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Synthesis of Both Enantiomers of Hiburipyranone

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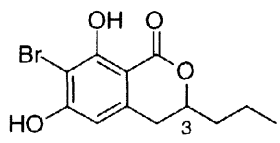
Abstract: Both enentiomers of hiburipyranone, a cytotoxic metabolite of marine sponge, was synthesized employing Sharpless' asymmetric dihydroxylation as a key step and absolute configuration of the natural compound at C-3 position was determined to be *R*.

Keywords: Asymmetric Synthesis; Cytotoxins; Isocoumarins; Hiburipyranone.

INTRODUCTION

Hiburipyranone (**1**, Fig. 1) was isolated[1] in 1991 by Fusetani *et al.* from a marine sponge *Mycale adhaerens*. It has a 3,4-dihydroisocoumarin skeleton and is cytotoxic against P388 murine leukemia cells (IC_{50} = 0.19 μg/ml). Although racemic hiburipyranone was synthesized[2] by us in 1997, absolute coufiguration at C-3 position has not been clarified. Herein, we report an enantioselective synthesis of (*R*)-**1** and (*S*)-**1** and determination of the absolute configuration of natural hiburipyranone as a part of our synthetic studies on isocoumarins, which have rather simple structures with many remarkable bioactivities.



1
Hiburipyranone

Fig. 1

RESULTS AND DISCUSSION

In our initial synthetic study, we adopted the same strategy with our acctophthalidin synthesis[3] as shown in Scheme 1. Dihydroxylation of an olefin **3** gave a phthalide **4** directly under the usual AD reaction conditions.[4] Deoxygenation at the benzylic position of the phthalide **4** was examined in detail; (a) hydrogenolysis using Pd

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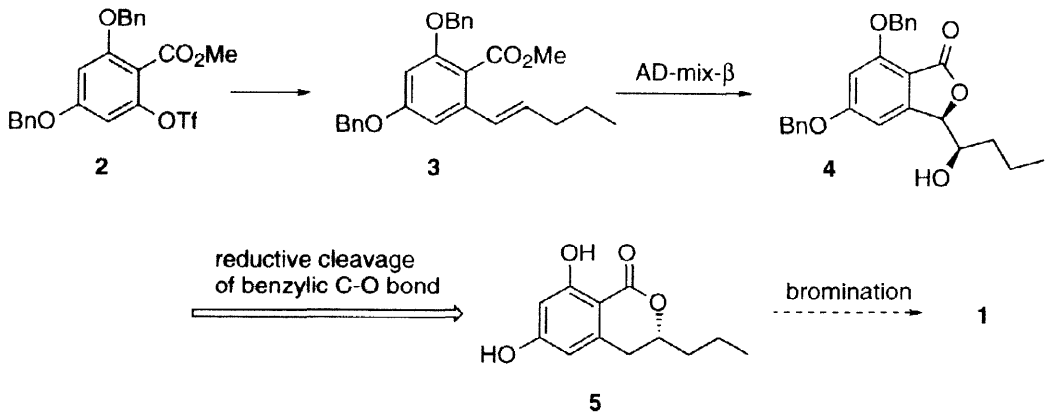
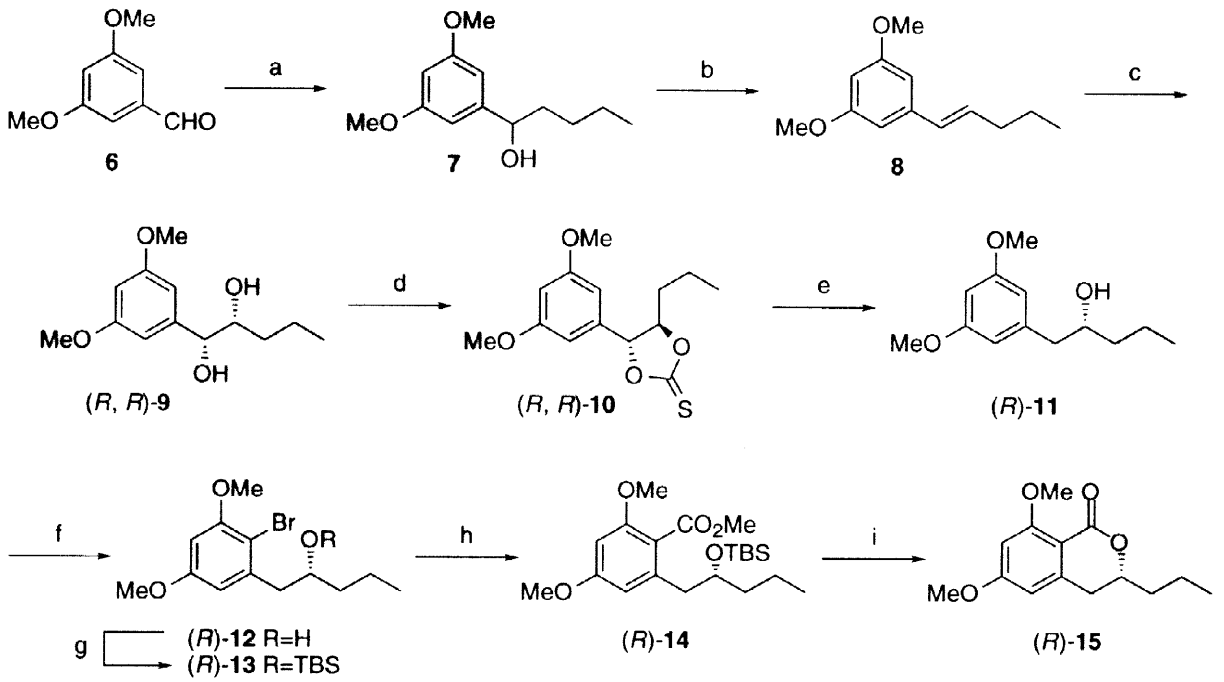
catalyst [10% Pd-C, $Pd(OH)_2$-C, Pd black], in acidic, neutral or basic media, under 1-50 atm, at rt-50°C; (b) nucleophilic lactone opening using iodotrimethylsilane,[5,6] alkyl or aryl mercaptan,[7,8] and benzeneselenol;[9] (c) dissolving metal reduction in liquid ammonia or ethylamine. Most of these reactions, however, resulted in recovery of phthalide skeleton or decomposition of the structure. Only in the case of the dissolving metal reduction, desired material **5** was obtained in very poor yield (<12%). It turned out that the phthalide group in **4** was extremely resistant to reductive elimination of the benzylic C-O bond, and then we concluded that methoxycarbonyl group had to be introduced after the Sharpless' asymmetric dihydroxylation in order to prevent the formation of phthalide.



