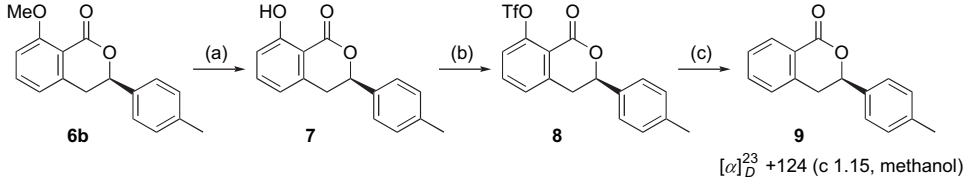


Figure 2. Silica gel-catalyzed lactonization of **5**.



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



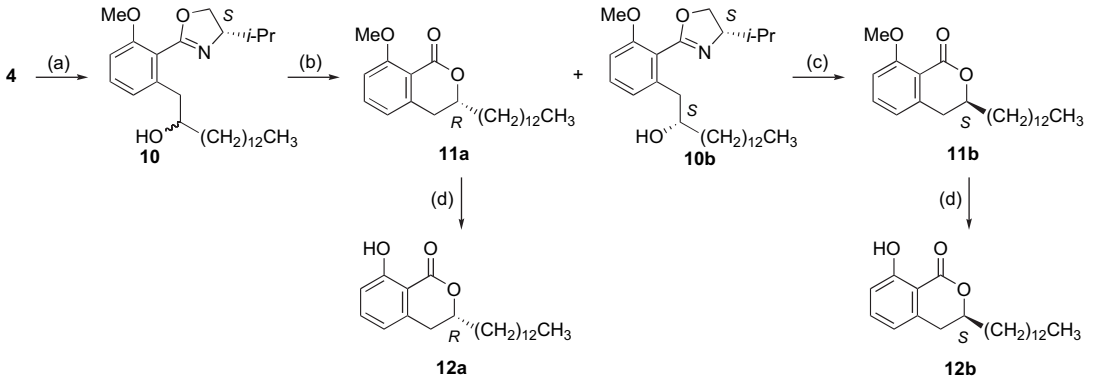
Scheme 3. Reagents and conditions: (a) BBr_3 (1.0 equiv), CH_2Cl_2, −78 °C, 3 h then 0 °C, 1 h (87%, 96% ee); (b) (1) Tf_2O (1.5 equiv), pyridine, 0 °C, 1 h then rt, 19 h, (2) Tf_2O (1.5 equiv), rt, 24 h (77%, 96% ee); (c) $Pd(OAc)_2$ (5 mol %), dppf (5 mol %), Et_3SiH (2.5 equiv), DMF, 60 °C, 30 min (97%, 96% ee).

of **7** was trifluoromethanesulfonated with Tf_2O in pyridine to generate **8**. Finally, the trifluoromethanesulfonyloxy group of **8** was removed by hydrogenolysis using Et_3SiH in the presence of $Pd(OAc)_2$ and 1,1′-bis(diphenylphosphino)ferrocene (dppf)[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*.

2.4. Asymmetric synthesis of the natural products 12 and 16

Next, we applied the aforementioned method for asymmetric synthesis of 3,4-dihydroisocoumarin 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 BBr_3 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.[9] It has been reported that (*R*)-enantiomer **16b** exhibits an intensely sweet taste, while

