Synthesis and Absolute Configuration of (−)-Neuchromenin, a Neurotrophic Metabolite of *Eupenicillium javanicum* var. *meloforme*, and Its Enantiomer[‡]

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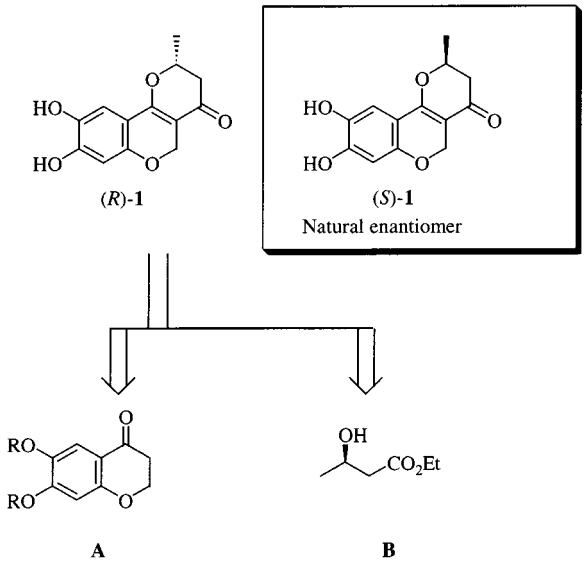
Keywords: Asymmetric synthesis / Configuration determination / Heterocycles / Natural products

Both the enantiomers of neuchromenin **1** (2,3-dihydro-8,9-dihydroxy-2-methyl-4*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-4-one) were synthesized starting from the enantiomers of ethyl 3-hydoxybutanoate (**7**). The naturally occurring (–)-neuchromenin, a neurotrophic metabolite of *Eupenicillium javanicum* var. *meloforme*, was shown to be (*S*)-**1**.

Introduction

In 1996 Hayakawa and co-workers isolated 10 mg of (−)-neuchromenin from 2 L of culture broth of *Eupenicillium javanicum* var. *meloforme* PF1181 as an inducer of neurite outgrowth of PC12 cells at concentrations of 2.5−10 μg/mL.[1] Its structure was deduced as **1** (Scheme 1) by extensive spectral analysis, although its absolute configuration remained unknown.[1] In order to settle that stereochemical problem, we undertook the synthesis of enantiomers of **1**, based on the retrosynthetic analysis as shown in Scheme 1.



Scheme 1. Structure and retrosynthetic analysis of neuchromenin

Results and Discussion

Our plan was to synthesize **1** from 6,7-dialkoxy-2,3-dihydro-4*H*-1-benzopyran-4-one (**A**) and ethyl 3-hydroxybutanoate (**B**). Both the enantiomers of **B** are commercially available. By synthesizing both (*R*)- and (*S*)-**1**, we found (*S*)-**1** to be identical with the naturally occurring (−)-neuchromenin.

Our synthesis of **1** is summarized in Scheme 2. Since we knew of only three preparative methods for 2,3-dihydro-6,7-dimethoxy-4*H*-1-benzopyran-4-one (**4**),[2−4] we first examined several possible pathways to reach **4**. After considerable experimentation, 3,4-dimethoxyphenol (**2**) was chosen as the starting material. Friedel−Crafts acylation of neat **2** with 3-chloropropanoyl chloride[5] in the presence of boron trifluoride−diethyl ether gave **3** in a modest yield of 25% after chromatographic purification and recrystallization. No regioisomers of **3** could be isolated. Ring closure of **3** was best effected by treating it with potassium carbonate in ethanol to give 6,7-dimethoxy-4-chromanone (**4**).[2−4] Because of the difficulty in converting the methoxy groups on the benzene ring to the hydroxy groups of **1** at a later stage, **4** was demethylated with boron tribromide in dichloromethane to give **5**. It was envisaged that the protection of the phenolic hydroxy groups as acetonide would give good results due to the ease of removal of that group in comparison to the difficult demethylation of the methoxy groups. Conventional methods[6] for the formation of 1,3-benzodioxole, however, could not be applied due to the poor solubility of **5** in most solvents. We chose an acetone/benzene mixture (1:3.75) as the solvent of choice, and we isolated the acetonide **6** in 84% yield after **5** was dissolved in a large amount (132 vol.) of acetone/benzene and reacted with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid under dehydration conditions with 4 Å molecular sieves.

