An Efficient Synthesis of the Optical Isomers of Nipradilol[1)]

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An efficient synthesis of all four optical isomers of nipradilol has been achieved. Thus, 8-methoxy-3-chromanone was reduced enantioselectively with baker's yeast to afford (3*R*)-8-methoxy-3-chromanol, which, after derivation to (3*R*)-8-acyloxy-3-chromanol, was led to (3*S*)- or (3*R*)-8-hydroxy-3-chromanyl nitrate (7 or 9) by selecting a reaction with retention (using acetyl nitrate) or inversion (using $Bu_4N^+NO_3^-$) of configuration. Futher, (3*S*)- and (3*R*)-8-methoxy-3-chromanol, prepared *via* chemical resolution of 8-methoxy-3-chromanyl *N*-mesyl-L-phenylalanylate, were also led to 7 or 9 in the same manner. Using 7 and 9, four optically active glycidyl ether derivatives (11—14) were synthesized by using a novel $Me_4N^+Cl^-$-catalyzed etherification reaction of phenol with (*S*)- and (*R*)-epichlorohydrin. Subsequent amination of 11—14 with isopropylamine afforded the four optical isomers of nipradilol.

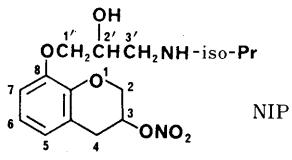
Keywords nipradilol; optical isomer; optically active 3-chromanol; enantioselective reduction; baker's yeast; nitrate; tetrabutylammonium nitrate; glycidyl ether; tetramethylammonium chloride; mechanism

Nipradilol (NIP) is an antihypertensive and antianginal agent with β-blocking and vasodilating actions,[2,3)] and is composed of four optical isomers (Fig. 1). Since these four optical isomers have very characteristic biological activities,[4)] we have been interested in the synthesis of each of them. We have already reported the synthesis of these four optical isomers *via* chemical resolution of the key intermediate.[4)] In this paper, we wish to report an improved synthesis of these four optical isomers making use of a combination of reactions which consist of enantioselective reduction of ketone with baker's yeast, nitration of an alcohol with inversion of configuration and a novel etherification of a phenol with a chiral epichlorohydrin by means of a catalytic reaction.

Synthesis of (3*R*)-8-Hydroxy-3-chromanol We have reported the synthesis of (3*S*)-8-hydroxy-3-chromanol (**1**) and (3*R*)-8-hydroxy-3-chromanol (**2**) *via* chemical resolution of a diastereomeric mixture of 8-methoxy-3-chromanyl *N*-mesyl-L-phenylalanylate which was obtained by a new cyclization reaction of 2-(2,3-epoxy)propyl-6-methoxyphenyl *N*-mesyl-L-phenylalanylate.[5)] Furthermore, while looking at other possible approaches to **1** or **2**, we investigated the synthesis of **1** or **2** by enantioselective reduction of 8-methoxy-3-chromanone (**4**) using baker's yeast (*Saccharomyces cerevisiae*) followed by demethylation. Initially, the relationship between the reduction yield and the amount of yeast used was studied. The ketone (**4**) was reduced with 1-, 3- and 5-fold weight of baker's yeast, respectively, in 30-fold weight of H_2O at 21 °C. The results, summarized in Table I, showed that this reaction was completed in the presence of more than 3-fold weight of baker's yeast with respect to **4**. Secondly, the relationship between the optical purity and the dilution was studied: the ketone (**4**) was reduced with 5-fold weight of baker's yeast for 3 h at 21 °C under various dilution conditions. It was found that the optical purity increased with increasing dilution, but the increase was not large (Table II).

