Synthesis of Optically Active 2-Methylchroman Derivatives and Application to Chiral Dopants for Nematic Liquid Crystals

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Chiral 2-methylchroman-2-carboxylic acid derivatives were prepared as new chiral dopants for nematic liquid crystals. The starting material, optically active 6-benzyloxy-2-methylchroman-2-carboxylic acid, was newly synthesized as a rigid core structure and resolved by a diastereomeric salt formation method. Its absolute configuration was determined by comparing its circular dichroism spectrum with that of the commercially available (*S*)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid derivative. The helical twisting power of the new dopants was determined and the relationship between their functional groups and flexible terminal structures was studied.

These days, about half of all computer monitors consist of liquid-crystalline materials, and almost all lap-top computers have a liquid-crystalline display (LCD). The liquid crystals (LCs) used in the display are mostly in the nematic phase and need to have chirality, which is interpreted to be helically twisted, and is called a 'cholesteric phase' (Ch) or a 'chiral nematic phase' (N*). A chiral nematic phase in a LCD is controlled by an electrical field. The interaction of polarized light with the nematic phase is the basic principle of the most widely used LCD, which is one of the most important applications of LCs.[1] Chiral nematic phases can be formed not only by optically active liquid-crystalline molecules, but also by non-chiral nematic phases doped with an optically active molecule (e.g. cholesteryl nonanoate, CN) as a chiral dopant.

The strength of chiral induction by a dopant, the helical twisting power (HTP), can be estimated by (Eq. 1),[2] where p is the pitch of the chiral nematic phase in μm and c is the mass fraction of the dopant. Initially, readily available cholesterol esters, such as CN, were used as chiral dopants. These days, new chiral dopants with larger HTP are required for a further improvement of the LCD performance.

$$\mathrm{HTP} = (pc)^{-1}. \quad (1)$$

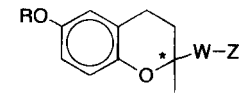
The HTP depends on the molecular structure of the guest (dopant) in a certain host (nematic LC) molecule. However, knowledge about the relationship between the HTP and the molecular structures is not well established.[3,4] A chiral dopant is usually designed to have a rigid core structure close to an asymmetric center and flexible terminal groups, just like liquid crystals. One interesting group of dopants has a cyclic structure together with a rigid core.[5] We have expected 2-methylchroman derivatives to also belong to this group, and would become interesting candidates as chiral dopants, because they have a more restricted cyclic structure and a quaternary carbon as the asymmetric center, like CN (Chart 1).

In a previous paper,[6] we reported on preliminary data about some new chiral dopants having a rigid core structure, 6-benzyloxy-2-methylchroman-2-carboxylic acid esters. In this work, we further studied the relationship between the chiral-induction ability, HTP, and the molecular structures using six optically pure 2-methylchroman-2-carboxylic acid derivatives, **1***—**4***, and newly prepared 2-methylchroman-2-carbonitrile derivatives, **5*** and **6***. They have different terminal groups (benzyl ether, alkyl ether, and aromatic ester). The absolute configuration of their starting material, optically active 6-benzyloxy-2-methylchroman-2-carboxylic acid (**7***), was determined by comparing the circular dichroism of its methyl ester and that of (*S*)-(−)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid ((*S*)-(−)-Trolox®, **8***).

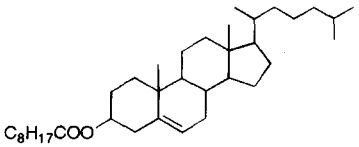
Results and Discussion

Optical Resolution of 6-Benzyloxy-2-methylchroman-2-carboxylic Acid. The optical resolution via diastereomeric salt formation is a practical method to obtain both chiral molecules, (+)- and (−)-isomers. In order to obtain chiral 2-methylchroman-2-carboxylic acid derivatives, this method was applied in the present study.

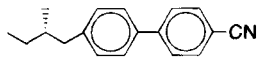
Ethyl 6-benzyloxy-2-methylchroman-2-carboxylate **1b** was easily prepared from the reaction of hydroquinone monobenzyl ether with ethyl methacrylate and paraformaldehyde under reflux conditions in the presence of dibutylamine and acetic acid. The reaction mixture was purified by silica-gel column chromatography to give **1b** in moderate yield. The racemic 6-benzyloxy-2-methylchroman-2-carboxylic acid **7** was prepared by the hydrolysis of **1** (Scheme 1),[7] which was supplied to optical resolution.



1*-6*
2-methylchroman derivatives

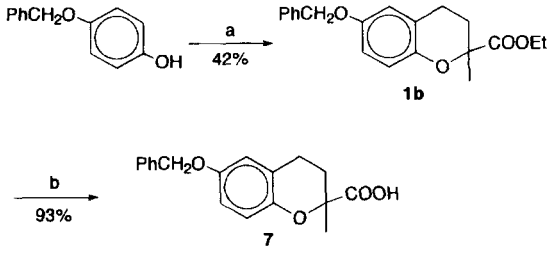


cholesteryl nonanoate



(*S*)-4'-(2-methylbutyl)biphenyl-4-carbonitrile

Chart 1.



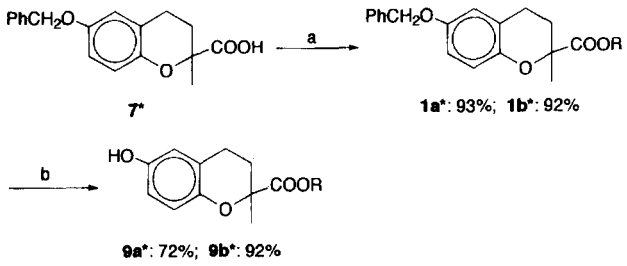
a) CH_2=C(CH_3)COOEt, $(HCHO)_n$, *n*-Bu_2NH, AcOH, 120 °C.
b) NaOH, MeOH, 50 °C.