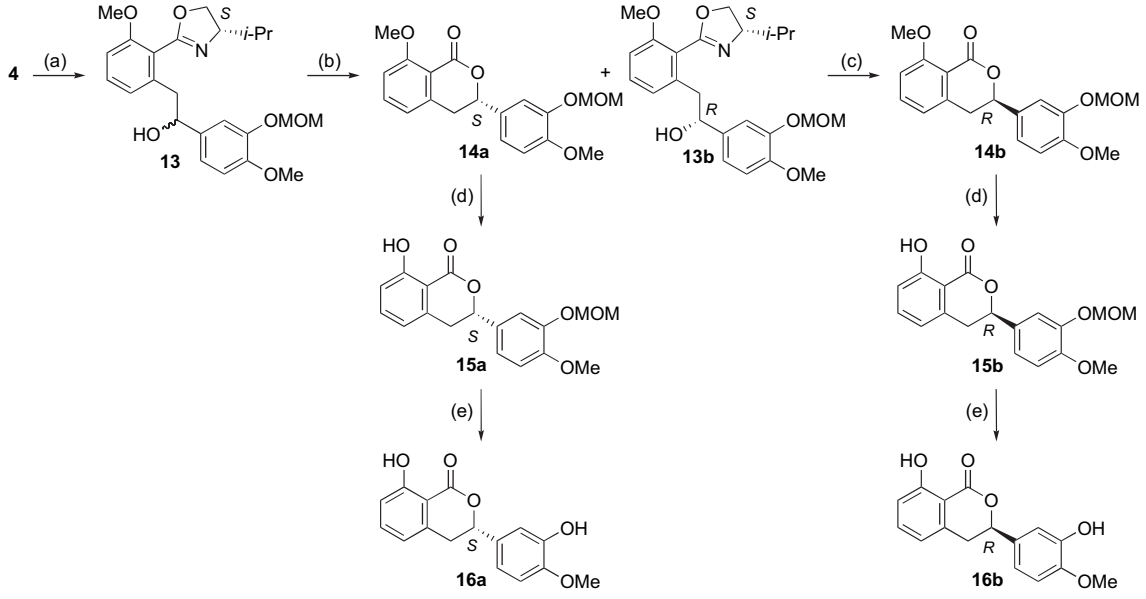


Scheme 4. Synthesis of (*R*)- and (*S*)-8-hydroxy-3-(1-tridecyl)-3,4-dihydroisocoumarins **12a**,**b**. Reagents and conditions: (a) (1) *sec*-BuLi (1.2 equiv), Et_2O, −78 °C, 1 h, (2) 1-tetradecanal, −78 °C, 1 h then rt [65%, (*S*,*R*):(*S*,*S*)=1.1:1]; (b) silica gel, CH_2Cl_2, 0 °C, 30 h (**11a**: 64%, 64% ee; **10b**: 34%, 99% de); (c) silica gel, CH_2Cl_2, 30 °C, 4 days (98%, 98% ee); (d) BBr_3, CH_2Cl_2, −78 °C, 10 min then 0 °C, 15 min (**12a**: 87%, 64% ee; **12b**: 95%, 98% ee).

the (*S*)-enantiomer **16a** is completely tasteless.[10] 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.[11] 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 BBr_3 afforded only completely racemized (±)-phyllodulcin even at −78 °C. After an extensive survey for deprotection conditions (BCl_3, TMSI, TMSBr, $Me_2NCH_2CH_2SNa$/DMF[12]), we found that the methyl group of **14b** could be removed by heating with lithium chloride in dry DMF[13] 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.



Scheme 5. Synthesis of (*S*)- and (*R*)-phyllodulcins **16a**,**b**. Reagents and conditions: (a) (1) *sec*-BuLi (1.2 equiv), Et_2O, −78 °C, 1 h, (2) *O*-methoxymethylisovanillin, −78 °C, 1 h then rt [78%, (*S*,*S*):(*S*,*R*)=1:1.2]; (b) silica gel, CH_2Cl_2, 0 °C, 30 h (**14a**: 57%, 49% ee; **13b**: 31%, 97% de); (c) silica gel, CH_2Cl_2, 30 °C, 4 days (73%, 91% ee); (d) LiCl (3 equiv), DMF, 150 °C, 17 h (**15a**: 41%, 43% ee; **15b**: 39%, 83% ee); (e) concd HCl, MeOH, rt, 3 h (**16a**: 98%, 42% ee; **16b**: quant., 83% ee).

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[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_2SO_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^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 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); ^{13}C NMR (100 MHz, $CDCl_3$): δ 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 *m*/*z* calcd for $C_{14}H_{19}NO_2$ (M^+): 233.1416; found: 233.1399.

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

The reactions summarized in Table 1 were conducted in a similar manner as described in the previous paper.[6] 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 Na_2SO_4, 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}; ^{1}H NMR (400 MHz, $CDCl_3$): 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), 6.81 (d, J=8.3 Hz, 0.56H, (*S*,*R*)-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 $C_{22}H_{27}NO_3$ (M^+): 353.1991; found: 353.1972.

4.3. Silica gel-catalyzed lactonization of 5: HPLC analysis

The results shown in Figure 2 were obtained as follows. The addition product **5** (**5a**/**5b**=1:1.3) (50 mg, 0.141 mmol) and 2,3-dimethylnaphthalene (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 2 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 to 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, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.17, 36.72, 56.21, 79.02, 111.09, 113.90, 119.22, 126.19, 129.25, 134.59, 135.61, 138.33, 141.81, 161.30, 162.34; $[\alpha]_D^{25}$ −140 (*c* 1.00, MeOH). HREIMS *m/z* calcd for $C_{17}H_{16}O_3$ (M^+): 268.1099; found: 268.1090.