As we secured a substantial amount of the 4-chromanone intermediate **6**, the next stage was the construction of the optically active framework of neuchromenin (**1**). Commercially available ethyl (*R*)-3-hydroxybutanoate (**7**) and its relatives were employed to achieve acylation of **6**. Unfortunately, all our attempts to acylate **6** at the position α to the carbonyl group failed. Accordingly, we turned our attention

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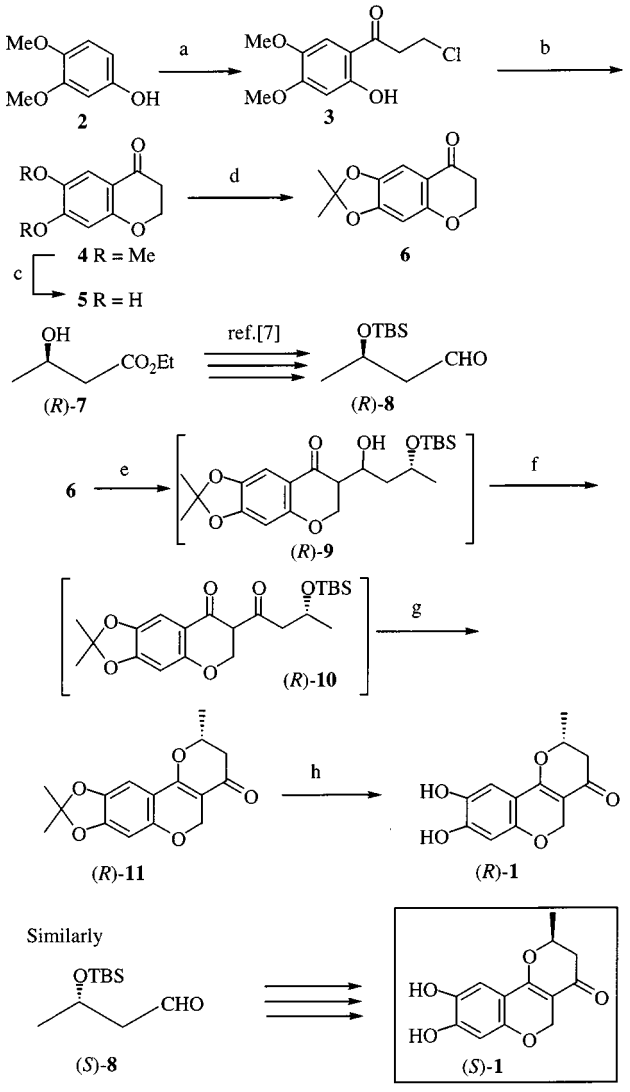

Scheme 2. Synthesis of neuchromenin (**1**); reagents and conditions: (a) $Cl(CH_2)_2COCl$, $BF_3{\cdot}OEt_2$, 65−85 °C, 3 h (25%); (b) K_2CO_3, EtOH, room temp., 14 h (76%); (c) BBr_3, CH_2Cl_2, −10 °C → room temp., 1 h (88%); (d) *p*-$TsOH{\cdot}H_2O$, $Me_2C(OMe)_2$, Me_2CO, C_6H_6, MS 4 A, reflux, 72 h (84%); (e) LDA, (*R*)-**8**, THF, below −60 °C, 1 h; (f) Dess−Martin periodinane, CH_2Cl_2, room temp., 4 h; (g) *p*-$TsOH{\cdot}H_2O$, C_6H_6, 18.5 h, then SiO_2 chromatography (25%, 3 steps); (h) 10% HCl, THF, MeOH, reflux, 14.5 h [82%; 38% after recrystallization from EtOAc/*n*-hexane to give (*R*)-**1** of 62% *ee*].

to the known aldehyde (*R*)-**8**,[7] whose cross aldol reaction with **6** would afford (*R*)-**9**. The lithium enolate of **6** was generated by treatment of **6** with lithium diisopropylamide (LDA) in THF, and treated with (*R*)-**8** at below −60 °C to give crude (*R*)-**9**. Dess−Martin oxidation[8] of (*R*)-**9** furnished (*R*)-**10** as a crude mixture. Oxidation of (*R*)-**9** with tetrapropylammonium perruthenate (TPPA)[9] gave poor results. Removal of the *tert*-butyldimethylsilyl (TBS) group of (*R*)-**10** and subsequent ring closure took place to give (*R*)-**11**, when crude (*R*)-**10** was heated with *p*-toluenesulfonic acid in wet benzene. After chromatographic purification, crystalline (*R*)-**11** was obtained in 25% yield based on **6**.

