A New Method for the Synthesis of 3-Chromanol Derivatives by Sodium Iodide-Catalyzed Cyclization of Epoxide[1)]

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Treatment of 2-(2,3-epoxy)propylphenyl acetate derivatives with catalytic amounts of NaI in organic solvent gave directly the corresponding 3-chromanyl acetate derivatives in good yields (86.6—98.0%). Similar treatment of 2-(2,3-epoxy)propyl-6-methoxyphenyl *N*-mesyl-L-phenylalanylate gave a diastereomeric mixture of 8-methoxy-3-chromanyl *N*-mesyl-L-phenylalanylate, which was fractionated into both diastereomers by silica gel column chromatography. Subsequent hydrolysis of these isomers afforded the enantiomers of 8-methoxy-3-chromanol.

Keywords 3-chromanol derivative; catalytic cyclization; epoxide; sodium iodide; synthesis; mechanism; optical resolution; nipradilol

Nipradilol (NIP) is a synthetic drug having β-blocking and vasodilating activities,[2,3)] and is used to treat hypertensive and cardiovascular diseases. In the synthetic study of NIP, we selected 8-methoxy-3-chromanol (**4b**) as the key intermediate[3)] (Chart 1).

Some reactions are known for the synthesis of 3-chromanol derivatives. Das *et al.*[4)] reported a method based on sodium borohydride reduction of 3-chromanone, but in this method, the preparation of the starting material ketone requires a large number of steps and the total yield is low. Collier and Porter[5)] reported a method involving oxidative cyclization of *p*-substituted allyl phenyl ether derivatives using $Tl_2(SO_4)_3$–H_2SO_4, but the yield is generally low and the desired compound is not obtained in some cases. Dhawan *et al.*[6)] succeeded in the synthesis of 3-chromanol from *o*-bromophenyl 2,3-epoxypropyl ether in good yield using $MgBr_2$–BuLi. However, the substituent effect is not clear because only one example was reported. So we considered that the above methods were not satisfactory for the synthesis of **4b**. In the synthesis of NIP[3)] and its metabolite,[7)] we previously reported the efficient synthesis of 3-chromanol derivatives (**3a, b**) by the reaction of anhydrous HCl with epoxides (**2a, b**), followed by cyclization with K_2CO_3. This method is adequate with regard to the total yield, but (2,3-dihydro-2-benzofuran)-methyl acetate derivatives (**6a, b**) are formed in about 15% yield as by-products, and therefore a recrystallization step for removing **6** can not be avoided (Chart 2). For these reasons, a better method was desired for the synthesis of **4b**. In this paper, we wish to report a new synthetic method

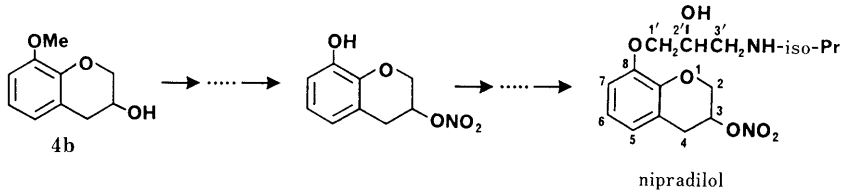
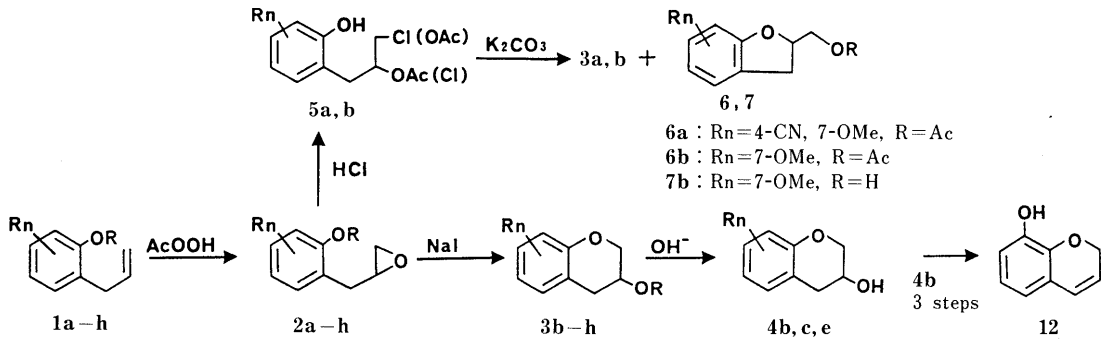