4.4.2. (*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}; ^1H NMR (400 MHz, $CDCl_3$): δ 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 (ddd, 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), 4.83 (dd, J=3.9 and 9.3 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, $CDCl_3$): δ 18.72, 19.07, 21.11, 32.89, 43.82, 56.05, 71.38, 72.03, 75.19, 109.28, 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 30 °C. 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 $NaHCO_3$ and extracted with dichloromethane. The extract was washed with brine, dried over Na_2SO_4, 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, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.20, 35.12, 80.83, 108.50, 116.40, 117.94, 126.13, 129.43, 134.99, 136.31, 138.81, 139.39, 162.29, 169.83; $[\alpha]_D^{24}$ +95.0 (*c* 0.730, MeOH). HREIMS *m/z* calcd for $C_{16}H_{14}O_3$ (M^+): 254.0943; found: 254.0930.

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 Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (toluene to 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, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; $[\alpha]_D^{23}$ +144 (*c* 0.500, $CHCl_3$). HREIMS *m/z* calcd for $C_{17}H_{13}F_3O_5S$ (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_2SO_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, 1121, 1066, 1006 cm^{-1}; ^1H 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 Section 4.2.1. After chromatographic purification over Chromatorex NH-DM1020 silica gel (hexane–ethyl acetate=5:1–3:1), **10** was obtained as colorless semi-solid (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}; ^1H 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 $C_{28}H_{47}NO_3$ (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), and dichloromethane (40 mL) was stirred for 30 h at 0 °C and worked up in a similar manner as described in Section 4.4. After chromatographic purification over Silica Gel 60N (toluene–ethyl acetate=5:1 to 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); ^{13}C 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; $[\alpha]_D^{26}$ −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-pentadecanol (10b). Colorless oil. HPLC (Daicel Chiralpak AD-H, hexane–*i*-PrOH=30:1): 99% de. 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; $[\alpha]_D^{26}$ −14.5 (*c* 1.00, MeOH). HREIMS *m*/*z* calcd for $C_{28}H_{47}NO_3$ (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 Section 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; $[\alpha]_D^{25}$ +87.2 (*c* 1.00, MeOH). HREIMS *m*/*z* calcd for $C_{23}H_{36}O_3$ (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 BBr_3 (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 Na_2SO_4, 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, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; $[\alpha]_D^{25}$ −34.4 (*c* 1.00, $CHCl_3$, >99% ee)

{lit.[8] $[\alpha]_D^{23}$ −31 (*c* 1, $CHCl_3$): (*R*)-isomer}. HREIMS *m/z* calcd for $C_{22}H_{34}O_3$ (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; $[\alpha]_D^{25}$ +34.7 (*c* 0.705, $CHCl_3$, >99% ee) {lit.[8] $[\alpha]_D^{23}$ +32 (*c* 1, $CHCl_3$): (*S*)-isomer}. HREIMS *m/z* calcd for $C_{22}H_{34}O_3$ (M^+): 346.2508; found: 346.2496.

4.7. Synthesis of (*S*)- and (*R*)-phyllodulcins (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*-methoxymethylisovanillin[17] (785 mg, 4.0 mmol) in a similar manner as described for **5** in Section 4.2.1. After chromatographic purification over Chromatorex NH-DM1020 silica gel (hexane–ethyl acetate=1:1), **13** was obtained as colorless semi-solid (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, $CDCl_3$): 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), and dichloromethane (80 mL) was stirred for 30 h at 0 °C and worked up in a similar manner as described in Section 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, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; $[\alpha]_D^{26}$ −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-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]-3-methoxyphenyl}-1-(4-methoxy-3-methoxymethoxyphenyl)ethanol (13b). Colorless semi-solid. 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, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; $[\alpha]_D^{26}$ −32.1 (*c* 1.00, MeOH). HREIMS *m/z* calcd for $C_{24}H_{31}NO_6$ (M^+): 429.2151; found: 429.2154.

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 Section 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; $[\alpha]_D^{25}$ +122 (*c* 1.00, MeOH). HREIMS *m/z* calcd for $C_{19}H_{20}O_6$ (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 NH_4Cl. The product was extracted with ethyl acetate and the extract was washed successively with water and brine, dried over Na_2SO_4, 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, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): δ 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–*i*-PrOH=1:1): 83% ee. Mp 92.0–94.0 °C; $[\alpha]_D^{25}$ +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 (two 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_2SO_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, $CDCl_3$): δ 3.09 (dd, J=3.2 and 16.5 Hz, 1H), 3.30 (dd, J=12.1 and 16.5 Hz, 1H), 3.91 (s, 3H), 5.50 (dd, 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 (dd, 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, $CDCl_3$): δ 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; $[\alpha]_D^{22}$ −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 (11.7 mg, quant.). HPLC (Daicel Chiralpak AD, hexane–EtOH=1:1): 83% ee. Mp 110.0–112.0 °C; $[\alpha]_D^{23}$ +56.1 (c 0.585, acetone) {lit.[10] $[\alpha]_D^{20}$ +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.

Acknowledgements

This research was supported by the president's discretionary fund of Nagasaki University, Japan.

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