Finally, acid hydrolysis of the acetonide group[10] of (*R*)-**11** afforded crude (*R*)-**1** in 82% yield [3.0% overall yield (1.4% after recrystallization) based on **2** (8 steps)], which was purified by recrystallization to give (*R*)-neuchromenin (**1**) (m.p. 217.0−220.0 °C). Its IR, UV, ^1H and ^{13}C NMR spectra were identical with those of the natural neuchromenin. The specific rotation of (*R*)-**1** was dextrorotatory: $[\alpha]_D^{34} = +318$ (MeOH), while that of the natural neuchromenin was recorded as $[\alpha]_D^{20} = -520$ (MeOH). It therefore became clear that the natural product must possess the *S* configuration. We then synthesized (*S*)-**1** in 1.9% overall yield based on **2** by employing (*S*)-**8** for the aldol reaction with **6**. Synthetic (*S*)-neuchromenin (**1**), m.p. 217.5−223.5 °C, was levorotatory as expected: $[\alpha]_D^{32} = -321$ (MeOH).

Rather small values of the specific rotations of (*R*)- and (*S*)-**1** in comparison to natural **1** caused us to check the enantiomeric purities of the enantiomers of **11** and **1**. Fortunately, they could be separated by HPLC on a chiral stationary phase (Daicel Chiralcel OD-H® for **11** and Daicel Chiralpak AD-RH® for **1**) and their enantiomeric purities were 77% *ee* for (*R*)-**11**, 86% *ee* for (*S*)-**11**, 62% *ee* for (*R*)-**1** and 59% *ee* for (*S*)-**1**. It thus became apparent that *p*-toluenesulfonic acid in hot wet benzene employed for the conversion of **10** to **11** and hot hydrochloric acid used for the removal of the acetonide group of **11** caused partial racemization presumably due to retro-aldol/aldol and/or retro-Michael/Michael reactions. Unfortunately, milder methods of deprotection such as hot dilute acetic acid or trifluoroacetic acid in dichloromethane were not effective enough to give **1** in appreciable yield.

Purer **1** could be obtained by further recrystallization of crude **1**, because (±)-**1** turned out to be less soluble than the optically active **1**. Accordingly, 5.8 mg of (*S*)-(−)-neuchromenin (91% *ee*), m.p. 211.0−215.0 °C; $[\alpha]_D^{33} = -491$ (*c* = 0.11, MeOH) {natural **1**:[1] m.p.195−200 °C; $[\alpha]_D^{20} = -520$ (*c* = 0.1, MeOH)}, could be obtained after five recrystallizations from ethyl acetate/*n*-hexane.

In conclusion, the proposed structure **1** for (−)- neuchromenin was confirmed by the present synthesis, and its absolute configuration was determined as *S*.

Experimental Section

Boiling and melting points: Uncorrected values. − Melting points: Yanaco MP-S3. − $[\alpha]_D$: Jasco DIP-1000. − IR: Jasco IRA-102. − ^1H NMR: Jeol JNM-EX 90A (90 MHz), Jeol JNM-LA 500, (TMS at $\delta_H = 0.00$, $CHCl_3$ at $\delta_H = 7.26$ or CH_3OH at $\delta_H = 3.30$ as an internal standard). − ^{13}C NMR: Jeol JNM-LA 500 (125 MHz), ($CDCl_3$ at $\delta_C = 77.0$ or CD_3OD at $\delta_C = 49.0$ as an internal standard). − MS: Jeol JMS-AX 505HA. − Column chromatography: Merck Kieselgel 60 Art 1.07734. or Kanto Chemical silica gel 60N(spherical neutral). − TLC: 0.25 mm Merck silica gel plates (60F-254). − HPLC: Column: Daicel Chiralcel OD − H® (4.6 mm φ × 250 mm). Daicel Chiralpak AD − RH® (4.6 mm φ ×150 mm). UV detector: SSC − 5200. Pump unit: SSC − Flow system 3100. Recorder: SIC − chromatocoder 12. −UV−VIS: Hitachi U-2010.