Scheme 1

We then selected commercially available 3,5-dimethoxybenzaldehyde (**6**) as a starting material (Scheme 2). This aldehyde was treated with *n*-butyllithium in tetrahydrofuran at −78°C to give racemic benzyl alcohol (**7**). The crude **7** was boiled with 20% sulfuric acid to give *trans*-**8** as a major product (77% in 2 steps, E/Z = ~30:1). We selected Sharpless' dihydroxylation[4] as an asymmetric introduction step.[10] Thus, olefin **8** was dihydroxylated to give (*R*, *R*)-diol **9** using AD-mix-β in 99% yield. Because the enantio- and diastereomeric purity could not be determined at this stage, we proceeded to some more steps. Unfortunately, direct reductive elimination of the benzylic alcohol of the diol (*R*, *R*)-**9** (*e.g.* Pd-catalyzed hydrogenolysis under various conditions) resulted in failure again. We then tried radical reduction of thionocarbonate. The diol (*R*, *R*)-**9** was treated with thiocarbonyldiimidazole to give thionocarbonate (*R*, *R*)-**10** in 97% yield, which was then heated together with tri-*n*-butyltin hydride and AIBN in benzene.[11,12] As we expected, the cleavage of C-O bond occurred at the benzylic position selectively and the desired (*R*)-**11** was obtained in very high yield (94%) along with a small amount of overreduced compound (see experimental section). The direction of the reductive cleavage was reasonable since it was considered that the benzylic radical was more stable than homobenzylic one. Now problem about the deoxygenation was solved and (*R*)-**11** was in hand, this alcohol was regioselectively brominated to give (*R*)-**12** as a colorless solid. The enantiomeric purity was determined at this stage to be 97.3% e.e. by HPLC employing a column with chiral stationary phase (see experimental). By recrystallization, (*R*)-**12** with ~100%e.e. was obtained as colorless fine needles (78% yield, mp 101.5-102.0°C). After the hydroxyl group of (*R*)-**12** was protected as TBS ether (quant.), the resulting (*R*)-**13** was lithiated by *n*-butyllithium and reacted with methyl chloroformate to give (*R*)-**14**. Desilylation by tetra-*n*-butylammonium fluoride gave a 3,4-dihydroisocoumarin skeleton (*R*)-**15** as colorless prisms (76% from (*R*)-**13**, mp 83.0-83.5°C).

The next task was regioselective bromination at C-7 position (Scheme 3). In our synthesis of the racemate,[2] bromination of 6,8-dihydroxy-3-propyl-3,4-dihydroisocoumarin (in which both the phenolic hydroxyl groups are free) gave only 16% of the desired hiburipyranone, in addition to 16% of isomeric monobromide and

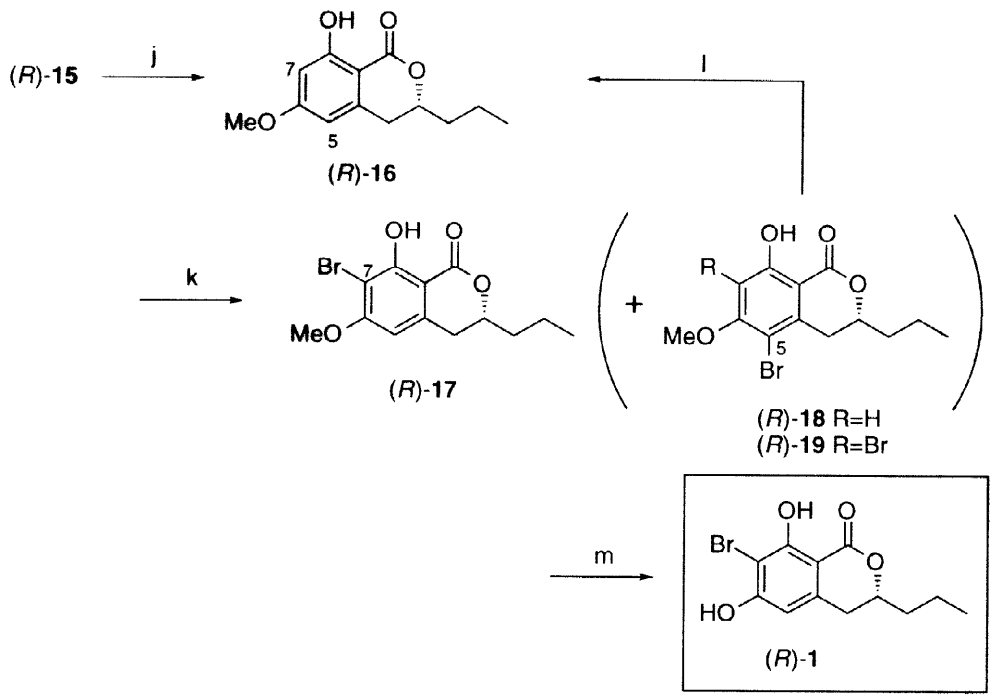


Scheme 2; a) *n*-BuLi, THF, –78°C, 2.5h; b) 20% H_2SO_4, reflux, 15h, 77% in 2 steps; c) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH, H_2O, 4°C, overnight, 99%; d) thiocarbonyldiimidazole, benzene, reflux, 2.5h, 97%; e) *n*-Bu_3SnH, benzene, reflux, 80 min, 94%; f) Pyr•HBr•Br_2, Pyr., CH_2Cl_2, –20°C, 30 min; recryst'n, 78%; g) TBSCl, imid., DMF, rt, overnight, quant.; h) *n*-BuLi, $ClCO_2Me$, THF, –78°C, 1h; 0°C, 30 min; i) TBAF, THF, 76% in 2 steps.

26% of dibromide with a recovery of 26% of recovered starting material. That is, the reaction was too activated by two phenolic groups. On the other hand, complete regioselectivity at C-5 position was observed in the case of bromination of (*R*)-**15**. We then tried bromination of (*R*)-**16**, which has one methoxy group and one hydroxyl group on the benzene ring. Selective demethylation of (*R*)-**15** with boron tribromide afforded (*R*)-**16** in 94% yield (mp 55.0-55.3°C). Bromination of (*R*)-**16** using pyridinium hydrobromide perbromide gave the desired (*R*)-**17** in 40% yield (mp 158.5-159.0°C) together with a mixture of regioisomer (*R*)-**18**, dibromide (*R*)-**19** and the starting material (*R*)-**16** (75:8:17 determined by ^{1}H-NMR, in totally 59% yield). There was no selectivity in this step, and it could not be improved under the known *ortho*- (to phenolic hydroxyl group) bromination conditions.[13,14] It was likely that the C-5 position was more activated and the regioselective bromination at the C-7 position was difficult.[15,16] Therefore, this undesired mixture of by-products was reduced with zinc powder in acetic acid to regenerate the original substrate for bromination ((*R*)-**15**) which could be recycled. The final deprotection of phenol proceeded in excellent yield (98%) to give (*R*)-**1** (mp 186.0-187.0°C). The ^{1}H-NMR, ^{13}C-NMR, and IR spectral data of our synthetic (*R*)-**1** were identical with those of natural **1**[1] and synthetic (±)-**1**.[2] Specific rotation of synthetic (*R*)-**1** was $[\alpha]_D^{20}$ –30.0 (*c* 0.600, $CHCl_3$), which had a same sign but much larger absolute value than natural hiburipyranone ($[\alpha]_D$ –2.30 (*c* 0.028, $CHCl_3$)).[1]

(*S*)-Hiburipyranone was also synthesized successfully in the same procedure by using AD-mix-α instead of AD-mix-β. The ^{1}H-NMR, ^{13}C-NMR, and IR spectral data of synthetic (*S*)-**1** were also identical with those of natural **1**[1] and synthetic (±)-**1**.[2] Its mp was 186.0-187.0°C. Specific rotation was $[\alpha]_D^{23}$ +30.2 (*c* 0.615, $CHCl_3$), which had almost the same absolute value as that of the synthetic (*R*)-**1** and had different sign from that of the natural **1**.