Thus, 8-methoxy-3-chromanone[6)] (**4**), prepared from 8-methoxy-2*H*-1-benzopyran-3-carboxylic acid (**3**), was reduced by using 5-fold weight of baker's yeast in 40-fold weight of H_2O for 3 h at room temperature, and recrystallization of the product afforded (3*R*)-8-methoxy-3-chromanol (**5**) in 86.0% yield with 88.4% enantiomeric excess (ee). The C_3-position was determined to have *R* configuration by comparison with the same compound previously reported.[5)] Treatment of **5** with 47% HBr and recrystallization afforded **2** in 84.6% yield with 98.4% ee (Chart 1).

Synthesis of (3*S*)- and (3*R*)-8-Hydroxy-3-chromanyl



NIP

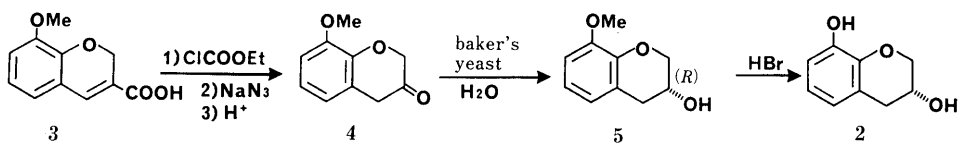
Fig. 1

TABLE I. The Relationship between the Reduction Yield and the Amount of Yeast Used

Run	Yeast/**4** (w/w)	Hour	Yield of **5** (%)
1	1	22	50
2	3	16	96
3	5	3	96

TABLE II. The Relationship between the Optical Purity and the Dilution

Run	Yeast/**4** (w/w)	H_2O/**4** (w/w)	Yield of **5** (%)	Opt. purity of **5** (% ee)
1	5	30	96	80.6
2	5	50	95	81.2
3	5	200	93	83.0
4	5	1000	91	84.2



3 4 5 2

Chart 1

Nitrate For the purpose of providing an efficient method to synthesize the four optical isomers of NIP, we investigated the synthesis of the desired (3*S*)- or (3*R*)-8-hydroxy-3-chromanyl nitrate (**7** or **9**) utilizing both **1** and **2**. In the course of our investigation, we have found an excellent method to synthesize the nitrate of alcohols, attaining inversion of configuration, through a reaction of sulfonate with quaternary ammonium nitrate[7] (method B). On the other hand, the nitration reaction with retention of configuration was achieved by the use of a fuming HNO_3–Ac_2O system (method A) (Chart 2).

Thus, **1** was acylated with trichloroacetyl chloride and subsequently esterified with fuming HNO_3–Ac_2O to give 8-trichloroacetyloxy-3-chromanyl nitrate (**6**), and then hydrolysis of **6** with NaOH gave (3*S*)-8-hydroxy-3-chromanyl nitrate (**7**) in 70.0% yield from **1** (method A). On the other hand, **1** was esterified with ethyl chloroformate and subsequently benzenesulfonyl chloride to afford 8-ethoxycarbonyloxy-3-chromanyl benzenesulfonate (**8**). Compound **8** was treated with tetrabutylammonium nitrate ($Bu_4N^+NO_3^-$) in toluene at 80 °C and subsequently hydrolyzed with NaOH to give (3*R*)-8-hydroxy-3-chromanyl nitrate (**9**) in 76.6% yield from **1** (method B). In the same way, **2** could be derived to **9** according to method A, and derived to **7** according to Method B.

Consequently, both **1** and **2** prepared *via* chemical resolution of a diastereomeric mixture and **2** obtained *via* enantioselective reduction of ketone with baker's yeast could be derived to the nitrate having desired configuration by selecting method A or method B. Therefore, it is possible to utilize the total amount of starting material for producing **7** or **9**.

Synthesis of Optical Isomers of NIP Optically active β-adrenergic blocking agents are usually prepared by optical resolution of the racemic compound[8] or by using (*S*)- and (*R*)-3-tosyloxy-1,2-propanediol acetonide as chiral building blocks.[9,10] In general, the former method is tedious, and the latter synthesis requires a great number of steps in the preparation of the chiral building blocks from D-mannitol. Under such conditions, we wanted to use (*S*)- and (*R*)-epichlorohydrin, which have recently become available industrially by means of bio-technology, as the chiral building blocks. In the investigation of the etherification of phenol with chiral epichlorohydrin, we found an efficient synthetic method using a catalytic reaction proceeding under mild conditions (Chart 3).