Chart 1



1, 2, 5	Rn	R
a	3-CN, 6-OMe	Ac
b	6-OMe	Ac
c	H	Ac
d	4-Br	Ac
e	6-NO_2	Ac
f	5-Me, 6-NO_2	Ac
g	6-OMe, 3-NO_2	Ac
h	6-OMe	L-$PhCH_2CH(NHMs)CO$

3, 4	Rn	R
a	5-CN, 8-OMe	Ac
b	8-OMe	Ac
c	H	Ac
d	6-Br	Ac
e	8-NO_2	Ac
f	7-Me, 8-NO_2	Ac
g	8-OMe, 5-NO_2	Ac
h	8-OMe	L-$PhCH_2CH(NHMs)CO$

Chart 2

for **4b**, which is applicable to the general synthesis of 3-chromanol derivatives having various substituents and to the optical resolution of 3-chromanol derivatives.

Synthesis of 3-Chromanol Derivatives We found a novel sodium iodide (NaI)-catalyzed cyclization reaction converting epoxides (**2**) to 3-chromanyl acylate derivatives (**3**) by highly regioselective epoxide ring opening in high yield (Chart 2).

Namely, treatment of 2-allylphenyl acetate derivatives (**1b—g**)[8] with *m*-chloroperbenzoic acid (*m*-CPBA) or 40% (w/v) peracetic acid in chloroform or methylene chloride afforded the corresponding epoxides (**2b—g**) in 88.3—95.4% yield. Compounds **2b—g** were led to 3-chromanyl acetate derivatives (**3b—g**) in the presence of 0.3—0.5 molar eq of NaI in solvents such as acetone, isopropyl alcohol, tertiary butanol and *N*,*N*-dimethylformamide (DMF) in 86.6—98.0% yield without accompanying formation of (2,3-dihydro-2-benzofuran)methyl acetate derivatives (**6**). In this reaction, when **2b** was treated with 2 N NaOH instead of NaI in MeOH, **4b** was not obtained but this treatment afforded only (2,3-dihydro-7-methoxy-2-benzofuran)methanol (**7b**) in nearly quantitative yield. Furthermore, 2-(2,3-epoxy)propyl-6-methoxyphenol, whch was prepared from 2-allyl-6-methoxyphenol with *m*-CPBA, was not transformed to **4b** under the acidic condition used for the synthesis of 2,2-dimethyl-3-chromanol derivatives.[9] In this case, compound **7b** was observed as the major product by thin-layer chromatography (TLC). Compounds **3b**, **3c** and **3e** were hydrolyzed by the conventional method to afford 3-chromanol derivatives (**4b**, **4c** and **4e**) in good yields (94.8— 98.0%).

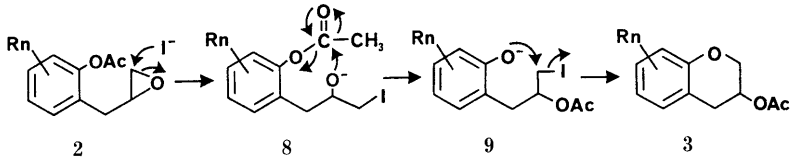
Mechanism of the Reaction with NaI This one-step cyclization procedure of the epoxide to the 3-chromanyl acetate derivative consists of three reaction processes: opening of the epoxide ring, migration of the acetyl moiety and ring closure to 3-chromanyl acetate. The reaction mechanism can be presumed to be as depicted below. Initial addition of NaI to the epoxide (**2**) affords the anti-Markownikoff adduct (**8**). Subsequently, the alkoxide anion of **8** attacks the carbonyl carbon atom of the ester moiety to cause migration of the acetyl moiety, giving the phenoxide (**9**). The phenolate anion of **9** finally attacks the carbon atom of halomethylene to afford 3-chromanyl acetate (**3**) (Chart 3).

Synthesis of (3*S*)- and (3*R*)-8-Methoxy-3-Chromanol Next we applied this method to the synthesis of optically active 8-methoxy-3-chromanol, which had been selected as the key intermediate for the synthesis of optical isomers of NIP. Thus, the acetyl moiety in **1b** was replaced by an *N*-mesyl-L-phenylalanyl moiety in order to confer protective and optically resolving functions on the new derivative (**1h**).