Though we proposed the absolute configuration of natural hiburipyranone to be *R*, there was no sufficient evidence because the absolute value of the specific rotation of the natural **1** was too small than those of our synthetic (*R*)-**1** and (*S*)-**1**.[17] We examined it by HPLC using a column with chiral stationary phase. (*R*)-**1**



Scheme 3; j) BBr_3, CH_2Cl_2, 4°C, overnight, 94%; k) Pyr•HBr•Br_2, pyridine, CH_2Cl_2, 0°C, 50 min, 40%; l) Zn powder, AcOH, reflux, 7d, 50% in 2 steps; m) BBr_3, CH_2Cl_2, rt, overnight, 98%.

and (*S*)-**1** were barely separable because the difference in retention time was only *ca.* 2 min. However, natural **1** was unambiguously proved to be *R* by co-injection with each samples (see experimental).

In conclusion, both enantiomers of hiburipyranone (**1**), the cytotoxic metabolite of marine sponge *Mycale adhaerens* were synthesized by employing Sharpless' asymmetric dihydroxylation as a key step. The overall yield of both (*R*)-**1** and (*S*)-**1** were 30% in 13 steps. The absolute configuration of **1** was determined to be *R* by the comparison of HPLC and specific rotation with our synthetic samples.

EXPERIMENTAL

IR spectra: Jasco FT / IR 230 spectrometer. ^{1}H-NMR spectra: a Jeol JNM EX-90 spectrometer (90 MHz) or a Jeol JNM GSX-500 spectrometer (500 MHz). ^{13}C-NMR spectra: Jeol JNM GSX-500 (125 MHz). Specific rotations: Jasco DIP-371 polarimeter. Refractive indexes: Atago 1T refractometer. HPLC: Shodex DS-4 and SSC UV detector 3000B (254 nm). High resolution mass spectra: Jeol JMS-SX102 / SX102. Column chromatography: Merck Kieselgel 60 (Art. Nr. 7734). Preparative silicagel TLC: Merck Kieselgel F-254. Melting points: Yanako micro-melting point apparatus. Boiling point and melting points are uncorrected.

1-(3,5-Dimethoxyphenyl)-1-pentanol (**7**).

A solution of *n*-butyllithium in hexane (1.61 M, 100 ml, 161 mmol) was added to a solution of 3, 5-dimethoxybenzaldehyde **6** (22.0 g, 132 mmol) in dry tetrahydrofuran (200 ml) below −50°C under argon. After stirring the mixture at −78°C for 2.5h, it was warmed to 0°C, quenched with saturated ammonium chloride solution and extracted with ether. The organic layer was washed with water and brine, dried with anhydrous magnesium sulfate and concentrated *in vacuo* to give crude **7** (30.2 g); IR (film): ν = 3440 (br), 2960, 2940, 1600, 1460, 1430, 1350, 1320, 1300, 1200, 1160, 840, 700 cm^{-1}; ^{1}H-NMR (90 MHz in $CDCl_3$): δ = 0.99 (3H, t, *J* = 5.7 Hz, 5-H), 1.14-1.45 (4H, m, 3- and 4-H), 1.74 (2H, m, 2-H), 1.90 (1H, br, -OH), 3.80 (6H, s,

-OCH_3), 4.59 (1H, t, J = 6.6 Hz, 1-H), 6.37 (1H, t, J = 2.6 Hz, Ar-H), 6.51 (2H, d, J = 2.6 Hz, Ar-H).

This was used in the next step without further purification.

1-(3,5-Dimethoxyphenyl)-1-pentene (**8**).

A suspension of the crude alcohol **7** (30.2 g) in 20% sulfuric acid solution (250 ml) was refluxed for 15h. It was then cooled and extracted with ether. The organic layer was washed successively with water, saturated sodium bicarbonate solution and brine, dried with anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel (300 g) and elution with hexane / ethyl acetate (30:1) gave crude **8** (22.7 g) as a slightly yellow oil. It was then distilled to give pure **8** (*E* / *Z* = ~30:1, 20.8 g, 77% from **6**) as a colorless oil; bp 122-123°C (1.6 mmHg); n_D^{20} = 1.5168; IR (film): ν = 2960, 2940, 1590, 1460, 1420, 1350, 1340, 1290, 1200, 1160, 960, 840, 830, 690 cm^{-1}; ^{1}H-NMR (500 MHz in $CDCl_3$) for *(E)-isomer*: δ = 0.95 (3H, t, J = 7.4 Hz, 5-H), 1.50 (2H, tq, J = 7.4 Hz, 7.4 Hz, 4-H), 2.18 (2H, br dt, J = 6.8 Hz, 7.4 Hz, 3-H), 3.80 (6H, s, -OCH_3), 6.22 (1H, dt, J = 15.8 Hz, 6.8 Hz, 2-H), 6.32 (1H, brd, J = 15.8 Hz, 1-H), 6.33 (1H, t, J = 2.0 Hz, Ar-H), 6.51 (2H, d, J = 2.0 Hz, Ar-H); for (Z)-isomer (partial): δ = 2.32 (2H, ddt, J = 1.8 Hz, 7.4 Hz, 7.4 Hz, 3-H), 5.66 (1H, dt, J = 12.0 Hz, 7.4 Hz, 2-H); *Anal.* Calcd. for $C_{13}H_{18}O_4$: C, 75.69; H, 8.80. Found: C, 75.90; H, 8.83.

1-(3,5-Dimethoxyphenyl)-1,2-pentanediol (**9**).

(a) *(1R, 3R)-isomer*: Methanesulfonamide (1.15 g) was added to a two-phase stirred mixture of AD-mix-β (16.9 g), water (60 ml) and *t*-butyl alcohol (60 ml) at rt, and the reaction mixture was then ice-cooled. The olefin **8** (2.49 g, 12.1 mmol) was added to the resulting orange suspension and the reaction mixture was vigorously stirred at 4°C overnight. After excess sodium sulfite was added, the mixture was warmed to rt and stirred for 1h. It was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried with anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel (100 g) and elution with hexane / ethyl acetate (5:1-0:1) gave (*R*, *R*)-**9** (2.87 g, 99%) as a slightly yellow oil; $[\alpha]_D^{23}$ –4.78 (*c* 1.32, $CHCl_3$); n_D^{19} = 1.5168; IR (film): ν = 3400 (br), 2960, 2940, 1600, 1460, 1430, 1340, 1320, 1295, 1205, 1160, 1060, 1030, 840, 700 cm^{-1}; ^{1}H-NMR (90 MHz in $CDCl_3$): δ = 0.87 (3H, t, J = 6.2 Hz, 5-H), 1.35 (4H, m, 3- and 4-H), 2.43 (2H, br, -OH), 3.69 (1H, m, 2-H), 3.79 (6H, s, -OCH_3), 4.34 (1H, d, J = 6.5 Hz, 1-H), 6.39 (1H, t, J = 2.3 Hz, Ar-H), 6.48 (2H, d, J = 2.3 Hz, Ar-H); HRFABMS *m/z* = 240.1358 $[M]^+$ (Calcd. for $C_{13}H_{20}O_4$: 240.1361).