Thus, compound **7** was treated with 3.0 molar eq of (*R*)-epichlorohydrin in the presence of 0.2 molar eq of tetramethylammonium chloride ($Me_4N^+Cl^-$)[11] for 48 h at room temperature to afford a mixture of 8-[3-chloro-(*R*)-

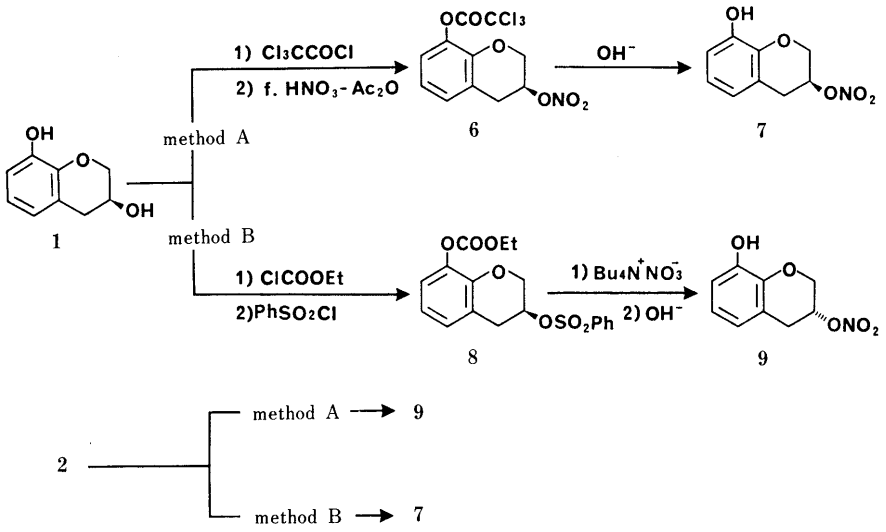


Chart 2

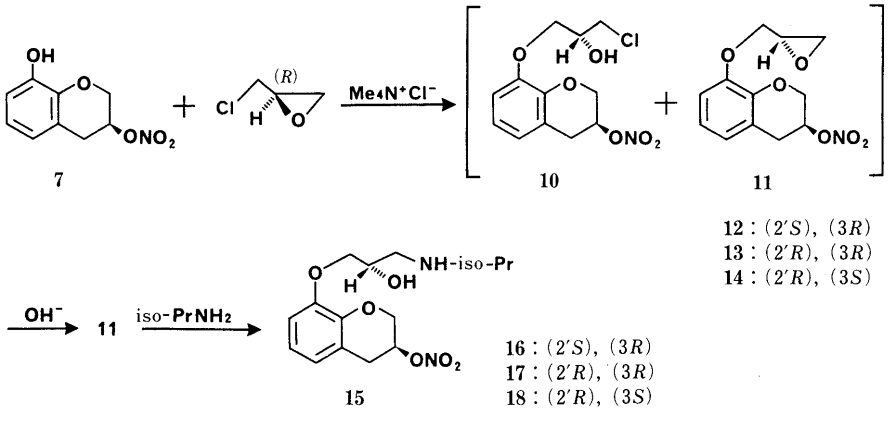


Chart 3

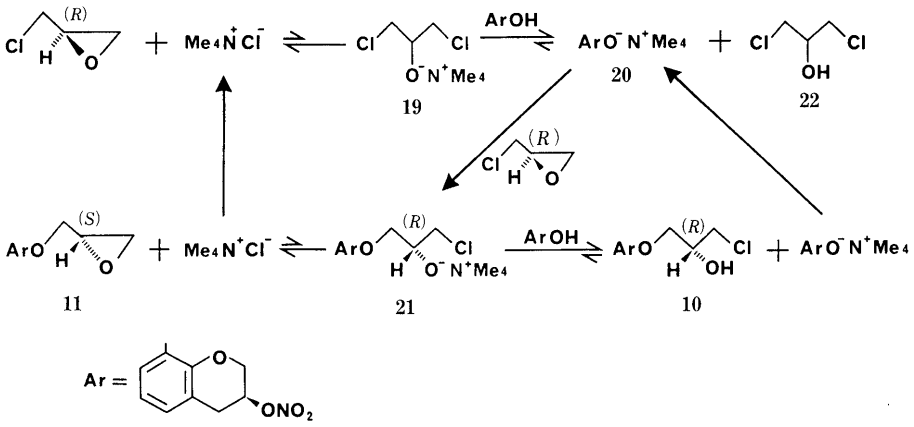


Chart 4

2-hydroxy]propoxy-(*S*)-3-chromanyl nitrate (**10**) and 8-[(*S*)-2,3-epoxy]propoxy-(*S*)-3-chromanyl nitrate (**11**). The mixture, without separation, was reacted with 1.3 molar eq of NaOH in MeOH to give **11** in 89.0% yield. In the reaction of **7** with (*S*)-epichlorohydrin under the same conditions, 8-[(*R*)-2,3-epoxy]propoxy-(*S*)-3-chromanyl nitrate (**14**) was obtained in 91.5% yield. In the same way, 8-[(*S*)-2,3-epoxy]propoxy-(*R*)-3-chromanyl nitrate (**12**) and 8-[(*R*)-2,3-epoxy]propoxy-(*R*)-3-chromanyl nitrate (**13**) were also prepared by the reaction of **9** with (*R*)- and (*S*)-epichlorohydrin in 89.6% and 91.0% yields, respectively. The configuration at the C_2-position in the side chain of these compounds was determined by comparison with the same compound previously reported.[4]

In this reaction, since the configuration of the C_2-position of epichlorohydrin was inverted, it is supposed that the phenoxide (**20**) which is generated by the reaction of the alkoxide (**19**) with the phenol attacks the less substituted epoxide carbon of epichlorohydrin to give the alkoxide (**21**), and subsequently **21** affords **10** and **11**. Further, the formation of 1,3-dichloro-2-propanol (**22**) was observed by