2-Allyl-6-methoxyphenol was reacted with *N*-mesyl-L-phenylalanyl chloride in pyridine to give an ester (**1h**). Compound **1h** was oxidized with *m*-CPBA to afford an epoxide (**2h**), and subsequent cyclization reaction with NaI afforded a diastereomeric mixture of 8-methoxy-3-chromanyl *N*-mesyl-L-phenylalanylate (**3h**) in good yield. The mixture was fractionated easily by silica gel column chromatography into (3*S*)-**3h** and (3*R*)-**3h**, and both were subsequently hydrolyzed to give (3*S*)-**4b** and (3*R*)-**4b**, respectively, in the usual manner. The total yields from 2-allyl-6-methoxyphenol and the values of optical purity of (3*S*)-**4b** and (3*R*)-**4b** were 45.4% and 46.4%, and 97.4% enantiomeric excess (ee) and 98.0% ee, respectively. The optical purity was measured by high-performance liquid chromatography (HPLC) using a chiral stationary phase after deriving these compounds to 3-mesylate derivatives. The absolute configurations of these compounds were determined as follows. Compounds (3*S*)-**4b** and (3*R*)-**4b** were demethylated with 47% HBr to give (3*S*)- and (3*R*)-8-hydroxy-3-chromanol (**10** and **11**), respectively. Compound **11** was identical with **11** derived from (3*R*)-8-hydroxy-3-chromanyl nitrate by catalytic hydrogenation over palladium charcoal[10,11] (Chart 4).

Results and Discussion

These results demonstrate that the NaI-catalyzed 3-chromanol ring formation reaction is useful not only for the general synthesis of racemic 3-chromanol derivatives, but also for the synthesis of optically active 3-chromanol derivatives. Furthermore, since the 3-chromanol derivative can be converted to the 2*H*-1-benzopyran derivative (**12**)[7]



2 8 9 3

Chart 3

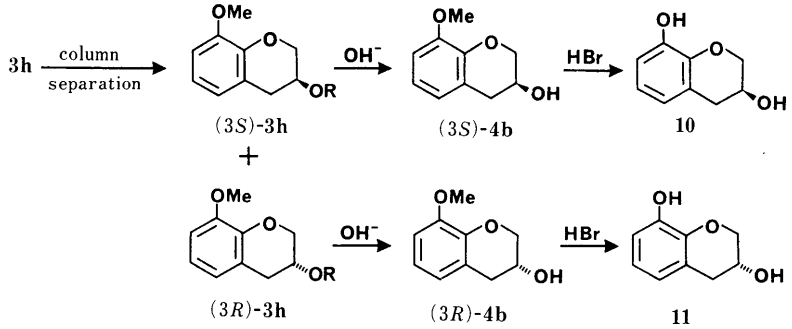


Chart 4

(Chart 2), it is considered that this method constitutes a general synthesis of 2*H*-1-benzopyran derivatives. A study of the synthesis of optical isomers of NIP using **10** and **11** will be presented in a subsequent paper.

Experimental

All melting points are uncorrected. Infrared (IR) absorption spectra were obtained with Shimadzu IR-435 spectrometers. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured with JEOL JNM MH-100 (100 MHz) and JEOL FX-200 (199.5 MHz) spectrometers. The chemical shifts are given in the δ (ppm) scale with tetramethylsilane as an internal standard. The following abbreviations are used; s = singlet, d = doublet, t = triplet, dd = double doublet, m = multiplet and br = broad. Low- and high-resolution mass spectra (MS) were obtained with JEOL JMS-D300 mass spectrometers in the electron impact mode at an ionization potential of 70 eV. Optical rotations were measured on a JASCO DIP-4 digital polarimeter. TLC was performed on E. Merck Silica gel 60 F_{254} plates. Column chromatography was performed on Wako Silica gel (C-200 and C-300). All the organic extracts were dried over anhydrous Na_2SO_4 prior to evaporation, which was performed under reduced pressure.

2-(2,3-Epoxy)propyl-6-methoxyphenyl Acetate (2b) A 40% (w/v) peracetic acid solution (20.5 ml) and AcONa (1.0 g) were added to 2-allyl-6-methoxyphenyl acetate (**1b**) (6.00 g) in CH_2Cl_2 (75 ml), and the mixture was stirred at room temperature for 24 h. The reaction mixture was added to $CHCl_3$ (200 ml) and the organic layer was washed twice with saturated $NaHCO_3$ (100 ml), 10% aqueous Na_2SO_3 (100 ml), and brine, and evaporated to give **2b** (6.17 g, 95.4%) as a pale yellow viscous oil. IR (film): 1761, 1477, 1274, 1212, 1168 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s, $OCOCH_3$), 2.47—2.86 (4H, m, CH_2CHCH_2), 3.00—3.20 (1H, m, CH_2CHCH_2), 3.83 (3H, s, OCH_3), 6.82—7.32 (3H, m, Ar-H). MS *m/z*: 222 (M^+). High-resolution MS Calcd for $C_{12}H_{14}O_4$: 222.0893. Found: 222.0895.