Scheme 1. Synthesis of 6-benzyloxy-2-methylchroman-2-carboxylic acid (**7**).

Eight optically active amines (Chart 2) were examined as basic resolving agents for optical resolution, and all of them formed crystalline diastereomeric salts (Table 1). Table 1 summarizes the physical data of the salts and the optical purities of the salts or the mother liquids remaining after fractional crystallization. It was shown that (1*R*,2*S*)-(+)-*cis*-2-(benzylamino)cyclohexylmethanol (*cis*-Amine)[8] was the best resolving agent because of the highest value of the optical purity of the crystal calculated from the specific rotation of the mother liquid. The salt of **7** and (1*R*,2*S*)-(+)-*cis*-Amine was further recrystallized; the result and some properties of (−)-**7** are summarized in Table 2.

Synthesis of Chiral Dopants and Determination of the Absolute Configuration. Simple ester-type dopants, **1a*** and **1b***, were derived from **7*** by esterification with methanol and ethanol (Scheme 2). In order to determine their absolute structure, they were further debenzylated over palladium-carbon to afford **9a*** and **9b*** (Scheme 2). On the other hand, **8*** was esterified with methanol to afford (*S*)-(−)-**10*** (Scheme 3).

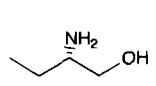
The circular-dichroism spectra of (*S*)-(−)-**10*** and (−)-**9a*** were measured, and both showed the same Cotton effect



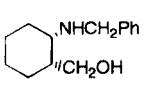
7*
1a*: 93%; **1b***: 92%
9a*: 72%; **9b***: 92%

a) ROH (**1a***: R = Me, **1b***: R = Et), H_2SO_4, rt.
b) H_2, Pd-C, ROH (**9a***: R = Me, **9b***: R = Et), rt.

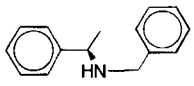
Scheme 2. Synthesis of methyl 6-hydroxy-2-methylchroman-2-carboxylate (**9a***).



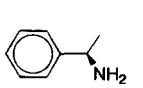
2-Amino-1-butanol
((*S*)-(+)-2AB)



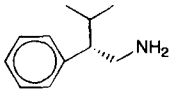
cis-2-(Benzylamino)cyclohetylmethanol
((1*R*)-(2*S*)-*cis*-Amine)



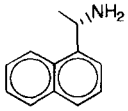
N-Benzyl-1-methylbenzylamine
((*R*)-(+)-BMBA)



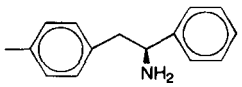
α-Methylbenzylamine
((*R*)-(+)-MBA)



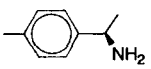
3-Methyl-2-phenylbutylamine
((*S*)-(+)-MPBA)



1-(1-Naphthyl)ethylamine
((*S*)-(-)-NEA)



1-Phenyl-2-(p-tolyl)ethylamine
((*S*)-(+)-PTE)



1-(*p*-Tolyl)ethylamine
((*R*)-(+)-TEA)

Chart 2.

Table 1. Results of Trial Resolution of **7** with Various Chiral Amines

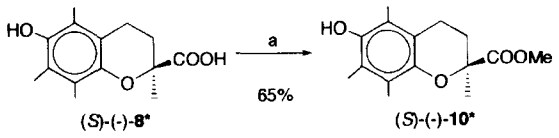
Resolving agent	Fractional crystallization solvent	Crystal Yield[a] %	Crystal Mp[b] °C	Crystal Op[c] %ee	Mother liquid Yield[a] %	Mother liquid $[\alpha]_D$[d] °	Mother liquid Op[e] %ee
(*S*)-(+)-2AB	AcOEt	89	89—105	4.1	122	0.9	—
(1*R*,2*S*)-(+)-*cis*-Amine	AcOEt+MTBE[f]	57	140—146	61	139	11.6	—
(*R*)-(+)-BMBA	AcOEt+C_6H_{14}	38	88—107	1.5	157	0.5	—
(*R*)-(+)-MBA	AcOEt+MeOH	24	134—135	3.0	75	1.1	—
(*S*)-(+)-MPBA	AcOEt	150	139—141	5.7	36	−4.3	—
(*S*)-(−)-NEA	AcOEt+MeOH	127	156—164	29	82	9.7	36.9
(*S*)-(+)-PTE	Et_2O	87	110—120	3.4	36	2.5	—
(*R*)-(+)-TEA	AcOEt+MeOH	122	142—148	4.4	70	1.7	—

a) The yields were calculated based on half the amount of racemic **7**. b) Mp of diastereomeric salts. c) The optical purity was calculated from the specific rotation of mother liquid. d) Specific rotation of **7**, Solvent: 99% EtOH, *c* 1.0, 27 °C. e) The optical purity of **7*** was determined as its ethyl ester using HPLC equipped with a chiral column, "CHIRALCEL OJ" (Daicel Chem. Ind., Ltd., 4.6 mm×250 mm, carrier solvent 35% 2-propanol/hexane). f) *t*-Butyl methyl ether.

Table 2. Optical Resolution of (±)-**7**

Salt[a] $[\alpha]_D$[b]/°	Salt[a] Mp/°C	(−)-**7** $[\alpha]_D$[b]/°	(−)-**7** Mp/°C	Op %ee[c]	Yield %[d]	Resolving efficiency[e]
−19.5	142—146	−33.4	112—116	96.9	54	52

a) (−)-**7**–(1*R*,2*S*)-(+)-*cis*-Amine. Found: C,74.06; H, 7.67; N, 2.65%. Calcd for $C_{22}H_{39}NO_5$: C, 74.24; H, 7.59; N, 2.70%. b) Solvent: 99% EtOH, *c* 1.0, 27 °C. c) The optical purity of **7*** was determined as its methyl ester using HPLC equipped with a chiral column, "CHIRALCEL OJ" (Daicel Chem. Ind., Ltd., 4.6 mm×250 mm, carrier solvent 35% 2-propanol/hexane). d) The yield was calculated based on half the amount of racemic **7**. e) Resolving efficiency = Yield×ee(%)/100.