(b) *(1S, 3S)-isomer*: In the same manner as described above, the olefin **8** (10.0 g, 48.5 mmol) was dihydroxylated using methanesulfonamide (4.61 g) and AD-mix-α (67.9 g) in water (240 ml) and *t*-butyl alcohol (240 ml) to give (*S*, *S*)-**9** (11.2 g, 96%) as a slightly yellow oil; $[\alpha]_D^{20}$ +4.69 (*c* 1.62, $CHCl_3$); n_D^{19} = 1.5169; Its IR spectrum was identical with that of (*R*, *R*)-**9**; ^{1}H-NMR (90 MHz in $CDCl_3$): δ = 0.87 (3H, t, J = 6.1 Hz, 5-H), 1.36 (4H, m, 3- and 4-H), 2.38 (2H, br, -OH), 3.69 (1H, m, 2-H), 3.79 (6H, s, -OCH_3), 4.34 (1H, d, J = 6.5 Hz, 1-H), 6.39 (1H, t, J = 2.2 Hz, Ar-H), 6.48 (2H, d, J = 2.2 Hz, Ar-H); HRFABMS *m/z* = 240.1365 $[M]^+$ (Calcd. for $C_{13}H_{20}O_4$: 240.1361).

4-(3,5-Dimethoxyphenyl)-5-propyl-1,3-dioxolane-2-thione (**10**).

(a) *(4R, 5R)-isomer*: A mixture of the diol (*R*, *R*)-**9** (6.43 g, 26.8 mmol), thiocarbonyldiimidazole (6.45 g, 36.2 mmol) and dry benzene (150 ml) was refluxed for 2.5h under argon. It was then cooled and evaporated. The residue was chromatographed over silica gel (100 g) and elution with hexane / ethyl acetate (10:1-1:1) gave (*R*, *R*)-**10** (7.30 g, 97%) as a colorless oil; $[\alpha]_D^{21}$ –9.71 (*c* 1.75, $CHCl_3$); n_D^{20} = 1.5168; IR (film): ν = 2960, 2940, 1600, 1460, 1430, 1320, 1280, 1205, 1160, 1060, 990, 950, 940, 840, 690 cm^{-1}; ^{1}H-NMR (90 MHz in $CDCl_3$): δ = 0.96 (3H, t, J = 6.8 Hz, -CH_2CH_3), 1.14-2.05 (4H, m, -$CH_2CH_2CH_3$), 3.80 (6H, s, -OCH_3), 4.67 (1H, m, 5-H), 5.26 (1H, d, J = 7.9 Hz, 4-H), 6.44 (3H, brs, Ar-H); *Anal.* Calcd. for $C_{14}H_{18}O_4S$: C, 59.55; H, 6.43. Found: C, 59.26; H, 6.47.

(b) *(4S, 5S)-isomer*: In the same manner as described above, (*S*, *S*)-**9** (10.7 g, 44.4 mmol) was treated with thiocarbonyldiimidazole (10.7 g, 59.9 mmol) in dry benzene (200 ml) to afford (*S*, *S*)-**10** (12.4 g, 99%) as

a colorless oil; $[\alpha]_D^{21}$ +9.49 (*c* 1.43, $CHCl_3$); n_D^{20} = 1.5167; Its IR and ^{1}H-NMR spectra were identical with those of (*R*, *R*)-**9**; *Anal.* Calcd. for $C_{14}H_{18}O_4S$: C, 59.55; H, 6.43. Found: C, 59.61; H, 6.43.

1-(3,5-Dimethoxyphenyl)-2-pentanol (**11**).

(a) *(R)-isomer.* A mixture of the thionocarbonate (*R*, *R*)-**10** (6.95 g, 24.6 mmol), tri-*n*-butyltin hydride (10.0 ml, 37.2 mmol), 2,2'-azobis(isobutyronitrile) (50.0 mg, 0.304 mmol) and dry benzene (130 ml) was refluxed for 80 min under argon. It was then cooled and evaporated. The residue was chromatographed over silica gel (200 g) and elution with hexane / ethyl acetate (1:0-3:1) gave (*R*)-**11** (5.18 g, 94%) as a colorless oil. An overreduced compound, 1,3-dimethoxy-5-pentylbenzene, was also obtained together with a decomposed stannan reagent (566 mg as a mixture). (*R*)-**11**; $[\alpha]_D^{21}$ −12.7 (*c* 1.38, $CHCl_3$); n_D^{19} = 1.5168; IR (film): ν = 3430 (br), 2960, 2940, 1600, 1460, 1430, 1340, 1320, 1295, 1205, 1150, 1060, 830, 700 cm^{-1}; ^{1}H-NMR (90 MHz in $CDCl_3$): δ = 0.94 (3H, t, *J* = 6.1 Hz, 5-H), 1.30-1.63 (4H, m, 3- and 4-H), 2.57 (1H, dd, *J* = 8.3 Hz, 13.6 Hz, 1-H), 2.76 (1H, dd, *J* = 4.5 Hz, 13.6 Hz, 1-H), 3.78 (6H, s, -OCH_3), 3.80 (1H, m, 2-H), 6.36 (3H, brs, Ar-H); *Anal.* Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.30; H, 8.97.

(b) *(S)-isomer.* In the same manner as described above, (*S*, *S*)-**10** (11.8 g, 41.7 mmol) was reduced using tri-*n*-butyltin hydride (16.8 ml, 62.5 mmol) and 2,2'-azobis(isobutyronitrile) (82.0 mg, 0.499 mmol) in dry benzene (100 ml) to give (*S*)-**11** (8.78 g, 94%) and 1,3-dimethoxy-5-pentylbenzene (1.80 g as a mixture). (*S*)-**11**; $[\alpha]_D^{23}$ +12.3 (*c* 1.34, $CHCl_3$); n_D^{19} = 1.5167; Its IR and ^{1}H-NMR spectra were identical with those of (*R*)-**11**; *Anal.* Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.50; H, 9.12.

1-(2-Bromo-3,5-dimethoxyphenyl)-2-pentanol (**12**).