2-(2,3-Epoxy)propyl-6-nitrophenyl Acetate (2e) *m*-CPBA (80%, 6.5 g) was added portionwise to a solution of 2-allyl-6-nitrophenyl acetate (**1e**) (4.40 g) in $CHCl_3$ (44 ml) with stirring and ice-cooling. The mixture was stirred for 20 h at room temperature, then 10% Na_2CO_3 was added dropwise. The organic layer was washed with 10% Na_2SO_3 and brine, and evaporated to give a crude product, which was chromatographed on a silica gel column (hexane : AcOEt = 3 : 1) to afford **2e** (4.40 g, 93.2%) as a pale yellow oil. IR (film): 1770, 1530, 1350, 1185 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 2.35 (3H, s, $OCOCH_3$), 2.35—2.90 (4H, m, CH_2CHCH_2), 2.90—3.12 (1H, m, CH_2CHCH_2), 7.28 (1H, t, J = 8 Hz, C_4-H), 7.58 (1H, dd, J = 8, 2 Hz, C_3- or C_5-H), 7.92 (1H, dd, J = 8, 2 Hz, C_3- or C_5-H). MS *m/z*: 177 ($M^+ - CH_3COOH$). High-resolution MS Calcd for $C_9H_7NO_3$: 177.0423. Found: 177.0422.

Compounds **2c**, **2d**, **2f** and **2g** were obtained in a manner similar to that described for **2e**.

2-(2,3-Epoxy)propylphenyl Acetate (2c) Yield 95.3%. A colorless oil. IR (film): 1757, 1204, 1169 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.34 (3H, s, $OCOCH_3$), 2.45—2.90 (4H, m, CH_2CHCH_2), 3.02—3.24 (1H, m, CH_2CHCH_2), 6.96—7.46 (4H, m, Ar-H). MS *m/z*: 192 (M^+). High-resolution MS Calcd for $C_{11}H_{12}O_3$: 192.0783. Found: 192.0777.

4-Bromo-2-(2,3-epoxy)propylphenyl Acetate (2d) Yield 90.5%. A colorless oil. IR (film): 1757, 1478, 1198, 1164 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.34 (3H, s, $OCOCH_3$), 2.48—2.90 (4H, m, CH_2CHCH_2), 3.00—3.24 (1H, m, CH_2CHCH_2), 6.98 (1H, d, J = 8 Hz, C_6-H), 7.36—7.60 (2H, m, C_3- and C_5-H). MS *m/z*: 270, 272 (M^+). High-resolution MS Calcd for $C_{11}H_{11}BrO_3$: 269.9892. Found: 269.9883.

2-(2,3-Epoxy)propyl-5-methyl-6-nitrophenyl Acetate (2f) Yield 90.7%. A pale yellow oil. IR (film): 1776, 1528, 1365, 1188 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s, $OCOCH_3$), 2.37 (3H, s, CH_3), 2.40—2.90 (4H, m, CH_2CHCH_2), 3.00—3.24 (1H, m, CH_2CHCH_2), 7.20 (1H, d, J = 8 Hz, C_4-H), 7.45 (1H, d, J = 8 Hz, C_5-H). MS *m/z*: 251 (M^+). High-resolution MS Calcd for $C_{12}H_{13}NO_5$: 251.0794. Found: 251.0805.

2-(2,3-Epoxy)propyl-6-methoxy-3-nitrophenyl Acetate (2g) Yield 88.3%. Pale yellow needles. mp 77 °C. IR (KBr): 1767, 1580, 1508, 1340, 1285 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s, $OCOCH_3$), 2.44—2.85 (2H, m, $CHCH_2O$), 3.12—3.36 (3H, m, CH_2CHCH_2O), 3.95 (3H, s, OCH_3), 6.98 (1H, d, J = 9 Hz, C_5-H), 8.05 (1H, d, J = 9 Hz, C_4-H). MS *m/z*: 267 (M^+). *Anal.* Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.86; H, 4.92; N, 5.19.