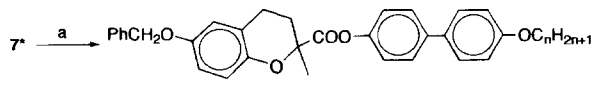
a) MeOH, H_2SO_4, rt.

Scheme 3. Synthesis of (*S*)-(−)-methyl 6-benzyloxy-2,5,7, 8-tetramethylchroman-2-carboxylate (**10***).

(Fig. 1). Therefore, it was concluded that (−)-**9a*** has the *S* configuration. Because the esterification of the carboxyl group should not affect the chirality, the absolute configuration of (−)-**7*** should be *S*.[9]

Other ester-type chiral dopants, **2a*** and **2b***, were obtained by the esterification of **7*** with the corresponding biphenyl-4,4′-diol derivatives (Scheme 4). They have a biphenyl group at the aliphatic side of the 2-methylchroman structure.

Debenzylation of **2b*** over palladium–carbon and successive etherification with methyl iodide afforded **3***



a) HO-OC_nH_{2n+1} (**2a***: n=6, **2b***: n=10), DCC, DMAP, CH_2Cl_2, rt.

Scheme 4. Synthesis of 4′-hexyloxy-4-biphenylyl 6-benzyloxy-2-methylchroman-2-carboxylate (**2a***).

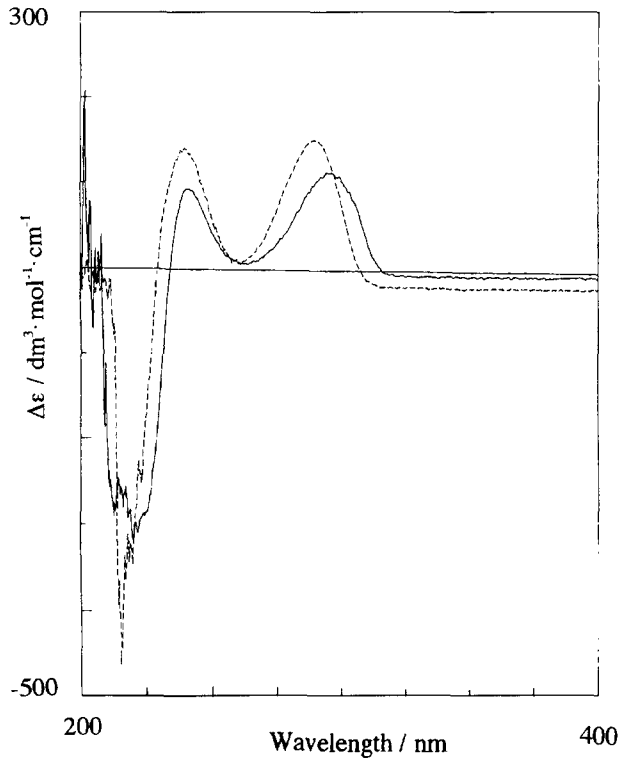
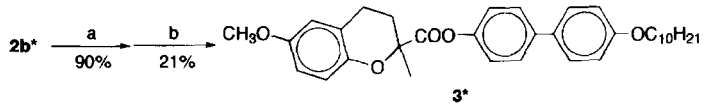


Fig. 1. CD spectrum of (*S*)-(−)-**10*** (···) and (−)-**9a*** (—) in ethanol.

(Scheme 5), which has no aromatic groups at the aromatic side of the 2-methylchroman structure.



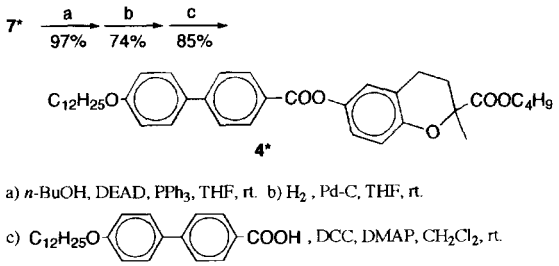
a) H_2, Pd-C, THF, rt. b) CH_3I, K_2CO_3, acetone, 63 °C.

Scheme 5. Synthesis of 4′-decyloxyl-4-biphenylyl 6-methoxy-2-methylchroman-2-carboxylate (**3***).

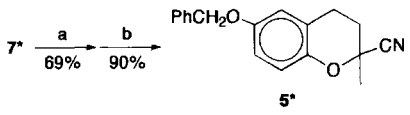
In order to study the effect of substitutions at the aromatic side, a biphenyl group was introduced at the 6-position of a chroman ring. The esterification of **7*** with 1-butanol, debenzylation, and subsequent esterification with 4′-(dodecyloxy)biphenyl-4-carboxylic acid gave **4*** (Scheme 6).

The carboxyl group of **7*** was replaced by a cyano group to give new dopants, **5*** and **6***. The chiral dopants **5*** was obtained by the amidation of **7*** with ammonia, and was then dehydration by Burgess reagent (Scheme 7).[10]

Benzyl ether of **5*** was changed to the alkyl one by the reaction of **9b*** with hexyl bromide, hydrolysis, and dehydration, as mentioned above, to give **6*** (Scheme 8).