(a) *(R)-isomer.* A solution of pyridinium hydrobromide perbromide (7.07 g, 22.1 mmol) in pyridine (15 ml) was added to a solution of the alcohol (*R*)-**11** (4.95 g, 22.1 mmol) in dry dichloromethane (60 ml) at −20°C. The mixture was stirred at this temp. for 30 min. It was then poured into 15% sodium thiosulfate solution and extracted with ether. The organic layer was successively washed with water, 1N hydrochloric acid solution, saturated sodium bicarbonate solution and brine, followed by drying with magnesium sulfate and it was concentrated *in vacuo* to give crude (*R*)-**12** as a colorless solid (6.49 g). This was recrystallized twice from hexane / ethyl acetate (3:1, 5:1) to give chemically and enantiomerically pure (*R*)-**12** (5.21 g, 78%) as colorless fine needles; $[\alpha]_D^{21}$ −24.4 (*c* 1.10, $CHCl_3$); mp 101.5-102.0°C; IR (KBr): ν = 3340, 3260, 2960, 2930, 1600, 1580, 1460, 1430, 1350, 1330, 1240, 1210, 1160, 1095, 1075, 1020, 950, 840, 810 cm^{-1}; ^{1}H-NMR (90 MHz in $CDCl_3$): δ = 0.94 (3H, t, *J* = 6.1 Hz, 5-H), 1.54 (4H, m, 3- and 4-H), 2.73 (1H, dd, *J* = 8.8 Hz, 13.6 Hz, 1-H), 3.05 (1H, dd, *J* = 3.8 Hz, 13.6 Hz, 1-H), 3.80 (3H, s, -OCH_3), 3.85 (1H, m, 2-H), 3.88 (3H, s, -OCH_3), 6.39 (1H, d, *J* = 2.5 Hz, Ar-H), 6.46 (1H, d, *J* = 2.5 Hz, Ar-H); *Anal.* Calcd. for $C_{13}H_{19}BrO_3$: C, 51.50; H, 6.32. Found: C, 51.56; H, 6.33.

(b) *(S)-isomer.* In the same manner as described above, the alcohol (*S*)-**11** (8.41 g, 37.5 mmol) was treated with pyridinium hydrobromide perbromide (12.1 g, 37.7 mmol) in dichloromethane (100 ml) and pyridine (25 ml) to afford crude (*S*)-**12** (11.2 g) as a colorless solid. This was recrystallized twice from hexane / ethyl acetate (5:1, 3:1) to give pure (*S*)-**12** (8.97 g, 79%) as colorless fine needles; $[\alpha]_D^{19}$ +24.3 (*c* 1.22, $CHCl_3$); mp 101.5-102.0°C; Its IR and ^{1}H-NMR spectra were identical with those of (*R*)-**12**; *Anal.* Calcd. for $C_{13}H_{19}BrO_3$: C, 51.50; H, 6.32. Found: C, 51.64; H, 6.30.

Determination of the enantiomeric purities of (R)- and (S)-12.

These were determined by HPLC (Chiralcel® OD, 4.6 mm ϕ × 250 mm; eluent, hexane / 2-propanol = 30:1; flow rate, 0.8 ml/min). (*R*)-**12**: (before recrystallization) t_R = 14.2 min (1.8%), 16.3 min (98.2%); (after recrystallization) t_R = 16.6 min (single peak). These figures proved the enantiomeric purity of crude (*R*)-**12** to be 96.4% e.e. and that of purified (*R*)-**12** to be about 100% e.e. (*S*)-**12**: (before recrystallization) t_R = 14.0 min (96.9%), 16.3 min (3.1%, with a small shoulder); (after recrystallization) t_R = 14.8 min (single peak). These figures proved the enantiomeric purity of crude (*S*)-**12** to be >93.8% e.e. and that of purified (*S*)-**12** to be about 100% e.e.

1-(2-Bromo-3,5-dimethoxyphenyl)-2-(t-butyldimethylsilyloxy)pentane (**13**).

(a) *(R)-isomer*: *t*-Butyldimethylsilyl chloride (4.16 g, 20.8 mmol) was added to an ice-cooled solution of (*R*)-**12** (4.16 g, 13.7 mmol) and imidazole (2.84 g, 41.8 mmol) in dimethylformamide (40 ml). The mixture was warmed to rt and stirred overnight. It was then poured into ice-water and extracted with ether. The organic layer was successively washed with water, saturated sodium bicarbonate solution and brine, dried with magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel (200 g) and elution with hexane / ethyl acetate (30:1) gave (*R*)-**13** (5.80 g, quant.) as a slightly yellow oil; $[\alpha]_D^{20}$ –22.7 (*c* 1.40, $CHCl_3$); n_D^{20} = 1.5102; IR (film): ν = 2960, 2930, 2860, 1590, 1460, 1420, 1330, 1255, 1205, 1160, 1090, 1070, 1040, 1025, 840, 810, 780 cm^{-1}; ^{1}H-NMR (90 MHz in $CDCl_3$): δ = –0.27 (3H, s, -$SiCH_3$), –0.08 (3H, s, -$SiCH_3$), 0.83 (9H, s, -SiBu^t), 0.91 (3H, m, 5-H), 1.45 (4H, m, 3- and 4-H), 2.72 (1H, dd, *J* = 7.9 Hz, 13.0 Hz, 1-H), 2.97 (1H, dd, *J* = 4.8 Hz, 13.0 Hz, 1-H), 3.79 (3H, s, -OCH_3), 3.86 (3H, s, -OCH_3), 4.03 (1H, m, 2-H), 6.36 (1H, d, *J* = 2.6 Hz, Ar-H), 6.43 (1H, d, *J* = 2.6 Hz, Ar-H); *Anal.* Calcd. for $C_{19}H_{33}BrO_3Si$: C, 54.67; H, 7.97. Found: C, 54.94; H, 8.05.

(b) *(S)-isomer*: In the same manner as described above, (*S*)-**12** (5.54 g, 18.3 mmol) was treated with *t*-butyldimethylsilyl chloride (4.10 g, 27.2 mmol) and imidazole (3.75 g, 55.1 mmol) in dimethylformamide (60 ml) to give crude (*S*)-**13** (7.75 g, quant.) as a slightly yellow oil; $[\alpha]_D^{19}$ +22.9 (*c* 1.29, $CHCl_3$); n_D^{19} = 1.5102; Its IR and ^{1}H-NMR spectra were identical with those of (*R*)-**13**; *Anal.* Calcd. for $C_{19}H_{33}BrO_3Si$: C, 54.67; H, 7.97. Found: C, 54.60; H, 7.96.

Methyl 2-[2-(t-butyldimethylsilyloxy)pentyl]-4,6-dimethoxybenzoate (**14**).