8-Methoxy-3-chromanyl Acetate (3b) NaI (3.4 g) was added to a solution of **2b** (10.0 g) in acetone (15 ml) at room temprature and the mixture was heated at 70 °C for 1.5 h. After removal of the organic solvent, the residue was dissolved in benzene. The benzene solution was washed with H_2O and evaporated to give a crude product, which was chromatographed on a silica gel column ($CHCl_3$) to give pure **3b** (9.80 g, 98.0%) as a colorless oil. IR (film): 1731, 1585, 1485, 1238 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.04 (3H, s, $OCOCH_3$), 2.70—3.32 (2H, m, C_4-H), 3.88 (3H, s, OCH_3), 4.08—4.48 (2H, m, C_2-H), 5.20—5.40 (1H, m, C_3-H), 6.60—6.98 (3H, m, Ar-H). MS *m/z*: 222 (M^+). High-resolution MS Calcd for $C_{12}H_{14}O_4$: 222.0893. Found: 222.0916.

Compounds **3c—g** were obtained in a manner similar to that described for **3b**.

3-Chromanyl Acetate (3c) Yield 93.0%. A colorless oil. IR (film): 1734, 1489, 1228 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.05 (3H, s, $OCOCH_3$), 2.70—3.33 (2H, m, C_4-H), 4.04—4.36 (2H, m, C_2-H), 5.20—5.40 (1H, m, C_3-H), 6.80—7.30 (4H, m, Ar-H). MS *m/z*: 192 (M^+). High-resolution MS Calcd for $C_{11}H_{12}O_3$: 192.0787. Found: 192.0798.

6-Bromo-3-chromanyl Acetate (3d) Yield 92.5%. Colorless prisms (Et_2O–hexane). mp 55—56 °C. IR (KBr): 1726, 1484, 1244 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (3H, s, $OCOCH_3$), 2.64—3.30 (2H, m, C_4-H), 4.00—4.36 (2H, m, C_2-H), 5.16—5.36 (1H, m, C_3-H), 6.75 (1H, d, J = 8 Hz, C_8-H), 7.15—7.36 (2H, m, C_5- and C_7-H). MS *m/z*: 270, 272 (M^+). *Anal.* Calcd for $C_{11}H_{11}BrO_3$: C, 48.73; H, 4.09; Br, 29.47. Found: C, 48.24; H, 4.06; Br, 29.73.

8-Nitro-3-chromanyl Acetate (3e) Yield 96.0%. Pale yellow prisms (EtOAc–Et_2O). mp 103—104 °C. IR (KBr): 1724, 1525, 1242 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, $OCOCH_3$), 2.82—3.40 (2H, m, C_4-H), 4.18—4.58 (2H, m, C_2-H), 5.28—5.48 (1H, m, C_3-H), 7.00 (1H, t, J = 8 Hz, C_6-H), 7.33 (1H, br d, J = 8 Hz, C_5- or C_7-H), 7.76 (1H, br d, J = 8 Hz, C_5- or C_7-H). MS *m/z*: 237 (M^+). *Anal.* Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.56; H, 4.54; N, 5.88.

7-Methyl-8-nitro-3-chromanyl Acetate (3f) Yield 94.8%. Pale yellow prisms (EtOAc–Et_2O). mp 133—134 °C. IR (KBr): 1735, 1528, 1237 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, $OCOCH_3$), 2.28 (3H, s, CH_3), 2.27—3.32 (2H, m, C_4-H), 4.10—4.45 (2H, m, C_2-H), 5.22—5.42 (1H, m, C_3-H), 6.80 (1H, d, J = 8 Hz, C_6-H), 7.10 (1H, d, J = 8 Hz, C_5-H). MS *m/z*: 251 (M^+). *Anal.* Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.24; H, 5.16; N, 5.56.

8-Methoxy-5-nitro-3-chromanyl Acetate (3g) Yield 86.6%. Pale yellow prisms (acetone–hexane). mp 185—187 °C. IR (KBr): 1725, 1510, 1275, 1236 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.05 (3H, s, $OCOCH_3$), 3.08—3.68 (2H, m, C_4-H), 4.00 (3H, s, OCH_3), 4.08—4.60 (2H, m, C_2-H), 6.88 (1H, d, J = 9 Hz, C_7-H), 7.85 (1H, d, J = 9 Hz, C_6-H). MS *m/z*: 267 (M^+). *Anal.* Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.91; H, 4.84; N, 5.26.