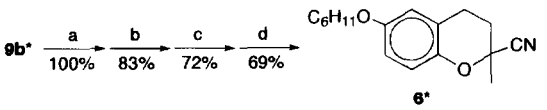


Scheme 6. Synthesis of butyl 6-(4′-dodecyloxybiphenyl-4-carboxy)-2-methylchroman-2-carboxylate (**4***).



a) $SOCl_2$, NH_3, rt.
b) $CH_3O_2CN^-SO_2N^+Et_3$ (Burgess reagent), CH_2Cl_2, rt.

Scheme 7. Synthesis of 6-benzyloxy-2-methylchroman-2-carbonitrile (**5***).



a) $C_6H_{11}Br$, NaH, KI, DMF, 80 °C. b) NaOH, MeOH, 50 °C.
c) $SOCl_2$, NH_3, rt. d) $CH_3O_2CN^-SO_2N^+Et_3$ (Burgess reagent), CH_2Cl_2, rt.

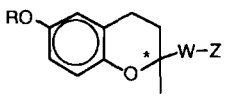
Scheme 8. Synthesis of 6-hexyloxy-2-methylchroman-2-carbonitrile (**6***).

Relationship between Structure and Helical Twisting Power of 2-Methylchroman Derivatives. The HTP of each chiral dopant was measured as a 1 wt% mixture with the host LC (ZLI-1132); the results are summarized in Table 3 together with the data of its specific rotation. The HTP of two commercially available chiral dopants, (*S*)-4′-(2-methylbutyl)biphenyl-4-carbonitrile and CN, are known to be 9.6 μm^{-1} and 4.4 μm^{-1}, respectively, to the same host LC.[1a] From the data of **1a***, **1b***, **2a***, and **2b***, it is shown that the 2-methylchroman structure potentially has a good chiral-induction ability.

However, the HTP was completely lost by the substitution of a benzyl group in R (Table 3) by a methyl group in **3***. From this drastic change, an additional aryl group at the 6-position of 2-methylchroman is requisite for chiral induction in the case of the ester-type derivatives.

The biphenyl group in R is also very effective, considering the molar ratio of **4*** in its 1 wt% sample. On the other hand, the structure at the asymmetric center has a smaller effect. Dopants **1a*** and **1b***, having an ethyl ester, exhibits the highest HTP, while **2a*** and **2b***, bearing a larger ester terminal, have a lower HTP. At this aliphatic side, the biphenyl group is not as effective as that at the aromatic part. For larger chiral induction by the 2-methylchroman moiety,

Table 3. Helical Twisting Power (HTP)[a] and Specific Rotations of Chiral Dopants



Chiral dopant	Config.	R	W	Z	$[\alpha]_D$[b] °	HTP μm^{-1}	(mol%)[c]
1a*	*S*	$PhCH_2$	CO_2	CH_3	−33.8	9.17	3.3
1b*	*R*	$PhCH_2$	CO_2	C_2H_5	29.5	11.2	3.8
2a*	*S*	$PhCH_2$	$CO_2C_6H_4C_6H_4O$	C_6H_{13}	3.3	3.01	1.9
2b*	*R*	$PhCH_2$	$CO_2C_6H_4C_6H_4O$	$C_{10}H_{21}$	−1.2	4.00	2.0
3*	*R*	CH_3	$CO_2C_6H_4C_6H_4O$	$C_{10}H_{21}$	8.4	0	1.8
4*	*R*	$C_{12}H_{25}OC_6H_4C_6H_4CO$	CO_2	C_4H_9	14.3	8.77	2.0
5*	*S*	$PhCH_2$	CN	—	69.4	5.23	3.9
6*	*S*	C_6H_{13}	CN	—	67.9	5.72	3.9

a) Host liquid crystal (ZLI-1132) : dopant = 99 : 1 (by weight). b) Solvent: $CHCl_3$, *c* 1.0, 27 °C. c) The mol% value of 1 wt% of each chiral dopant.

although an additional aryl group on its aromatic side is important, a small functional group seems to be sufficient at the chiral center (W and Z in Table 3).

In order to certify this hypothesis, the carboxyl group of **1a*** and **1b*** was changed to a cyano group and the HTP was determined. Dopant **5***, however, showed a much lower chiral-induction ability. A further replacement of the benzyl group by a hexyl group (**6***) did not affect the HTP value at all. Therefore, the difference is mostly caused by the difference of an ester group and a cyano group. A MOPAC calculation (PM3) was applied to simulate and provide stereochemical information about the structures of **1b***. Although the calculation gave many conformations due to the structural flexibility, Fig. 2 shows the most stable conformation for **1b***. From the figure, both a bulky methyl group and an ester group seem to have some interaction with its vicinity, while a small cyano group is not effective. On the other hand, the dopant **3***, which has a very large group at the W–Z position, shows no chiral-induction ability. The chirality at the asymmetric center could be impaired by too long side groups. Apparently, further study is necessary to understand the structural effect on the HTP.

Conclusion

It was shown that 2-methylchroman-2-carboxylic acid derivatives can be good chiral dopants, which are as good as some commercial products, like (*S*)-4′-(2-methylbutyl)biphenyl-4-carbonitrile and cholesterylnonanoate.[1a] The racemic starting material, 6-benzyloxy-2-methylchroman-2-carboxylic acid, was easily prepared from inexpensive raw materials. It was efficiently resolved by a diastereomeric salt formation method using (1*R*,2*S*)-(+)-*cis*-2-(benzylamino)-cyclohexylmethanol ((1*R*,2*S*)-(+)-*cis*-Amine); the absolute configuration was easily determined. On the other hand, a nitrile group was not appropriate as a substituent at the chiral center of the 2-methylchroman unit. To design effective chiral dopants, it was found that a compact ester group and an additional aryl group at its 6-position of 2-methylchroman-2-carboxylic acid are effective.