proton nuclear magnetic resonance (^{1}H-NMR) spectral analysis. The ^{1}H-NMR spectrum of the distillate, obtained from the reaction mixture by direct distillation, showed signals due to a hydroxyl proton at δ 2.58 (d, $J=7$ Hz), two methylene protons at δ 3.70 (d, $J=6$ Hz) and a methine proton δ 4.00—4.12 (m). Thus, the major reaction mechanism can be presumed to be as shown in Chart 4.

Compound **11** was transformed in the usual manner to 8-[3-isopropylamino-(*S*)-2-hydroxy]propoxy-(*S*)-3-chromanyl nitrate (**15**) with isopropylamine in 90.5% yield. The other three optical isomers of NIP (**16**, **17** and **18**) were also synthesized in a similar manner.

Results and Discussion

In our synthetic study of the optical isomers of NIP, we have developed an efficient synthetic method by employing a combination of three reactions. In particular, this nitrate formation reaction using $Bu_4N^+NO_3^-$ has a wide range of utility for alcohol derivatives having an aromatic ring,[7] which are not well transformed to desired nitrates by the use of HNO_3 because of the introduction of a nitro group in the aromatic ring. So it is considered that this method has utility not only as a method for inversion of configuration of an alcohol (nitrate is readily converted to a hydroxy group under reductive conditions), but also as a general method of nitrate synthesis. Furthermore, the etherification reaction of phenols with chiral epichlorohydrin, considering that these reagents are becoming available through the application of bio-technology, will provide an efficient method for the synthesis of optically active β-blocking agents.