8-Methoxy-3-chromanol (4b) A solution of **3b** (10.0 g) in MeOH (100 ml) was treated with 2 N NaOH (33.7 ml), and the mixture was stirred for 1 h at room temperature. The reaction mixture was neutralized with 1 N HCl, concentrated and extracted with $CHCl_3$. The extract was evaporated to dryness, and the residual oil was crystallized from benzene–hexane to give **4b** (7.95 g, 98.0%) as colorless prisms, mp 80—82 °C. IR (KBr): 3295, 1584, 1484, 1262 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.48 (1H, d, J = 5 Hz, OH), 2.60—3.24 (2H, m, C_4-H), 3.85 (3H, s, OCH_3), 4.04—4.35 (3H, m, C_2- and C_3-H), 6.60—6.96 (3H, m, Ar-H). MS *m/z*: 180 (M^+). *Anal.* Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.78; H, 6.72.

Compounds **4c** and **4e** were obtained in a manner similar to that described for **4b**.

3-Chromanol (4c) Yield 94.8%. Colorless needles (Et_2O–hexane). mp 82—83 °C. IR (KBr): 3278, 1580, 1488, 1234 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (1H, d, J = 8 Hz, OH), 2.70—3.16 (2H, m, C_4-H), 4.04—4.12 (2H, m, C_2-H), 4.16—4.32 (1H, m, C_3-H), 6.80—7.16 (4H, m, Ar-H). *Anal.* Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.69; H, 6.71.

8-Nitro-3-chromanol (4e) Yield 95.5%. Pale yellow prisms (AcOEt–hexane). mp 80—82 °C. IR (KBr): 3295, 1526, 1472, 1365 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.70—3.28 (2H, m, C_4-H), 2.74 (1H, d, J = 5 Hz, OH), 4.14—4.44 (3H, m, C_2- and C_3-H), 6.92 (1H, t, J = 8 Hz, C_6-H), 7.28 (1H, d, J = 8 Hz, C_7- or C_8-H), 7.66 (1H, d, J = 8 Hz, C_7- or C_8-H). *Anal.* Calcd for $C_9H_9NO_4$: C, 55.39; H, 4.65; N, 7.18. Found: C, 55.43; H, 4.62; N, 7.17.

(2,3-Dihydro-7-methoxy-2-benzofuran)methanol (7b) A 2 N NaOH solution (1.8 ml) was added to a solution of **2b** (471 mg) in MeOH (3.0 ml), and the mixture was stirred for 1 h at room temperature, then neutralized with 1 N HCl, concentrated and extracted with $CHCl_3$. The extract was evaporated to dryness, and the residual oil was crystallized from Et_2O–hexane to give **7b** (377 mg, 98.7%) as colorless prisms, mp 51—52 °C. IR (KBr): 3269, 1490, 1197, 1085 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ:

2.08—2.36 (1H, br s, OH), 2.96—3.40 (2H, m, C_3-H), 3.76—4.06 (2H, m, C$\underline{H}_2$OH), 3.90 (3H, s, OCH_3), 4.84—5.15 (1H, m, C_2-H), 6.70—6.96 (3H, m, Ar-H). *Anal.* Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.60; H, 6.75.

2-Allyl-6-methoxyphenyl *N*-Mesyl-L-phenylalanylate (1h) *N*-Mesyl-L-phenylalanyl chloride[12] (4.00 g) was added in portions to a solution of 2-allyl-6-methoxyphenol (1.67 g) in pyridine (16.0 ml) with ice-cooling, and the mixture was stirred for 15 h at room temperature. After addition of H_2O (2.5 ml), the reaction mixture was stirred for 20 min at room temperature, then evaporated to dryness and extracted with $CHCl_3$. The extract was washed with 1 N HCl, saturated Na_2CO_3, and H_2O, and evaporated to give crude crystals, which were recrystallized from MeOH to give **1h** (3.6 g, 90.8%) as colorless prisms, mp 141—142 °C. $[\alpha]_D^{22}$ −32.4° (c=4.0, $CHCl_3$). IR (KBr): 3267, 1767, 1327, 1144 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.70 (3H, s, SO_2CH_3), 3.06—3.46 (2H, m, CH_2=CHC$\underline{H}_2$), 3.24 (2H, d, J=7 Hz, CH_2Ar), 3.80 (3H, s, OCH_3), 4.62—4.74 (1H, m, C$\underline{H}$NH), 4.88—5.12 (3H, m, NH and CH=C$\underline{H}_2$), 5.76—5.96 (1H, m, CH_2=C$\underline{H}$), 6.82—6.92 (2H, m, C_3- and C_5-H), 7.18 (1H, t, J=8 Hz, C_4-H), 7.34 (5H, s, Ar-H). *Anal.* Calcd for $C_{20}H_{23}NO_5S$: C, 61.68; H, 5.95; N, 3.60. Found: C, 61.72; H, 6.00; N, 3.61.