Experimental

Infrared spectra were recorded on a Perkin–Elmer 1640 spectrometer. ^{1}H NMR spectra were measured on a Bruker ARX 400 spectrometer. The optical purity was determined by high-performance liquid chromatography using a set of JASCO LC 900 series (chiral column, "CHIRALCEL OJ" (Daicel Chem. Ind., Ltd., 4.6 mm×250 mm)). Specific rotations were measured with a JASCO DIP-370 polarimeter. The circular dichroism spectra were obtained using a JASCO J-720W spectrometer. The helical pitch of a chiral nematic phase was measured using wedge-shaped samples, contained between a convex lens and a plane glass plate (Cano-wedge cell, tan $\theta = 0.0083$, 0.0140, 0.0194, 0.0288, E. H. C. Ind., Ltd.,) by means of the resulting Cano lines.[11] The liquid crystal (LC) sample was prepared by adding 1 wt% of a chiral dopant into the achiral host LC mixture ZLI-1132 (Merck). Simulation of the dopant **1b*** by semiempirical molecular orbital calculation was performed using MOPAC (PM3).

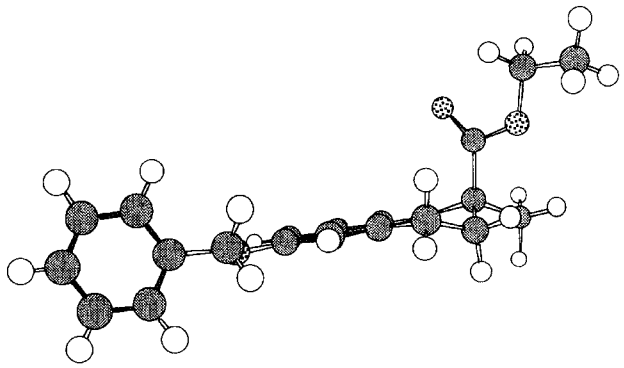


Fig. 2. Optimized geometry of **1b*** (MOPAC PM3).

Synthesis of Ethyl 6-Benzyloxy-2-methylchroman-2-carboxylate (1b): Hydroquinone monobenzyl ether (6.071 g, 30.3 mmol) was added to a mixture of ethyl methacrylate (17.060 g, 149.4 mmol), paraformaldehyde (0.972 g, ca. 32.4 mmol), dibutylamine (0.486 g, 3.7 mmol), and acetic acid (0.914 g, 15.2 mmol). After the reaction mixture was refluxed for 23 h, the liquids were evaporated off. After diluting the remaining residue with toluene (60 ml), the organic layer was washed with distilled water and the insoluble materials were filtered off using celite 545. The filtrate was washed with sat. Na_2CO_3 aq soln and sat. NaCl aq soln. The organic layer was concentrated under reduced pressure, and the residue was purified by column chromatography (silica-gel: 120 g, 20% ethyl acetate in hexane) to yield light yellow solid (3.892 g, 39%, mp 79—83 °C). ^{1}H NMR ($CDCl_3$) δ = 1.19 (3H, t, J = 6.9 Hz), 1.60 (3H, s), 1.86—1.89 (1H, m), 2.36—2.39 (1H, m), 2.67—2.70 (2H, m), 4.16 (2H, q, J = 7.0 Hz), 4.97 (2H, s), 6.64 (1H, s), 6.76 (1H, d, J = 8.6 Hz), 6.84 (1H, d, J = 8.6 Hz), 7.27—7.45 (5H, m). IR (KBr) 3031, 2979, 2934, 2868, 1748, 1495 cm^{-1}. Found: C, 73.19; H, 6.82%. Calcd for $C_{20}H_{22}O_4$: C, 73.59; H, 6.79%.

Synthesis of 6-Benzyloxy-2-methylchroman-2-carboxylic Acid (7): A solution of **1b** (2.035 g, 6.24 mmol) in methanol (25 ml) was added to a mixture of sodium hydroxide (0.662 g, 16.55 mmol) in distilled water (1 ml) and methanol (3 ml). The solution was stirred for 1 h at 50 °C and then concentrated under reduced pressure. After the remaining residue was dissolved into distilled water (60 ml), diethyl ether was added. The aqueous layer was acidified by concd HCl aq (2 ml) and the organic layer was extracted with ethyl acetate, and dried with anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give a light yellow solid (1.558 g, 84%). ^{1}H NMR ($CDCl_3$) δ = 1.61 (3H, s), 1.96 (1H, m), 2.35 (1H, m), 2.74 (2H, m), 4.98 (2H, s), 6.68 (1H, s), 6.78(1H, d, J = 8.6 Hz), 6.83 (1H, d, J = 8.6 Hz), 7.27—7.45 (5H, m). IR (KBr) 3030, 2932, 2910, 1706, 1495 cm^{-1}.

Optical Resolution of 6-Benzyloxy-2-methylchroman-2-carboxylic Acid (7): A salt of (±)-**7**·(1*R*,2*S*)-(+)-*cis*-Amine (2.476 g, 4.79 mmol) was stirred in a solvent mixture of *t*-butyl methyl ether (9 ml) and ethyl acetate (3 ml) at r.t. The insoluble solid was filtered (1.672 g, 3.23 mmol), which was recrystallized from ethyl acetate (12 ml) to yield the second crop (0.669 g, 1.29 mmol, mp 142—146 °C).

A part of this salt was liberated by 1 M(= mol dm^{-3}) NaOH soln and then esterified by methanol in the presence of 2 drops of concd H_2SO_4 at r.t. for 4 d. The optical purity of the methyl ester was 96.2%ee by HPLC analysis; carrier solvent, 35% 2-propanol/hexane; flow rate, 0.5 ml min^{-1}; detection wavelength, 254 nm; retention time, (−)-form, 46 min, (+)-form, 59 min). From the second crop, (−)-**7** was obtained, $[\alpha]_D^{30} -33.4°$ (c 0.8, EtOH).