6-(3-Chloropropanoyl)-3,4-dimethoxyphenol (3): A mixture of 3,4-dimethoxyphenol (**2**; 3.0 g, 19 mmol) and chloropropanoyl chloride (3.6 mL, 38 mol) was heated to 60 °C with stirring. When the mixture became homogenous, $BF_3{\cdot}Et_2O$ (2.5 mL, 20 mmol) was added over 3 min. The resulting mixture was stirred at 65−85 °C for 3 h,

and was then gradually cooled to 50 °C. It was poured into ice-water (50 mL)/CH_2Cl_2 (50 mL) and vigorously stirred for several minutes. The resulting bilayer mixture was filtered. The residue was washed with $CHCl_3$ (3 × 70 mL). The resulting $CHCl_3$ solution was combined with the above mentioned bilayer solution. The organic phase was separated, washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 7.5 g of crude product as an oil. The obtained oil was purified by silica gel chromatography (150 g, CH_2Cl_2 as an eluent) to give a yellow solid (2.1 g), which was recrystallized from EtOAc to give **3** (1.17 g, 25%) as yellow granules; m.p. 130.5−131.5 °C, − IR (KBr): $\tilde{\nu}_{max}$ = 3000 cm^{-1} (m, O−H), 1630 (s, C=O), 1520 (m, C=C), 1450 (m, C=C), 1260 (m, C−O−C), 1035 (w, C−O−C). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 3.40 (t, *J* = 6.1 Hz, 2 H, COC*H*$_2$CH$_2$), 3.75−4.08 (m, 2 H, CH$_2$C*H*$_2$Cl), 3.88 (s, 3 H, OC*H*$_3$), 3.92 (s, 3 H, OC*H*$_3$), 6.47 (s, 1 H, Ar-H), 7.03 (s, 1 H, Ar-H), 12.4 (s, 1 H, Ar−O*H*). − $C_{11}H_{13}ClO_4$ (244.7): calcd. C 54.00, H 5.36; found C 54.23, H 5.52.

2,3-Dihydro-6,7-dimethoxy-4*H*-1-benzopyran-4-one (4): A mixture of **3** (8.7 g, 36 mmol) and K_2CO_3 (9.8 g, 72 mmol) suspended in EtOH (435 mL) was stirred at room temperature for 14 h. The mixture was filtered, and the resulting filtrate was concentrated in vacuo. The residue was diluted with EtOAc, and the solution was washed with water, 5% aq. $NaHCO_3$ and brine, and then dried over $MgSO_4$, filtered and concentrated in vacuo to give 7.8 g of a solid. This was purified by silica gel chromatography (390 g, EtOAc/*n*-hexane 1:2 as an eluent) to give **4** as a pure yellow solid (5.7 g, 76%), which was recrystallized from EtOAc/*n*-hexane to give an analytical sample as yellow needles; m.p. 120.0−121.0 °C (EtOAc/*n*-hexane) {ref.[3] m.p. 123 °C (H_2O)}. − IR (KBr): $\tilde{\nu}_{max}$ = 1680 cm^{-1} (s, C=O), 1620 (s, C=C), 1510 (m, C=C), 1270 (s, C−O−C), 1170 (m), 1045 (w, C−O−C). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 2.75 (t, *J* = 6.2 Hz, 2 H, COC*H*$_2$CH$_2$), 3.89 (s, 3 H, OC*H*$_3$), 3.91 (s, 3 H, OC*H*$_3$), 4.51 (t, *J* = 6.2 Hz, 2 H, CH$_2$C*H*$_2$O), 6.43 (s, 1 H, Ar-H), 7.30 (s, 1 H, Ar-H). − $C_{11}H_{12}O_4$ (208.2): calcd. C 63.45, H 5.81; found C 63.55, H 5.90.