2-(2,3-Epoxy)propyl-6-methoxyphenyl *N*-Mesyl-L-phenylalanylate (2h) In the same manner as described for **2e**, crude **2h** was prepared from **1h** (1.80 g) and *m*-CPBA (80%, 1.40 g), and chromatographed on a silica gel column ($CHCl_3$: MeOH = 100 : 1) to give pure **2h** (1.80 g, 96.0%) as colorless crystals, mp 126—129 °C. $[\alpha]_D^{22}$ −31.8° (c=4.0, $CHCl_3$). IR (KBr): 3260, 1771, 1314, 1145 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.36—2.88 (4H, m, C$\underline{H}_2$CHC$\underline{H}_2$), 2.71 (1/2×3H, s, SO_2CH_3), 2.74 (1/2×3H, s, SO_2CH_3), 3.00—3.24 (2H, m, CH_2Ar), 3.34—3.48 (1H, m, CH_2C$\underline{H}$$CH_2$), 3.81 (3H, s, OCH_3), 4.62—4.76 (1H, m, C$\underline{H}$NH), 5.10 (1/2×1H, d, J=9 Hz, CHN$\underline{H}$), 5.24 (1/2×1H, d, J=9 Hz, CHN$\underline{H}$), 6.88—6.96 (2H, m, Ar-H), 7.16—7.28 (1H, m, Ar-H), 7.30—7.40 (5H, m, Ar-H). MS m/z: 405 (M^+). *Anal.* Calcd for $C_{20}H_{23}NO_6S$: C, 59.25; H, 5.72; N, 3.45; S, 7.91. Found: C, 59.35; H, 5.57; N, 3.56; S, 7.81.

(3*S*)-8-Methoxy-3-chromanyl *N*-Mesyl-L-phenylalanylate ((3*S*)-3h) and (3*R*)-8-Methoxy-3-chromanyl *N*-Mesyl-L-phenylalanylate ((3*R*)-3h) In the same manner as described for **3b**, a diastereomeric mixture (**3h**) was prepared from **2h** (2.00 g), NaI (0.74 g) and acetone (10 ml), and was chromatographed on a silica gel column (benzene : AcOEt = 5 : 1) to give (3*S*)-**3h** (0.952 g, 47.6%) as a colorless glass and (3*R*)-**3h** (0.946 g, 47.3%) as colorless crystals. (3*S*)-**3h**: $[\alpha]_D^{22}$ −37.4° (c=3.33, $CHCl_3$). IR ($CHCl_3$): 1737, 1329, 1149 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.62 (3H, s, SO_2CH_3), 2.78—3.26 (4H, m, CH_2Ar and C_4-H), 3.88 (3H, s, OCH_3), 4.08—4.44 (3H, m, C$\underline{H}$NH- and C_2-H), 4.82 (1H, d, J=9 Hz, NH), 5.26—5.34 (1H, m, C_3-H), 6.62—6.80 (2H, m, C_5- and C_7-H), 6.88 (1H, t, J=8 Hz, C_6-H), 7.14—7.40 (5H, m, Ar-H). MS m/z: 405 (M^+). High-resolution MS Calcd for $C_{20}H_{23}NO_6S$: 405.1246. Found: 405.1262. (3*R*)-**3h**: Colorless needles (MeOH), mp 126.0—127.5 °C. $[\alpha]_D^{22}$ −1.8° (c=3.33, $CHCl_3$). IR (KBr): 3212, 1743, 1321, 1166 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.65 (3H, s, SO_2CH_3), 2.74—3.24 (4H, m, CH_2Ar and C_4-H), 3.88 (3H, s, OCH_3), 4.12—4.48 (3H, m, C$\underline{H}$NH and C_2-H), 4.82 (1H, d, J=9 Hz, NH), 5.24—5.34 (1H, m, C_3-H), 6.62—6.80 (2H, m, C_5- and C_7-H), 6.88 (1H, t, J=8 Hz, C_6-H), 7.06—7.15 (2H, m, Ar-H), 7.20—7.33 (3H, m, Ar-H). MS m/z: 405 (M^+). *Anal.* Calcd for $C_{20}H_{23}NO_6S$: C, 59.25; H, 5.72; N, 3.45. Found: C, 59.09; H, 5.81; N, 3.48.