Experimental

All melting points are uncorrected. Infrared (IR) absorption spectra were obtained with Shimadzu IR-435 spectrometers. ^{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, q = quartet and m = multiplet. 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. Column chromatography was performed on Wako Silica gel (C-200). Thin-layer chromatography (TLC) was performed on E. Merck Silica gel 60 F_{254}. All the organic extracts were dried over anhydrous Na_2SO_4 prior to evaporation, which was performed under reduced pressure.

(3*R*)-8-Methoxy-3-chromanol (5) Powdered 8-methoxy-3-chromanone (**4**) (3.00 g) and dry yeast (*Saccharomyces cerevisiae*)[12] (15.0 g) were added to H_2O (120 ml), then the mixture was stirred for 3 h at room temperature. AcOEt (120 ml) was added and the whole was stirred for 10 min, then filtered on Celite. The Celite was washed thoroughly with AcOEt. The AcOEt layer was separated from the filtrate, washed with brine and evaporated to give crude crystals, which were chromatographed on a silica gel column (AcOEt : hexane = 1 : 1). Recrystallization from AcOEt–hexane gave **5** (2.61 g, 86.0%) as colorless needles, mp 100—102 °C. $[\alpha]_D^{22}$ +15.0° ($c=4.0$, $CHCl_3$). *Anal.* Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.46; H, 6.70. The IR and ^{1}H-NMR spectra of **5** were identical with those of the same compound prepared by chemical resolution of racemic **5**.[5] The optical purity was measured in the same manner as previously reported,[5] 88.4% ee.

(3*R*)-8-Hydroxy-3-chromanol (2) In the same manner as previously reported,[5] crude **2** was obtained from **5** (2.00 g) and 47% HBr (12.0 ml), and was recrystallized from acetone–hexane to give **2** (1.56 g, 84.6%) as colorless plates, mp 154—156 °C. $[\alpha]_D^{23}$ −45.5° ($c=3.0$, THF). MS *m/z*: 166 (M^+). *Anal.* Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.96; H, 6.14. The IR and ^{1}H-NMR spectra of this compound were identical with those of the same compound previously reported.[5] After this product had been derived to **5** by reaction with methyl iodide in the presence of K_2CO_3 in acetone, the optical purity was measured in the same manner as for **5**, 98.4% ee.

Syntheses of (3*S*)-8-Hydroxy-3-chromanyl Nitrate (7) and (3*R*)-8-Hydroxy-3-chromanyl Nitrate (9) Method A: Compound **7** was synthesized by the reaction of **1** with $AcONO_2$ according to the method previously reported[3] in 70.0% yield. mp 129—130 °C (recrystallized from acetone–hexane). $[\alpha]_D^{23}$ −40.4° ($c=3.0$, $CHCl_3$). *Anal.* Calcd for

$C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 51.21; H, 4.28; N, 6.55. The IR and ^{1}H-NMR spectra of this compound were identical with those of the same compound prepared by chemical resolution of the racemate.[4]

Compound **9** was synthesized from **2** in the same manner as described for **7** in 72.0% yield. mp 129—130 °C (recrystallized from acetone–hexane). $[\alpha]_D^{23}$ +40.6° (c=3.0, $CHCl_3$). *Anal.* Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 51.20; H, 4.27; N, 6.53. The IR and ^{1}H-NMR spectra of this compound were identical with those of **7**.