2,3-Dihydro-6,7-dihydroxy-4*H*-1-benzopyran-4-one (5): To a cooled and stirred solution of **4** (7.6 g, 37 mmol) in CH_2Cl_2 (80 mL) at −10 °C, was added a solution of 1 M BBr_3 in CH_2Cl_2 (120 mL, 120 mmol). The resulting solution was stirred for 1 h at room temperature, poured into ice/water (400 mL), and extracted with EtOAc (1 × 1000 mL, 4 × 400 mL). The combined organic solution was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give 7.4 g of crude **5** as a dark solid. This was purified by silica gel chromatography (290 g, CH_2Cl_2/MeOH 100:0 → 10:1 as an eluent) to give **5** as a tan solid (5.8 g, 88%), which was recrystallized from EtOH to give an analytical sample as pale brown granules; m.p. 229.0−230.0 °C (EtOH). − IR (KBr): $\tilde{\nu}_{max}$ = 3440 cm^{-1} (m, O−H), 3240 (s, O−H), 1660 (s, C=O), 1610 (s, C=C), 1510 (s, C=C), 1290 (m, C−O−C), 1180 (m, C−O), 1150 (m, C−O), 1045(w, C−O−C). − ^{1}H NMR (90 MHz, CD_3OD): δ = 2.65 (t, *J* = 6.5 Hz, 2 H, COC*H*$_2$CH$_2$), 4.41 (t, *J* = 6.2 Hz, 2 H, CH$_2$C*H*$_2$O), 6.33 (s, 1 H, Ar−H), 7.15 (s, 1 H, Ar−H). − $C_9H_8O_4$ (180.2): calcd. C 60.00, H 4.48; found C 59.95, H 4.60.

2,3-Dihydro-7,7-dimethyl-[1,3]dioxolo[4,5-*d*]-4*H*-1-benzopyran-4-one (6): A mixture of **5** (2.87 g, 16.7 mmol), *p*-TsOH·H_2O (0.10 g), 2,2-dimethoxypropane (6.94 g, 66.6 mmol), benzene (300 mL) and acetone (80 mL) was stirred and refluxed with a Dean−Stark water trap containing MS 4Å (50 g). Additional portions of 2,2-dimethoxypropane (4 × 6.94 g, 4 × 66.6 mmol), acetone (1 × 50 mL), benzene (1 × 40 mL) and *p*-TsOH·H_2O (0.10 g) were added during reflux. After 72 h, the reaction mixture was concentrated in vacuo to give 8.27 g of crude product as a dark oil. This was purified by silica gel chromatography (240 g, EtOAc/*n*-hexane 1:4 as an eluent) to give **6** as a yellow solid (3.10 g, 84%), which was recrystallized from Et_2O/*n*-hexane to give an analytical sample as pale yellow needles; m.p. 107.0−108.0 °C (Et_2O/*n*-hexane). − IR (KBr): $\tilde{\nu}_{max}$ = 1660 cm^{-1} (s, C=O), 1620 (m, C=C), 1605 (m, C=C), 1480 (s, C=C), 1440(m), 1260 (s, C−O−C), 1180 (m, C−O), 1150 (m, C−O), 1040 (w, C−O−C). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.68 [s, 6 H, (C*H*$_3$)$_2$C], 2.71 (t, *J* = 6.5 Hz, 2 H, COC*H*$_2$CH$_2$), 4.47 (t, *J* = 6.5 Hz, 2 H, CH$_2$C*H*$_2$O), 6.33 (s, 1 H, Ar−H), 7.18 (s, 1 H, Ar−H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.0, 37.3, 67.6, 98.1, 104.0, 114.7, 119.7, 143.2, 154.4, 159.8, 190.3. − $C_{12}H_{12}O_4$ (220.2) calcd. C 65.45, H 5.49; found C 65.61, H 5.48.

(*R*)-(+)-2,3-Dihydro-2,9,9-trimethyl-[1,3]dioxolo[4′,5′-*g*]-4*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-4-one (11). (i) Aldol Condensation: To a stirred and cooled solution of LDA in THF [prepared from 1.6 M BuLi in *n*-hexane (8 mL, 12.8 mmol), *i*Pr$_2$NH (1.80 mL, 12.8 mmol) and THF (40 mL) at 0 °C] was added a solution of **6** (2.40 g, 10.9 mmol) in THF (15 mL) dropwise with a cannula under Ar below −60 °C. An additional portion of THF (15 mL) was added to the mixture. The resulting mixture was stirred below −60 °C for 2.5 h. A solution of (*R*)-**8** (2.43 g, 12.0 g) in THF (10 mL) was added dropwise with a cannula to the above reaction mixture under Ar below −60 °C. An additional portion of THF (10 mL) was added to the mixture. The resulting solution was stirred below −60 °C for 1.0 h, quenched with sat. aq. NH_4Cl (100 mL), warmed to room temperature and extracted with EtOAc (200 mL). The organic solution was washed with sat. aq. $NaHCO_3$ (100 mL), brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 5.0 g of crude (*R*)-**9** as a red oil. The obtained oil was used for the next oxidation step without any purification.