(a) *(R)-isomer*: A solution of *n*-butyllithium in hexane (1.53, 11.1 ml, 17.0 mmol) was added dropwise to a solution of (*R*)-**13** (5.43 g, 13.0 mmol) in dry tetrahydrofuran (70 ml) at –78°C under argon, and the mixture was stirred at this temp. for 1h. Methyl chloroformate (1.31 ml, 17.0 mmol) was then added dropwise to the solution, and it was stirred at –78°C for further 1h. After the reaction mixture was warmed to 0°C and stirred for 30 min, it was poured into water and extracted with ether. The organic layer was washed with brine, dried with magnesium sulfate and concentrated *in vacuo* to give crude (*R*)-**14** (5.88 g) as a slightly yellow oil. This was used in the next step without further purification. For analysis, a small portion of this oil was chromatographed over silica gel and elution with hexane / ethyl acetate (30:1-20:1) gave pure (*R*)-**14** as a colorless oil; $[\alpha]_D^{19}$ –23.6 (*c* 0.87, $CHCl_3$); n_D^{19} = 1.4933; IR (film): ν = 2960, 2940, 2860, 1730, 1605, 1590, 1460, 1430, 1330, 1270, 1205, 1160, 1100, 1070, 1050, 840, 780 cm^{-1}; ^{1}H-NMR (90 MHz in $CDCl_3$): δ = –0.23 (3H, s, -$SiCH_3$), –0.07 (3H, s, -$SiCH_3$), 0.84 (9H, s, -SiBu^t), 0.87 (3H, m, 5-H), 1.38 (4H, m, 3- and 4-H), 2.59 (1H, dd, *J* = 7.6 Hz, 13.3 Hz, 1-H), 2.78 (1H, dd, *J* = 5.1 Hz, 13.3 Hz, 1-H), 3.79 (6H, s, -CO_2CH_3 and -OCH_3), 3.80 (1H, m, 2-H), 3.87 (3H, s, -OCH_3), 6.34 (1H, d, *J* = 2.3 Hz, Ar-H), 6.37 (1H, d, *J* = 2.3 Hz, Ar-H); *Anal.* Calcd. for $C_{21}H_{36}O_5Si$: C, 63.60; H, 9.15. Found: C, 63.78; H, 9.12.

(b) *(S)-isomer*: In the same manner as described above, (*S*)-**13** (7.05 g, 16.9 mmol) was treated with *n*-butyllithium in hexane (1.53 M, 14.3 ml, 21.9 mmol) and methyl chloroformate (1.70 ml, 22.0 mmol) in dry tetrahydrofuran (100 ml) to afford crude (*S*)-**14** (7.56 g) as a slightly yellow oil. This was used in the next step without further purification. For analysis, a small portion of this oil was purified to give pure (*S*)-**14** as a colorless oil; $[\alpha]_D^{23}$ +23.1 (*c* 0.76, $CHCl_3$); n_D^{19} = 1.4934; Its IR and ^{1}H-NMR spectra were identical with those of (*R*)-**14**; *Anal.* Calcd. for $C_{21}H_{36}O_5Si$: C, 63.60; H, 9.15. Found: C, 63.86; H, 9.22.

6,8-Dimethoxy-3-propyl-3,4-dihydroisocoumarin (**15**).

(a) *(R)-isomer*: Tetra-*n*-butylammonium fluoride (hydrate, Tokyo Chem. Ind., Ltd., T1037, 8.50 g) was added to a solution of crude (*R*)-**14** (5.30 g) in dry tetrahydrofuran (25 ml) at rt. After the mixture was stirred at rt overnight, it was evaporated and the residue was chromatographed over silica gel (150 g) and elution with hexane / ethyl acetate (3:1-1:1) gave (*R*)-**15** (2.44 g) as a slightly yellow solid. This was recrystallized from hexane / ethyl acetate (1:1) to give pure (*R*)-**15** as colorless prisms (2.23 g, 76% from (*R*)-**13**); $[\alpha]_D^{19}$ –151 (*c* 1.10, $CHCl_3$); mp 83.0-83.5°C; IR (KBr): ν = 2960, 1720, 1700, 1600, 1580, 1460, 1430, 1360, 1340, 1240, 1220, 1160, 1085, 1040, 840 cm^{-1}; ^{1}H-NMR (90 MHz in $CDCl_3$): δ = 0.90 (3H, t, *J* = 6.8 Hz, -CH_2CH_3),

1.25-1.95 (4H, m, -C*H*$_2$C*H*$_2$CH$_3$), 2.78 (2H, m, 4-H), 3.82 (3H, s, -OCH$_3$), 3.87 (3H, s, -OCH$_3$), 4.30 (1H, m, 3-H), 6.27 (1H, d, J = 2.1 Hz, Ar-H), 6.36 (1H, d, J = 2.1 Hz, Ar-H); *Anal.* Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.31; H, 7.24.

(b) *(S)-isomer*: In the same manner as described above, crude (*S*)-**14** (7.19 g) was desilylated using tetra-*n*-butylammonium fluoride (hydrate, Tokyo Chem. Ind., Ltd., T1037, 11.6 g) in dry tetrahydrofuran (35 ml) to give crude (*S*)-**15** (3.40 g) as a slightly yellow solid. This was recrystallized from hexane / ethyl acetate (1:2) to give pure (*S*)-**15** (2.92 g, 73% from (*S*)-**13**); $[\alpha]_D^{24}$ +150 (*c* 1.46, $CHCl_3$); mp 83.0-83.5°C; Its IR and ^{1}H-NMR spectra were identical with those of (*R*)-**15**; *Anal.* Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.18; H, 7.29.

8-Hydroxy-6-methoxy-3-propyl-3,4-dihydroisocoumarin (**16**).

(a) *(R)-isomer*: The dimethoxy lactone (*R*)-**15** (1.00 g, 4.00 mmol) was diluted with dry dichloromethane (15 ml) and then cooled to −78°C. Boron tribromide (380 µl, 4.02 mmol) was added to this solution, and the reaction mixture was warmed to 4°C and stirred overnight. It was poured into ice-water, extracted with dichloromethane and ether. The organic layer was washed with water and brine, dried with magnesium sulfate and concentrated *in vacuo* to give crude (*R*)-**16** as a colorless solid. Recrystallization from hexane / ethyl acetate (10:1) gave pure (*R*)-**16** as colorless leaflets (886 mg, 94%); $[\alpha]_D^{20}$ −35.3 (*c* 1.36, $CHCl_3$); mp 55.0-55.3°C; IR (KBr): ν = 3450 (w, br), 2960, 1650, 1630, 1580, 1510, 1430, 1375, 1315, 1260, 1205, 1160 cm^{-1}; ^{1}H-NMR (500 MHz in $CDCl_3$): δ = 0.97 (3H, t, J = 7.3 Hz, -CH$_2$C*H*$_3$), 1.43-1.64 (2H, m, -CH$_2$C*H*$_2$CH$_3$), 1.67 (1H, dddd, J = 5.0 Hz, 5.0 Hz, 10.0 Hz, 13.5 Hz, -C*H*$_2$CH$_2$CH$_3$), 1.85 (1H, dddd, J = 5.0 Hz, 7.4 Hz, 10.0 Hz, 13.5 Hz, -C*H*$_2$CH$_2$CH$_3$), 2.84 (1H, br dd, J = 4.0 Hz, 16.2 Hz, 4-H), 2.88 (1H, br dd, J = 4.0 Hz, 16.2 Hz, 4-H), 3.82 (3H, s, -OCH$_3$), 4.53 (1H, dddd, J = 4.0 Hz, 5.0 Hz, 7.4 Hz, 10.5 Hz, 3-H), 6.24 (1H, m, Ar-H), 6.36 (1H, d, J = 2.2 Hz, Ar-H), 11.25 (1H, s, 8-OH); *Anal.* Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.89; H, 6.81.