Method B: Ethyl chloroformate (0.68 g) in tetrahydrofuran (THF) (5.5 ml) was added dropwise to a solution of **1** (1.00 g) and triethylamine (0.67 g) in THF (17 ml) at −5 °C and the mixture was stirred at the same temperature for 0.5 h, then filtered. The filtrate was concentrated under reduced pressure. The residue was dissolved in pyridine (2.6 ml), then benzenesulfonyl chloride (1.60 g) was added at 0 °C and the mixture was stirred for 24 h at room temperature. After addition of H_2O (1.8 ml), the reaction mixture was stirred for 0.5 h at room temperature, then the mixture was evaporated to dryness. The residue was dissolved in benzene, washed with 2 N HCl, saturated $NaHCO_3$, and brine, and evaporated to give a crude product, which was chromatographed on a silica gel column (benzene) to give **8** (2.21 g, 97.0%) as a colorless oil. $[\alpha]_D^{24}$ +21.0° (c=2.4, $CHCl_3$). IR (film): 1761, 1480, 1366, 1251 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.80—3.28 (2H, m, C_4-H), 4.05—4.36 (2H, m, C_2-H), 4.30 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.90—5.15 (1H, m, C_3-H), 6.80—7.10 (3H, m, Ar-H), 7.44—7.80 (3H, m, Ar-H), 7.85—8.04 (2H, m, Ar-H). MS m/z: 378 (M^+). High-resolution MS Calcd for $C_{18}H_{18}O_7S$: 378.0770. Found: 378.0763.

Tetrabutylammonium nitrate (4.2 g) was added to a solution of **8** (2.10 g) in toluene (5.3 ml), and the mixture was heated at 80 °C for 18 h. The reaction mixture was dissolved in benzene, washed with H_2O, and evaporated to give an oil (1.50 g). A solution of this oil in MeOH (22 ml) was treated with 2 N NaOH (3.5 ml) at 0 °C, and the mixture was stirred for 0.5 h at room temperature. The reaction mixture was adjusted to a pH of about 4 with 1 N HCl, concentrated and extracted with $CHCl_3$. The extract was evaporated to give crude crystals, which were purified by silica gel column chromatography ($CHCl_3$). Recrystallization from AcOEt–hexane gave **9** (0.93 g, 79.0%) as colorless prisms, mp 129—130 °C. $[\alpha]_D^{24}$ +40.4° (c=3.0, $CHCl_3$). IR (KBr): 3317, 1619, 1285 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.84—3.42 (2H, m, C_4-H), 4.12—4.52 (2H, m, C_2-H), 5.32—5.50 (1H, m, C_3-H), 5.44 (1H, s, OH), 6.48—6.90 (3H, m, Ar-H). MS m/z: 211 (M^+). *Anal.* Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 51.26; H, 4.28; N, 6.60.

Compound **7** was obtained from **2** (1.10 g) in the same way as described for the synthesis of **9** from **1**, in 75.5% yield. mp 129—130 °C. $[\alpha]_D^{24}$ −40.9° (c=3.0, $CHCl_3$). *Anal.* Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 51.16; H, 4.26; N, 6.57. The IR and ^{1}H-NMR spectra of **7** were identical with those of **9**.

Isolation of 8-[3-Chloro-(*R*)-2-hydroxy]propoxy-(*S*)-3-chromanyl Nitrate (10) and 8-[(*S*)-2,3-Epoxy]propoxy-(*S*)-3-chromanyl Nitrate (11) A mixture of **7** (1.00 g), (*R*)-epichlorohydrin[13] (1.32 g) and tetramethylammonium chloride (0.10 g) was stirred for 48 h at room temperature, then the reaction mixture was dissolved in $CHCl_3$, washed with H_2O, and evaporated to give a solid. The solid was chromatographed on a silica gel column ($CHCl_3$: AcOEt = 15 : 1) to give **10** (0.797 g, 55.4%) and **11** (0.443 g, 35.0%). **10**: Colorless needles (recrystallized from AcOEt–hexane), mp 110—112 °C, $[\alpha]_D^{24}$ −7.2° (c=3.0, $CHCl_3$). IR (KBr): 3506, 1617, 1484, 1294 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.86 (1H, d, J=6 Hz, OH), 2.95—3.37 (2H, m, C_4-H), 3.66—3.85 (2H, m, CH_2Cl), 4.05—4.50 (5H, m, $ArOC\underline{H}_2C\underline{H}$ and C_2-H), 5.40—5.50 (1H, m, C_3-H), 6.70—6.93 (3H, m, Ar-H). MS m/z: 303, 305 (M^+). *Anal.* Calcd for $C_{12}H_{14}ClNO_6$: C, 47.46; H, 4.65; Cl, 11.67; N, 4.61. Found: C, 47.52; H, 4.56; Cl, 11.76; N, 4.61.