(ii) Dess−Martin Oxidation: A mixture of the crude (*R*)-**9** (5.0 g), and Dess−Martin reagent (6.90 g, 16 mmol) in CH_2Cl_2 (60 mL) was stirred at room temperature for 4 h. The reaction mixture was washed with sat. aq. $NaHCO_3$ (100 mL), 5% aq. $Na_2S_2O_3$ (100 mL), brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 8.0 g of crude (*R*)-**10** as a solid. The crude solid was purified by silica gel chromatography (400 g, EtOAc/*n*-hexane 1:8 as an eluent) to give 2.23 g of a red oil. The red oil was purified again by silica gel chromatography (240 g, EtOAc/*n*-hexane 1:15 as an eluent) to give 1.59 g of a pale red oil. This was chromatographed on silca gel column [Kanto Chemical silica gel 60N (spherical neutral) 240 g, CH_2Cl_2/*n*-hexane 1:1 as an eluent] to give 1.4 g of (*R*)-**10** as the major product of oxidation (R_f = 0.5, EtOAc/*n*-hexane 1:8) as a yellow oil. This was used for the following ring closure step without any further purification.

(iii) Ring Closure Reaction: A mixture of the crude (*R*)-**10** (1.4 g), *p*-TsOH·H_2O (0.14 g), and H_2O (1.4 mL) in benzene (600 mL) was stirred and refluxed. Additional portions of benzene (2 × 80 mL), *p*-TsOH·H_2O (4 × 0.14 g) and H_2O (6 × 1.4 mL) were added during reflux. After refluxing for 18.5 h, the reaction mixture was concentrated in vacuo to give the crude product as a red gum. This gum was chromatographed on silica gel [Kanto Chemical silica gel 60N (spherical neutral) 100 g, EtOAc/*n*-hexane 1:2 as an eluent] to give 0.756 g of (*R*)-**11** as a yellow solid (25% in three steps), which was recrystallized from EtOAc/*n*-hexane to give an analytical sample as pale yellow granules; m.p. 125.0−126.5 °C. − $[\alpha]_D^{31}$ = +347 (*c* = 1.01 in $CHCl_3$). − IR (KBr): $\tilde{\nu}_{max}$ = 1650 cm^{-1} (m, shoulder), 1640 (s, C=O), 1595 (m, C=C), 1495 (s, C=C), 1450 (s, C=C), 1380 (s), 1260 (m, C− O−C), 1020 (w, C− O−C). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.54 (d, *J* = 6.4 Hz, 3 H, C*H*$_3$), 1.668 [s, 3 H, (C*H*$_3$)$_2$C], 1.674 [s, 3 H, (C*H*$_3$)$_2$C], 2.49 (dd, *J* = 16.8 Hz, 4.6 Hz, 1 H, COC*H*$_2$), 2.55 (dd, *J* = 16.8 Hz, 12.2 Hz, 1 H, COC*H*$_2$), 4.61−4.70 [m, 1 H, OC*H*(CH$_3$)], 4.82 (d, *J* =

12.2 Hz, 1 H, ArOCH*H*), 5.13 (d, *J* = 12.2 Hz, 1 H, ArOCH*H*), 6.32 (s, 1 H, Ar−H), 6.94 (s, 1 H, Ar−H)− $C_{16}H_{16}O_5$ (288.3): calcd. C 66.66, H 5.59; found C 66.76, H 5.61. − HPLC: The enantiomeric excess was determined to be 77% by chiral HPLC column. Analytical conditions: Column, Daicel Chiralcel OD-RH® (4.6 mm × 250 mm); Eluent, *i*PrOH/MeCN (10:90); Flow rate, 0.5 mL/min.; Detection at λ = 254 nm; Sample concentration and injection volume, 0.1 mg/mL in *i*PrOH/MeCN (10:90) × 5 μL. (*R*)-**11** was detected at t_R = 13.4 min., and (*S*)- **11** was detected at t_R = 14.6 min.