Synthesis of Methyl 6-Benzyloxy-2-methylchroman-2-car-

boxylate (1a*): To a solution of compound **7*** (0.159 g, 0.53 mmol) in methanol (6 ml) was added 7 drops of H_2SO_4; the resulting mixture was stirred for 4 d at r.t. A saturated aqueous sodium carbonate solution (10 ml) and distilled water (10 ml) were added to the solution, and the organic layer was extracted with diethyl ether. The solvent was removed, and the remaining mixture was purified by column chromatography (silica-gel: 8 g, 20% ethyl acetate in hexane) to give a colorless liquid (0.154 g, 93%). ^{1}H NMR ($CDCl_3$) δ = 1.60 (3H, s), 1.84—1.92 (1H, m), 2.35—2.41 (1H, m), 2.66—2.69 (2H, m), 3.70 (3H, s), 4.97 (2H, s), 6.64 (1H, s), 6.76 (1H, d, J = 8.6 Hz), 6.84 (1H, d, J = 8.6 Hz), 7.27—7.52 (5H, m). $[\alpha]_D^{23} = -33.8°$ (c 1.5, $CHCl_3$).

Synthesis of Ethyl 6-Benzyloxy-2-methylchroman-2-carboxylate (1b*): Following a similar procedure to that mentioned above for **1a***, a white solid was obtained after purification by thin-layer chromatography (silica-gel, 30% ethyl acetate in hexane) (0.063 g, 92%). The ^{1}H NMR and IR spectra were identical with those of **1b**. $[\alpha]_D^{28} = 29.5°$ (c 0.6, $CHCl_3$).

Synthesis of Methyl 6-Hydroxy-2-methylchroman-2-carboxylate (9a*): To a solution of **1a*** (0.145 g, 0.46 mmol) in methanol (5 ml) was added 5% palladium carbon (0.032 g). The mixture was stirred under a hydrogen atmosphere for 6 d at r.t. The solvent was evaporated under reduced pressure and the remaining mixture was purified by thin-layer chromatography (silica-gel, ethyl acetate) to give a white solid (0.074 g, 72%). ^{1}H NMR ($CDCl_3$) δ = 1.60 (3H, s), 1.83—1.91 (1H, m), 2.34—2.40 (1H, m), 2.64—2.67 (2H, m), 3.70 (3H, s), 4.52 (1H, s), 6.50 (1H, s), 6.60 (1H, d, J = 8.6 Hz), 6.78 (1H, d, J = 8.6 Hz). $[\alpha]_D^{28} = -36.0°$ (c 0.6, EtOH).

Synthesis of Ethyl 6-Hydroxy-2-methylchroman-2-carboxylate (9b*): In a similar manner to that mentioned above, a light-yellow liquid was obtained (0.216 g, 92%), which was supplied to the synthesis of **6*** without further purification.

Synthesis of Methyl 6-Benzyloxy-2,5,7,8-tetramethylchroman-2-carboxylate (10*): To a solution of (*S*)-(−)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (0.098 g, 0.39 mmol) in methanol (5 ml) was added 3 drops of H_2SO_4; the resulting mixture was stirred for 24 h at r.t. Sat. Na_2CO_3 aq soln (10 ml) was added to the solution and the organic layer was extracted with diethyl ether. The solvent was removed under reduced pressure, and the residue was purified by thin-layer chromatography (silica-gel, 50% ethyl acetate in hexane) to give a white solid (0.067 g, 65%). ^{1}H NMR ($CDCl_3$) δ = 1.59 (3H, s), 1.85—1.89 (1H, m), 2.06 (3H, s), 2.16 (3H, s), 2.18 (3H, s), 2.40—2.63 (3H, m), 3.66 (3H, s), 4.20 (1H, s). $[\alpha]_D^{20} = -42.1°$ (c 0.2, $CHCl_3$).

Synthesis of 4′-Hexyloxy-4-biphenylyl 6-Benzyloxy-2-methylchroman-2-carboxylate (2a*): To a dry dichloromethane (3 ml) solution of **7*** (0.089 g, 0.30 mmol), 4′-hexyloxybiphenyl-4-ol (0.083 g, 0.30 mmol) and a catalytic amount of 4-(dimethylamino)pyridine (0.039 g, 0.32 mmol) was added a solution of dicyclohexylcarbodiimide (0.065 g, 0.31 mmol) in dry dichloromethane (2 ml). The mixture was stirred for 2 d at r.t. Diethyl ether (20 ml) was added to the solution and the solid was filtered off by celite 545. Sat. sodium chloride soln (10 ml) was added to the filtrate and the mixture was stirred for 2 h at r.t. The organic layer was extracted with diethyl ether and the organic layer was washed with 1 M hydrochloric acid and sat. sodium hydrogencarbonate soln. The organic solvent was removed and the remaining mixture was purified by column chromatography (silica-gel: 8 g, dichloromethane) to give a white solid (0.125 g, 75%). ^{1}H NMR ($CDCl_3$) δ = 0.90 (3H, t, J = 7.0 Hz), 1.34—1.48 (6H, m), 1.79 (3H, s), 2.01—2.10 (1H, m), 2.54—2.57 (1H, m), 2.80—2.87 (2H, m), 3.98 (2H, t, J = 6.5 Hz), 4.99 (2H, s), 6.69 (1H, s), 6.79 (1H, d, J = 8.6 Hz), 6.89 (1H, d, J = 8.6 Hz), 6.94 (2H, d, J = 8.6 Hz), 7.00 (2H, d, J = 8.6 Hz), 7.37—7.49 (9H, m). IR (KBr) 3032, 2931, 2857, 1769, 1604 cm^{-1}. $[\alpha]_D^{26} = 3.3°$ (c 1.1, $CHCl_3$). Found: C, 78.53; H, 7.01%. Calcd for $C_{36}H_{38}O_5$: C, 78.51; H, 6.95%.