(3*S*)-8-Methoxy-3-chromanol ((3*S*)-4b) In the same manner as described for **4b**, crude (3*S*)-**4b** was prepared from (3*S*)-**3h** (0.864 g), 2 N NaOH (2.2 ml) and MeOH (10.0 ml), and was chromatographed on a silica gel column (AcOEt : hexane = 1 : 1) to give pure (3*S*)-**4b** (0.366 g, 95.3%) as colorless crystals, mp 102—103.5 °C. $[\alpha]_D^{23}$ −16.4° (c=4.0, $CHCl_3$). IR (KBr): 3483, 1486, 1077 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (1H, d, J=8 Hz, OH), 2.74—3.16 (2H, m, C_4-H), 3.88 (3H, s, OCH_3), 4.14—4.22 (2H, m, C_2-H), 4.20—4.32 (1H, m, C_3-H), 6.64—6.78 (2H, m, C_5- and C_7-H), 6.86 (1H, t, J=8 Hz, C_6-H). *Anal.* Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.70; H, 6.60. The optical purity was measured by HPLC using the chiral stationary phase after deriving (3*S*)-**4b** to the 3-methanesulfonate derivative; 97.4% ee.

(3*R*)-8-Methoxy-3-chromanol ((3*R*)-4b) In the same manner as described for (3*S*)-**4b**, (3*R*)-**4b** was prepared from (3*R*)-**3h**. Yield 98.0%. Colorless crystals, mp 102—103.5 °C. $[\alpha]_D^{23}$ +16.0° (c=4.0, $CHCl_3$). *Anal.* Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.69; H, 6.77. The IR and ^{1}H-NMR spectra of (3*R*)-**4b** were identical with those of (3*S*)-**4b**. The optical purity was measured in the same manner as described for (3*S*)-**4b**; 98.0% ee.

Measurement of Optical Purity by HPLC Methanesulfonates of (3*S*)-**4b** and (3*R*)-**4b** were prepared by reacting (3*S*)-**4b** and (3*R*)-**4b** with excess methanesulfonyl chloride in pyridine for 15 h at room temperature, respectively. The crude product was purified by preparative TLC ($CHCl_3$: MeOH = 100 : 1) to give a pure sample, which was examined for optical purity by HPLC using the chiral stationary phase[13] (mobile phase, hexane : iso-PrOH : NEt_3 = 100 : 40 : 0.14; flow rate, 1 ml/min; detection, UV 275 nm; retention times, (3*S*)-derivative 4.3 min and (3*R*)-derivative 6.5 min).

(3*S*)-8-Hydroxy-3-chromanol (10) Compound (3*S*)-**4b** (0.854 g) was heated in 47% HBr (5.2 ml) for 70 min at 115 °C. The reaction mixture was cooled to 5 °C, 30% NaOH was added slowly with ice-cooling, and the pH was adjusted to about 3. The solution was extracted with AcOEt, and the extract was washed with brine. After removal of the organic solvent, the residue was chromatographed on a silica gel column ($CHCl_3$: acetone = 1 : 1) to give pure **10** (0.743 g, 94.4%) as colorless crystals, mp 154—156.5 °C. $[\alpha]_D^{25}$ +45.5° (c=3.0, THF). IR (KBr): 3360 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.52—3.18 (2H, m, C_4-H), 3.80—4.28 (3H, m, C_2- and C_3-H), 6.44—6.78 (3H, m, Ar-H). MS m/z: 166 (M^+). *Anal.* Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.10; H, 6.11.

(3*R*)-8-Hydroxy-3-chromanol (11) This compound was prepared from (3*R*)-**4b** in the same manner as described for **10**. Yield 95.2%. mp 154—156.5 °C. $[\alpha]_D^{25}$ −45.8° (c=3.0, THF). MS m/z: 166 (M^+). *Anal.* Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.03; H, 6.06. The IR and ^{1}H-NMR spectra of this compound were identical with those of **10**.

Acknowledgement The authors wish to thank Dr. M. Shiratsuchi for encouragement throughout this work, and Mr. M. Yoneda for HPLC measurement.

References and Notes

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