(*R*)-(+)-2,3-Dihydro-8,9-dihydroxy-2-methyl-4*H*,5*H*-pyrano-[3,2-*c*][1]benzopyran-4-one [(+)-Neuchromenin (1)]: A solution of (*R*)-**11** (400 mg, 1.39 mmol) in 10% HCl/THF/MeOH (7 ml:7 ml:7 mL) was refluxed under Ar for 14.5 h. It was then poured into sat. aq. $NaHCO_3$ (80 mL) and extracted with EtOAc (150 mL). The extract was washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated to give 0.40 g of a yellow solid. It was purified by silica gel chromatography (70 g, CH_2Cl_2/MeOH 100:0 → 25:1 as an eluent) to give (*R*)-**1** as a yellow solid (282 mg, 82%), which was recrystallized from EtOAc/*n*-hexane to give 132 mg (38%) of the first crop of (*R*)-**1** as yellow granules; m.p. 217.0−220.0 °C (EtOAc/*n*-hexane), $[\alpha]_D^{34}$ = +318 (*c* = 0.10 in MeOH). − IR (KBr): $\tilde{\nu}_{max}$ = 3500 cm^{-1} (s, O−H), 3300−2200 (br, O−H), 1610 (m, C=O), 1565 (s, C=C), 1550 (s, C=C), 1450 (s, C=C), 1430 (s, C=C), 1300 (s), 1260 (m, C−O−C), 1020 (w, C−O−C). − ^{1}H NMR (500 MHz, CD_3OD): δ = 1.52 (d, *J* = 6.4 Hz, 3 H, C*H*$_3$), 2.46 (dd, *J* = 17.0 Hz, 4.0 Hz, 1 H, COCH_2), 2.54 (dd, *J* = 17.0 Hz, 12.9 Hz, 1 H, COCH_2), 4.62−4.71 [m, 1 H, OC*H*(CH_3)], 4.70 (d, *J* = 12.2 Hz, 1 H, ArOCH_2), 5.00 (d, *J* = 12.2 Hz, 1 H, ArOCH_2), 6.31 (s, 1 H, Ar−H), 6.93 (s, 1 H, Ar−H). − ^{13}C NMR (125 MHz, CD_3OD): δ = 20.6 (11-C), 43.5 (3-C), 64.0 (5-C), 77.1 (2-C), 102.5 (4a-C), 104.4 (7-C), 109.2 (10a-C), 111.0 (10-C), 141.8 (9-C), 153.3 (8-C), 155.2 (6a-C), 166.0 (10b-C), 191.0 (4-C). − $C_{13}H_{12}O_5$ (248.2): calcd. C 62.90, H 4.87; found C 62.75, H 4.93. − UV/Vis (MeOH): λ_{max} (ε) = 205 (15100), 254 (13100), 309 (10200), 388 (15800). {ref.[1] 223 (8100), 256 (12200), 309 (9700), 387 (14700)}. − UV/Vis (0.01 N NaOH/MeOH, 1:9) λ_{max} (ε) = 272 (10100), 324 (7400), 422 (33000). {ref.[1] 273 (8900), 324 (7000), 423 (29500)}. − HPLC (analytical conditions are reported at the end of this Experimental Section): 62% *ee*

(*S*)-(−)-2,3-Dihydro-2,9,9-trimethyl-[1,3]dioxolo[4′,5′-*g*]-4*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-4-one (11). (i) Aldol Condensation: In the same manner as described for (*R*)-**11**, **6** (2.48 g) and (*S*)-**8** (2.53 g) afforded 5.40 g of crude (*S*)-**9**.