(b) *(S)-isomer*: In the same manner as that already described, (*S*)-**15** (0.80 g, 3.2 mmol) was treated with boron tribromide (303 µl, 3.20 mmol) in dry dichloromethane (12 ml) to afford crude (*S*)-**16** (767 mg) as a colorless solid. Recrystallization from hexane / ethyl acetate (10:1) gave pure (*S*)-**16** as colorless leaflets (714 mg, 94%); $[\alpha]_D^{19}$ +36.2 (*c* 1.35, $CHCl_3$); mp 55.5-55.8°C; Its IR and ^{1}H-NMR spectra were identical with those of (*R*)-**16**; *Anal.* Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.41; H, 6.91.

7-Bromo-8-hydroxy-6-methoxy-3-propyl-3,4-dihydroisocoumarin (**17**).

(a) *(R)-isomer*: A solution of pyridinium hydrobromide perbromide (684 mg, 2.14 mmol) in pyridine (10 ml) was added dropwise to a solution of (*R*)-**16** (501 mg, 2.12 mmol) in dry dichloromethane (15 ml) at 0°C. The reaction mixture was stirred at 0°C for 50 min, poured into 1N hydrochloric acid and extracted with ethyl acetate and ether. The organic layer was successively washed with 1N hydrochloric acid, water and brine, dried with magnesium sulfate and concentrated *in vacuo* to give crude solid mixture with slightly orange color. It was chromatographed over silica gel (50 g) and elution with hexane / ethyl acetate / acetic acid (800:100:9-300:100:4) gave (*R*)-**17** (268 mg, 40%) as colorless solid together with a mixture of (*R*)-**18**, (*R*)-**19** and (*R*)-**16** (385 mg, 59%, 75:8:17 by ^{1}H-NMR). Although each components of this mixture were separable by preparative TLC using hexane / ethyl acetate / acetic acid (300:100:4), the mixture was directly used in the next recovering step. An analytical sample of (*R*)-**17** was prepared by recrystallization from hexane / ethyl acetate (2:1) to give pure colorless small plates; $[\alpha]_D^{19}$ −42.1 (*c* 1.08, $CHCl_3$); mp 158.5-159.0°C; IR (KBr): ν = 3450 (w, br), 2960, 1645, 1570, 1520, 1420, 1380, 1330, 1270, 1210, 1150, 1120, 800 cm^{-1}; ^{1}H-NMR (500 MHz in $CDCl_3$): δ = 0.98 (3H, t, J = 7.4 Hz, -CH$_2$C*H*$_3$), 1.44-1.66 (2H, m, -CH$_2$C*H*$_2$CH$_3$), 1.70 (1H, dddd, J = 5.0 Hz, 5.5 Hz, 10.0 Hz, 13.8 Hz, -C*H*$_2$CH$_2$CH$_3$), 1.88 (1H, dddd, J = 5.0 Hz, 7.5 Hz, 10.0 Hz, 13.8 Hz, -C*H*$_2$CH$_2$CH$_3$), 2.88 (1H, dd, J = 5.0 Hz, 16.0 Hz, 4-H), 2.91 (1H, ddd, J = 0.9 Hz, 10.0 Hz, 16.0 Hz, 4-H), 3.96 (3H, s, -OCH$_3$), 4.56 (1H, dddd, J = 5.0 Hz, 5.0 Hz, 7.5 Hz, 10.0 Hz, 3-H), 6.31 (1H, brs, 5-H), 11.86 (1H, s, 8-OH); *Anal.* Calcd. for $C_{13}H_{15}BrO_4$: C, 49.54; H, 4.80. Found: C, 49.59; H, 4.81.

(*R*)-**18**; IR (KBr): ν = 2960, 2930, 2880, 2860, 1650, 1615, 1570, 1470, 1435, 1390, 1370, 1335, 1300, 1285,

1245, 1205, 1180, 1100, 1080, 1060, 1000, 830, 800, 760, 750 cm^{-1}; ^{1}H-NMR (500 MHz in $CDCl_3$): δ = 0.99 (3H, t, *J* = 7.4 Hz, -CH_2CH_3), 1.44-1.68 (2H, m, -$CH_2CH_2CH_3$), 1.73 (1H, dddd, *J* = 5.0 Hz, 5.5 Hz, 11.0 Hz, 13.8 Hz, -$CH_2CH_2CH_3$), 1.88 (1H, dddd, *J* = 5.0 Hz, 7.5 Hz, 10.0 Hz, 13.8 Hz, -$CH_2CH_2CH_3$), 2.80 (1H, dd, *J* = 11.8 Hz, 17.0 Hz, 4-H), 3.22 (1H, dd, *J* = 3.3 Hz, 17.0 Hz, 4-H), 3.93 (3H, s, -OCH_3), 4.52 (1H, dddd, *J* = 3.3 Hz, 5.0 Hz, 7.5 Hz, 11.8 Hz, 3-H), 6.45 (1H, s, 7-H), 11.49 (1H, s, 8-OH).
(*R*)-**19**; IR (KBr): ν = 3080 (sh), 2960, 2870, 1670, 1600, 1580, 1550, 1430, 1400, 1385, 1330, 1280, 1270, 1235, 1120, 945, 820 cm^{-1}; ^{1}H-NMR (500 MHz in $CDCl_3$): δ = 1.00 (3H, t, *J* = 7.3 Hz, -CH_2CH_3), 1.45-1.69 (2H, m, -$CH_2CH_2CH_3$), 1.75 (1H, dddd, *J* = 5.0 Hz, 5.2 Hz, 10.0 Hz, 14.8 Hz, -$CH_2CH_2CH_3$), 1.90 (1H, dddd, *J* = 5.0 Hz, 7.5 Hz, 10.0 Hz, 14.8 Hz, -$CH_2CH_2CH_3$), 2.80 (1H, dd, *J* = 11.8 Hz, 17.2 Hz, 4-H), 3.22 (1H, dd, *J* = 3.2 Hz, 17.2 Hz, 4-H), 3.93 (3H, s, -OCH_3), 4.56 (1H, dddd, *J* = 3.2 Hz, 5.0 Hz, 7.5 Hz, 11.8 Hz, 3-H), 12.05 (1H, s, 8-OH).

(b) *(S)-isomer*: In the same manner as described above, (*S*)-**16** (502 mg, 2.13 mmol) was treated with pyridinium hydrobromide perbromide (688 mg, 2.15 mmol) in pyridine (10 ml) and dry dichloromethane (15 ml) to give (*S*)-**17** (278 mg, 41%) and a mixture of (*S*)-**18**, (*S*)-**19** and (*S*)-**16** (368 mg, 58%, 75:4:20 by ^{1}H-NMR). This mixture was used in the next recovering step without further purification. An analytical sample of (*S*)-**17** was prepared by recrystallization from hexane / ethyl acetate (2:1) to give pure colorless small plates; $[\alpha]_D^{18}$ +42.5 (*c* 1.31, $CHCl_3$); mp 158.5-159.0°C; Its IR and ^{1}H-NMR spectra were identical with those of (*R*)-**17**; *Anal.* Calcd. for $C_{13}H_{15}BrO_4$: C, 49.54; H, 4.80. Found: C, 49.76; H, 4.84.

Regeneration of ***16***.