8-[(*S*)-2,3-Epoxy]propoxy-(*S*)-3-chromanyl Nitrate (11) A mixture of **7** (750 mg), (*R*)-epichlorohydrin (990 mg) and tetramethylammonium chloride (75 mg) was stirred for 48 h at room temperature, then NaOH (250 mg) in MeOH (13 ml) was added at 0 °C and the mixture was stirred for 2 h at room temperature. After being neutralized with AcOH, the reaction mixture was evaporated to dryness. The residue was dissolved in $CHCl_3$, washed with H_2O, and evaporated to give crude crystals, which were purified by silica gel column chromatography ($CHCl_3$: acetone = 50 : 1), then recrystallized from acetone–hexane to give **11** (845 mg, 89.0%) as colorless needles, mp 136—138.5 °C. $[\alpha]_D^{25}$ −30.5° (c=3.0, $CHCl_3$). *Anal.* Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.74; H, 4.80; N, 5.10. The IR and ^{1}H-NMR data for **11** were identical with those previously reported.[4]

Compounds **12**, **13** and **14** were prepared in the same manner as described for **11**, and the IR and ^{1}H-NMR data for these compounds were identical with the reported values.[4] Elemental analyses for C, H and N of all compounds satisfied the calculated values within ±0.3%.

8-[(*S*)-2,3-Epoxy]propoxy-(*R*)-3-chromanyl Nitrate (12) Crude **12** was prepared from **9** (700 mg), (*R*)-epichlorohydrin (920 mg) and tetramethylammonium chloride (70 mg), and purified by silica gel column chromatography ($CHCl_3$), then recrystallized from acetone–hexane to give **12** (794 mg, 89.6%) as colorless needles, mp 127—128 °C. $[\alpha]_D^{25}$ +24.7° (c=3.0, $CHCl_3$).

8-[(*R*)-2,3-Epoxy]propoxy-(*R*)-3-chromanyl Nitrate (13) Crude **13** was prepared from **9** (500 mg), (*S*)-epichlorohydrin[13] (657 mg) and tetramethylammonium chloride (50 mg), and purified by silica gel column chromatography ($CHCl_3$), then recrystallized from acetone–hexane to give **13** (576 mg, 91.0%) as colorless needles, mp 136—138 °C. $[\alpha]_D^{25}$ +31.3° (c=3.0, $CHCl_3$).

8-[(*R*)-2,3-Epoxy]propoxy-(*S*)-3-chromanyl Nitrate (14) Crude **14** was prepared from **7** (820 mg), (*S*)-epichlorohydrin (1.08 g) and tetramethylammonium chloride (80 mg), and purified by silica gel column chromatography ($CHCl_3$), then recrystallized from acetone–hexane to give **14** (950 mg, 91.5%) as colorless needles, mp 126—127 °C. $[\alpha]_D^{25}$ −24.2° (c=3.0, $CHCl_3$).

8-[3-Isopropylamino-(*S*)-2-hydroxy]propoxy-(*S*)-3-chromanyl Nitrate (15) A mixture of **11** (727 mg), isopropylamine (7.4 ml) and MeOH (15 ml) was heated to reflux for 1 h. After evaporation, the residue was recrystallized from AcOEt to give **15** (804 mg, 90.5%) as colorless needles, mp 139—139.5 °C. $[\alpha]_D^{24}$ −14.2° (c=3.0, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{22}N_2O_6$: C, 55.21; H, 6.79; N, 8.58. Found: C, 55.30; H, 6.80; N, 8.54. The IR and ^{1}H-NMR data for **15** were identical with the reported values.[4]

Compounds **16**, **17**, and **18** were prepared in the same manner as described for **15**, and the IR and ^{1}H-NMR data for these compounds were identical with the reported values.[4] Elemental analyses for C, H and N of all compounds satisfied the calculated values within ±0.3%.