(ii) Dess−Martin Oxidation: In the same manner as described for (*R*)-**10**, (*S*)-**9** (5.40 g) was oxidized with Dess−Martin periodinane (6.16 g) to give (*S*)-**10** (1.84 g): HRMS (FAB) [M + H^+] ($C_{22}H_{33}O_6Si$): calcd. 421.2046; found 421.2067 (error + 4.9 ppm)

(iii) Ring Closure Reaction: In the same manner as described for (*R*)-**11**, crude (*S*)-**10** (1.8 g) furnished (*S*)-**11** (0.9 g, 27%; 3 steps). This was recrystallized from EtOAc/*n*-hexane to give an analytical sample as pale yellow granules; m.p. 125.0−126.5 °C. − $[\alpha]_D^{34}$ = −374 (*c* = 1.00 in $CHCl_3$). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.5, 25.72, 25.75, 42.9, 63.5, 75.6, 98.4, 101.5, 102.5, 109.2, 119.3, 142.6, 152.2, 155.4, 163.0, 188.4 − $C_{16}H_{16}O_5$ (288.3): calcd. C 66.66, H 5.59; found C 66.62, H 5.66. − HPLC (analytical conditions same as those described for (*R*)-**11** in this Experimental Section): 86% *ee* − Its IR and ^{1}H NMR spectra were identical to those described for (*R*)-**11**.

(*S*)-(−)-2,3-Dihydro-8,9-dihydroxy-2-methyl-4*H*,5*H*-pyrano-[3,2-*c*][1]benzopyran-4-one [(−)-Neuchromenin (1)]: In the same manner as described for (*R*)-**1**, (*S*)-**11** (500 mg) gave (*S*)-**1** (200 mg, 47%) together with 180 mg of the second crop. Properties of (*S*)-**1**: yellow granules: m.p. 217.5−223.5 °C (EtOAc/*n*-hexane) {ref.[1] m.p. 195−200 °C (decomp)}, $[\alpha]_D^{32}$ = −321 (*c* = 0.10 in MeOH), {ref.[1] $[\alpha]_D^{20}$ = −520 (*c* = 0.1 in MeOH)}. − $C_{13}H_{12}O_5$ (248.2): calcd. C 62.90, H 4.87; found C 62.97, H 4.58. − The IR, UV and NMR spectroscopic data were in good agreement with those of (*R*)-**1** and also with the reported data.[1] − HPLC (analytical conditions are reported at the end of this Experimental Section): 59% *ee*.

Recovery of (*S*)-1 from Mother Liquor: The material recovered from the mother liquor showed $[\alpha]_D^{34}$ = −471 (*c* = 0.11 in MeOH) − The IR and NMR spectroscopic data were identical with those of the first crop and were in good agreement with the reported data. − HPLC (analytical conditions are reported at the end of this Experimental Section): 79% *ee*.

Purification of (−)-Neuchromenin by Recrystallization: The recovered crystals from the mother liquor of the first recrystallization were recrystallized from EtOAc/*n*-hexane again. After fine granules had precipitated, these granules were filtered off. The obtained second mother liquor was concentrated to give enantiomerically purer (−)-neuchromenin. This cycle was repeated until sufficient enantiomeric purity was observed by chiral HPLC. The HPLC conditions were as below: Column, Daicel Chiralpak AD − RH® (4.6 mm ×150 mm); Eluent, pH 2.0 [0.2 M H_3PO_4/KH_2PO_4/MeCN (4:1)]; Flow rate, 0.6 mL/min.; Detection at λ = 254 nm; Sample concentration and injection volume, 0.1 mg/ml in MeCN solution × 5μL. Under these conditions, (*R*)-(+)-**1** was detected at t_R = 14.3 min., and (*S*)-(−)-**1** was detected at t_R = 17.3 min.; The third crop of fine granules (25 mg, 6.9% from **11**): m.p. 210.5−218.0 °C (EtOAc/*n*-hexane), $[\alpha]_D^{33}$ = −475 (*c* = 0.10 in MeOH). Its NMR spectroscopic data were identical with those of the first crop. The fourth crop of microcrystalline powder (20 mg, 5.6% from **11**): m.p. 210.5−215.5 °C (EtOAc/*n*-hexane), $[\alpha]_D^{33}$ = −484 (*c* = 0.12 in MeOH). Its NMR spectroscopic data were identical with those of the first crop of granules.; The fifth crop of microcrystalline powder (5.8 mg, 1.7% from **11**): m.p. 211.0−215.0 °C (EtOAc/*n*-hexane), $[\alpha]_D^{33}$ = −491 (*c* = 0.11 in MeOH) {ref.[1] m.p.195−200 °C (decomp), $[\alpha]_D^{20}$ = −520 (*c* = 0.1 in MeOH)}. Its ^{1}H NMR spectroscopic data were identical with those of the first crop and were in good agreement with those previously reported.[1]

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