Synthesis of 4′-Decyloxy-4-biphenylyl 6-Benzyloxy-2-methylchroman-2-carboxylate (2b*): In a similar manner to that mentioned above, **2b*** was prepared as a white solid (0.120 g, 76%). ^{1}H NMR ($CDCl_3$) δ = 0.88 (3H, t, J = 7.0 Hz), 1.27 (12H, br), 1.44—1.48 (2H, m), 1.75—1.81 (2H, m), 1.77 (3H, s), 2.01—2.03 (1H, m), 2.54—2.57 (1H, m), 2.79—2.87 (2H, m), 3.98 (2H, t, J = 6.5 Hz), 4.99 (2H, s), 6.69 (1H, s), 6.79 (1H, d, J = 8.6 Hz), 6.89 (1H, d, J = 8.6 Hz), 6.94 (2H, d, J = 8.6 Hz), 7.00 (2H, d, J = 8.6 Hz), 7.35—7.56 (9H, m). IR (KBr) 3062, 3031, 2923, 2853, 1769, 1603, 1499 cm^{-1}. $[\alpha]_D^{23} = -1.2°$ (c 1.0, $CHCl_3$).

Synthesis of 4′-Decyloxy-4-biphenylyl 6-Methoxy-2-methylchroman-2-carboxylate (3*): To a solution of **2b*** (0.109 g, 0.17 mmol) in tetrahydrofuran (5 ml) was added 5% palladium carbon (0.025 g); the resulting mixture was stirred under a hydrogen atmosphere for 2 d at r.t. After filtration, the solvent was removed under reduced pressure to give a white solid of the corresponding phenol (0.079 g, 90%). To a solution of the phenol (0.079 g, 0.15 mmol) in acetone (4 ml) were added potassium carbonate (0.045 g, 32 mmol) and methyl iodide (0.137 g, 0.94 mmol); the resulting mixture was stirred for 24 h at 63 °C. After diluting with water, the organic layer was extracted with diethyl ether. After removing the organic solvent, the remaining mixture was purified by thin-layer chromatography (silica-gel, dichloromethane) to give a white solid (0.016 g, 21%). ^{1}H NMR ($CDCl_3$) δ = 0.88 (3H, t, J = 7.0 Hz), 1.27 (12H, br), 1.44—1.42 (2H, m), 1.75—1.82 (2H, m), 1.77 (3H, s), 2.01—2.03 (1H, m), 2.54—2.57 (1H, m), 2.80—2.88 (2H, m), 3.75 (3H, s), 3.97 (2H, t, J = 6.5 Hz), 6.60 (1H, s), 6.72 (1H, d, J = 8.6 Hz), 6.89 (1H, d, J = 8.6 Hz), 6.94 (2H, d, J = 8.6 Hz), 7.00 (2H, d, J = 8.6 Hz), 7.44 (2H, d, J = 8.6 Hz), 7.48 (2H, d, J = 8.6 Hz). IR ($CDCl_3$) 3038, 2928, 2855, 1765, 1607, 1496 cm^{-1}. $[\alpha]_D^{25} = 8.48°$ (c 0.3, $CHCl_3$).

Synthesis of Butyl 6-(4′-Dodecyloxybiphenyl-4-carboxy)-2-methylchroman-2-carboxylate (4*): To a stirred solution of **7*** (0.326 g, 1.09 mmol) and triphenylphosphine (0.348 g, 1.33 mmol) in dry tetrahydrofuran (4 ml) were added 1-butanol (0.435 g, 5.88 mmol) and a solution of diethyl azodicarboxylate (0.262 g, 1.50 mmol) in dry tetrahydrofuran (2 ml). After stirring for 24 h at r.t., the solvent was removed under reduced pressure and the remaining mixture was purified by column chromatography (silica-gel: 61 g, 20% ethyl acetate in hexane) to give a yellow liquid of ester (0.377 g, 97%). To a solution of the ester (0.377 g, 1.06 mmol) in tetrahydrofuran (10 ml) was added 5% palladium carbon (0.043 g); and the mixture was stirred under a hydrogen atmosphere for 7 d at r.t. The organic solvent was evaporated under reduced pressure and the remaining mixture was purified by column chromatography (silica-gel: 15 g, ethyl acetate) to give a yellow liquid of the corresponding phenol (0.209 g, 74%). To a solution of the phenol (0.209 g, 0.79 mmol) in dry dichloromethane (8 ml) were added 4′-dodecyloxybipenyl-4-carboxylic acid (0.305 g, 0.79 mmol) and a catalytic amount of 4-(dimethylamino)pyridine (0.120 g, 0.98 mmol); a solution of dicyclohexylcarbodiimide (0.202 g, 0.97 mmol) in dry dichloromethane (2 ml). After stirring for 3 d at r.t., diethyl ether (20 ml) was added and the mixture was filtered by celite 545. To the filtrate was added sat. sodium chloride soln (20 ml), and stirred for 1 h at r.t. The organic layer was extracted with diethyl ether and the combined organic layer was washed with 1 M hydrochloric acid and sat. sodium hydrogencarbonate soln. The solvent was evaporated under reduced pressure and the residue was

purified by column chromatography (silica-gel: 25 g, 20% ethyl acetate in hexane) to give a white solid (0.423 g, 85%). ^{1}H NMR ($CDCl_3$) δ = 0.88 (6H, t, J = 7.2 Hz), 1.27 (20H, br), 1.47 (2H, br), 1.54—1.58 (2H, m), 1.63 (3H, s), 1.79 (2H, m), 1.81—1.83 (1H, m), 2.39 (1H, m), 2.72—2.75 (2H, m), 4.01 (2H, t, J = 6.4 Hz), 4.12 (2H, m, J = 13.3 Hz), 6.90—7.00 (5H, m), 7.56 (2H, d, J = 8.6 Hz), 7.67 (2H, d, J = 8.6 Hz), 8.20 (2H, d, J = 8.6 Hz). IR (KBr) 3073, 3041, 2910, 2846, 1736, 1603, 1494 cm^{-1}. $[\alpha]_D^{26}$ = 14.3° (*c* 1.0, $CHCl_3$). Found: C, 76.23; H, 8.57%. Calcd for $C_{40}H_{52}O_6$: C, 76.39; H, 8.33%.