8-[3-Isopropylamino-(*S*)-2-hydroxy]propoxy-(*R*)-3-chromanyl Nitrate (16) Crude **16** was prepared from **12** (600 mg), ispropylamine (6.0 ml) and MeOH (12 ml), and then recrystallized from benzene–hexane to give **16** (669 mg, 91.2%) as colorless needles, mp 101.5—102.5 °C. $[\alpha]_D^{24}$ +14.7° (c=3.0, $CHCl_3$).

8-[3-Isopropylamino-(*R*)-2-hydroxy]propoxy-(*R*)-3-chromanyl Nitrate (17) Crude **17** was prepared from **13** (705 mg), isopropylamine (7.0 ml) and MeOH (14 ml), and then recrystallized from AcOEt to give **17** (764 mg, 88.7%) as colorless needles, mp 139—139.5 °C. $[\alpha]_D^{24}$ +14.5° (c=3.0, $CHCl_3$).

8-[3-Isopropylamino-(*R*)-2-hydroxy]propoxy-(*S*)-3-chromanyl Nitrate (18) Crude **18** was prepared from **14** (780 mg), isopropylamine (7.8 ml) and MeOH (16 ml), and then recrystallized from benzene–hexane to give **18** (862 mg, 90.5%) as colorless needles, mp 101—101.5 °C. $[\alpha]_D^{24}$ −14.2° (c=3.0, $CHCl_3$).

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References and Notes

1) A part of this work was presented at the 9th Symposium on Medicinal Chemistry, Pharmaceutical Society of Japan, Tokyo, Nov. 1988.
2) Y. Uchida, M. Nakamura, S. Shimizu, Y. Shirasawa, and M. Fujii, *Arch. Int. Pharmacodyn. Ther.*, **262**, 132 (1983).
3) M. Shiratsuchi K. Kawamura, T. Akashi, M. Fujii, H. Ishihama, and Y. Uchida, *Chem. Pharm. Bull.*, **35**, 632 (1987).
4) M. Shiratsuchi, K. Kawamura, T. Akashi, H. Ishihama, M. Nakamura, and F. Takenaka, *Chem. Pharm. Bull.*, **35**, 3691 (1987).
5) K. Kawamura, T. Ohta, and G. Otani, *Chem. Pharm. Bull.*, **38**, 2088 (1990).
6) Kowa Co., Ltd., Japan laid-open Patent 59-29681 (1984) [*Chem. Abstr.*, **101**, 90765*j* (1982)].
7) Kowa Co., Ltd. (K. Kawamura, K. Shibuya, H. Ishihama), Japan laid-open Patent 61-15847 (1986) [*Chem. Abstr.*, **105**, 152233*c* (1986)]. This same synthetic method was reported by G. Cainelli, F. Manescalchi, G. Martelli, M. Panunzio, and L. Plessi, *Tetrahedron Lett.*, **1985**, 3369.
8) R. Howe and R. G. Shanks, *Nature* (London), **210**, 1336 (1966).
9) W. L. Nelson and T. R. Burke, Jr., *J. Org. Chem.*, **43**, 3641

(1978).
10) W. L. Nelson, J. E. Wennerstrom, and S. R. Sankar, *J. Org. Chem.*, **42**, 1006 (1977).
11) It is known that tetraethylammonium iodide, tetrabutylammonium bromide and tetrabutylammonium iodide also have good catalytic properties.
12) The baker's yeast was supplied in dry form by Oriental Yeast Ind., Ltd. (Tokyo, Japan).
13) The (*R*)- and (*S*)-epichlorohydrin were supplied by Daiso Co., Ltd. (Osaka, Japan); optical purity, >98% ee.