(a) *(R)-isomer*: Zinc powder (5.2 g) was added to a solution of the mixture of (*R*)-**18**, (*R*)-**19** and (*R*)-**16** (385 mg) in acetic acid (10 ml). The suspension was stirred and refluxed vigorously for 7d. After cooling, it was filtered through Celite® and the filter cake was washed with ethyl acetate. The combined filtrate and washings were concentrated *in vacuo* to give a brown oil, which was chromatographed over silica gel (10 g) and elution with hexane / ethyl acetate (6:1) gave recovered (*R*)-**16** (249 mg, 50% in 2 steps).

(b) *(S)-isomer*: In the same manner as described above, the mixture of (*R*)-**18**, (*R*)-**19** and (*R*)-**16** (368 mg) was treated with zinc powder (5.5 g) in acetic acid (10 ml) to give (*S*)-**16** (247 mg, 49% in 2 steps).

7-Bromo-6,8-dihydroxy-3-propyl-3,4-dihydroisocoumarin (Hiburipyranone, **1**).

(a) *(R)-isomer*: A solution of (*R*)-**17** (101 mg, 0.322 mmol) in dry dichloromethane (1.5 ml) was cooled to –78°C to give precipitate. Boron tribromide (60.0 μl) was added to this suspension and the mixture was warmed to rt. The precipitate gradually dissolved, and then the reaction mixture was stirred at room temp. overnight. After addition of ice-water, the mixture was extracted with dichloromethane and ether. The combined organic layer was washed with water and brine, dried with magnesium sulfate and concentrated *in vacuo* to give crude (*R*)-**1** as a slightly yellow solid. It was chromatographed over silica gel (5 g) and elution with hexane / ethyl acetate (3:1) gave (*R*)-**1** (95.4 mg, 98%) as a slightly yellow solid. An analytical sample was prepared by recrystallization from hexane / ethyl acetate (1:1) to give pure colorless needles; $[\alpha]_D^{20}$ –30.0 (*c* 0.600, $CHCl_3$); mp 186.0-187.0°C; IR (KBr): ν = 3080 (br), 2960, 2930, 1610, 1500, 1430, 1390, 1320, 1260, 1240, 1190, 1150, 1130, 1070, 1040, 1000, 920, 830, 800, 770 cm^{-1}; ^{1}H-NMR (500 MHz in $CDCl_3$): δ = 0.98 (3H, t, *J* = 7.4 Hz, -CH_2CH_3), 1.44-1.65 (2H, m, -$CH_2CH_2CH_3$), 1.69 (1H, dddd, *J* = 5.0 Hz, 5.5 Hz, 10.0 Hz, 13.6 Hz, -$CH_2CH_2CH_3$), 1.87 (1H, dddd, *J* = 5.0 Hz, 7.5 Hz, 10.0 Hz, 13.6 Hz, -$CH_2CH_2CH_3$), 2.85 (1H, br dd, *J* = 6.5 Hz, 16.5 Hz, 4-H), 2.87 (1H, ddd, *J* = 1.0 Hz, 8.8 Hz, 16.5 Hz, 4-H), 4.55 (1H, dddd, *J* = 5.0 Hz, 6.5 Hz, 7.5 Hz, 8.8 Hz, 3-H), 6.16 (1H, s, 6-OH), 6.45 (1H, brs, 5-H), 11.99 (1H, s, 8-OH); ^{13}C-NMR (125 MHz in $CDCl_3$): δ = 13.8, 18.1, 32.8, 36.7, 79.1, 97.0, 102.5, 106.0, 140.2, 158.5, 160.3, 169.5; *Anal.* Calcd. for $C_{12}H_{13}BrO_4$: C, 47.86; H, 4.35. Found: C, 47.77; H, 4.30; HRFABMS *m/z* = 299.9990 $[M]^+$ (Calcd. for $C_{12}H_{13}{}^{79}BrO_4$: 299.9997).

(b) *(S)-isomer*: In the same manner as described above, (*S*)-**17** (99.9 mg, 0.317 mmol) was treated with boron tribromide (60.0 μl) and dichloromethane (1.5 ml) to give (*S*)-**1** (93.6 mg, 98%) as a slightly yellow solid. An analytical sample was prepared by recrystallization from hexane / ethyl acetate (1:1) to give pure colorless

needles; $[\alpha]_D^{23}$ +30.2 (*c* 0.615, $CHCl_3$); mp 186.0-187.0°C; Its IR spectrum was identical with that of (*R*)-**1**; ^{1}H-NMR (500 MHz in $CDCl_3$): δ = 0.98 (3H, t, *J* = 7.4 Hz, -CH_2CH_3), 1.44-1.65 (2H, m, -$CH_2CH_2CH_3$), 1.69 (1H, dddd, *J* = 5.0 Hz, 5.5 Hz, 10.0 Hz, 13.6 Hz, -$CH_2CH_2CH_3$), 1.87 (1H, dddd, *J* = 5.0 Hz, 7.5 Hz, 10.0 Hz, 13.6 Hz, -$CH_2CH_2CH_3$), 2.85 (1H, ddd, *J* = 0.9 Hz, 6.5 Hz, 16.5 Hz, 4-H), 2.87 (1H, ddd, *J* = 1.0 Hz, 8.8 Hz, 16.5 Hz, 4-H), 4.55 (1H, dddd, *J* = 5.0 Hz, 6.5 Hz, 7.5 Hz, 8.8 Hz, 3-H), 6.16 (1H, s, 6-OH), 6.45 (1H, brs, 5-H), 11.99 (1H, s, 8-OH); ^{13}C-NMR (125 MHz in $CDCl_3$): δ = 13.8, 18.1, 32.8, 36.7, 79.1, 97.0, 102.5, 106.0, 140.2, 158.5, 160.3, 169.5; *Anal.* Calcd. for $C_{12}H_{13}BrO_4$: C, 47.86; H, 4.35. Found: C, 47.63; H, 4.33; HRFABMS *m/z* = 300.0023 $[M]^+$ (Calcd. for $C_{12}H_{13}{}^{79}BrO_4$: 299.9997).

Determination of the absolute configuration of natural 1.

This was determined by HPLC (Chiralcel® OB, 4.6 mm ϕ × 250 mm; eluent, hexane / 2-propanol / acetic acid = 12:1:0.13; flow rate, 1.0 ml/min). (*R*)-**1**: t_R = 25.9 min (single peak). (*S*)-**1**: t_R = 29.0 min (single peak). Natural **1**: t_R = 26.4 min (single peak). (*R*)-**1** and (*S*)-**1** (co-injection): t_R = 26.8 min and 28.9 min. (*R*)-**1** and natural **1** (co-injection): t_R = 26.1 min (single peak). (*S*)-**1** and natural **1** (co-injection): t_R = 26.5 min and 28.6 min. These figures proved the absolute configuration of natural **1** to be *R*.

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17. The specific rotation of our synthetic **1** showed similar value as described above in different concentration (*e.g.* $[\alpha]_D^{20}$ +29.5 (*c* 1.10, $CHCl_3$), $[\alpha]_D^{23}$ +32 (*c* 0.070, $CHCl_3$) for (*S*)-**1**).