Synthesis of 6-Benzyloxy-2-methylchroman-2-carbonitrile (5*): **7*** (0.222 g, 0.74 mmol) was stirred in thionyl chloride (2 ml) for 1 h at 50 °C and the mixture was concentrated. To the remaining mixture was added dry benzene (20 ml). The solution was slowly added dropwise to a stirred ammonia solution (30 ml) at ice-water temperature, and the organic layer was extracted with diethyl ether. The solvent was removed under reduced pressure, and the remaining mixture was purified by column chromatography (silica-gel: 12 g, ethyl acetate) to give a dark-yellow solid of amide (0.151 g, 69%). To a stirred solution of crude amide (0.179 g, 0.61 mmol) in dry dichloromethane (2 ml) was added triethyl(methylcarbonylsulfamoyl)ammonium hydroxide inner salt (Burgess reagent) (0.404 g, 1.69 mmol) and kept stirring for 24 h at r.t. under nitrogen. After removing the solvent, the remaining mixture was purified by thin-layer chromatography (silica-gel, dichloromethane) to give a light yellow solid of **5*** (0.127 g, 90%). ^{1}H NMR ($CDCl_3$) δ = 1.79 (3H, s), 1.95—2.02 (1H, m), 2.21—2.27 (1H, m), 2.75—2.81 (1H, m), 3.11—3.20 (1H, m), 5.00 (2H, s), 6.71 (1H, s), 6.78 (2H, s), 7.30—7.43 (5H, m). IR (KBr) 3062, 3026, 2936, 2907, 2856, 2234, 1495 cm^{-1}. $[\alpha]_D^{24}$ = 69.4° (*c* 0.9, $CHCl_3$). Found: C, 76.88; H, 6.14; N, 4.89%. Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01%.

Synthesis of 6-Hexyloxy-2-methylchroman-2-carbonitrile (6*): To a solution of **9b*** (0.211 g, 0.91 mmol) in dry *N*,*N*-dimethylformamide (10 ml) were added sodium hydride (paraffin suspension, 0.057 g, ca. 1.42 mmol) and 1-bromohexane (0.3 ml, ca. 2.14 mmol) with a catalytic amount of potassium iodide (0.066 g, 0.40 mmol). After being stirred for 2 d at 80 °C, diethyl ether (20 ml) was added and the organic layer was washed with 1 M hydrochloric acid and distilled water. The organic solvent was removed under reduced pressure and the remaining mixture was purified by column chromatography (silica-gel: 15 g, 30% ethyl acetate in hexane) to give a yellow liquid of the hexyl ether of **9b*** (0.328 g, 100%). A solution of the ether (0.328 g, 1.02 mmol) in methanol (5 ml) was added to a solution of sodium hydroxide (0.119 g, 2.99 mmol) in distilled water (1 ml) and methanol (1 ml). The mixture was stirred for 1 h at 50 °C and concentrated. After the remaining mixture was dissolved into distilled water (60 ml), diethyl ether was added. After acidifying the aqueous layer by sulfuric acid (1 ml), the organic layer was extracted with diethyl ether, and the organic layer was dried with anhydrous sodium sulfate. The organic solvent was removed under reduced pressure to give a light-green solid of carboxylic acid (0.253 g, 83%). This acid (0.247 g, 0.84 mmol) was supplied to the preparation of **6*** using the same dehydration procedure for **5*** as that mentioned above. A light-yellow solid was obtained after purification by thin-layer chromatography (silica-gel, dichloromethane) (0.115 g, 69%). ^{1}H NMR ($CDCl_3$) δ = 0.91 (3H, t, J = 6.8 Hz), 1.31—1.34 (4H, m), 1.43—1.44 (2H, m), 1.72—1.76 (2H, m), 1.79 (3H, s), 1.98—2.10 (1H, m), 2.20—2.30 (1H, m), 2.75—2.81 (1H, m), 3.12—3.16 (1H, m), 3.88 (2H, t), 6.62 (1H, s), 6.70 (1H, d, J = 8.6 Hz), 6.79 (1H, d, J = 8.6 Hz). IR (KBr) 2940, 2868, 2234, 1496 cm^{-1}. $[\alpha]_D^{26}$ = 67.9° (*c* 1.1, $CHCl_3$).

CD Spectrum of (*S*)-(−)-10*: The CD was measured as an ethanol solution with a concentration of 4.04×10^{-4} mol dm^{-3}. A cell of 1.0 cm long was used in the wavelength range of 200—400 nm. The integrated spectrum is shown in Fig. 1. The following peaks were identified (wavelength and $\Delta\varepsilon$ are given): 215.4 (−463.7), 239.8 (141.3), 289.9 (152.9).

CD Spectrum of (−)-9a*: In the same way, the CD spectra were obtained with a concentration of 2.60×10^{-4} mol dm^{-3}. The following peaks were identified (wavelength and $\Delta\varepsilon$ are given): 219.8 (−321.0), 241.6 (93.2), 296.4 (114.0).

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