[Chem. Pharm. Bull. 35(9)3691—3698(1987)]

Synthesis and Activity of Optical Isomers of Nipradilol[1)]

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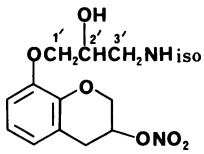
(Received January 21, 1987)

Four optical isomers of nipradilol (NIP) were prepared from (3*R*)- or (3*S*)-3,4-dihydro-8-hydroxy-3-nitroxy-2*H*-1-benzopyran by glycidylation and amination, and evaluated for β-blocking and vasodilating activities. The order of potency of β-blocking activity was *S,R*-NIP ≫ *S,S*-NIP > *R,R*-NIP ≫ *R,S*-NIP. As regards vasodilating activity, *S,R*-NIP and *R,R*-NIP were more potent than *S,S*-NIP and *R,S*-NIP.

Keywords——nipradilol; synthesis; optical isomer; β-blocking activity; α-blocking activity; vasodilating activity; benzopyran

Nipradilol (NIP) is a synthetic drug having β-blocking and vasodilating activities (direct vasodilating activity and α-blocking acitivitiy),[2)] and is used to treat cardiovascular diseases.



NIP

Since NIP has asymmetric carbon atoms at the 3-position of the benzopyran ring and the 2′-position of the side chain, four optical isomers can exist theoretically. The *N,O*-bis-L-menthoxyacetyl derivatives show four peaks on high-performance liquid chromatography (HPLC), and the areas of the peaks are nearly equal (Fig. 1). We reported the resolution of NIP in this journal previously.[3)] The result of further studies on the optical isomers of NIP and their pharmacological activities are presented here.

Chemistry

The starting compounds (3*R*)-3,4-dihydro-8-hydroxy-3-nitroxy-2*H*-1-benzopyran (**4**) and (3*S*)-3,4-dihydro-8-hydroxy-3-nitroxy-2*H*-1-benzopyran (**5**), were obtained by optical resolution of 3,4-dihydro-8-hydroxy-3-nitroxy-2*H*-1-benzopyran (**1**) (Chart 1).[2)] Esterification was carried out by the action of (L)-*N*-mesylphenylalanine on **1** in the presence of a condensing agent (*e.g.*, dicyclohexylcarbodiimide). (3*R*)-3,4-Dihydro-8-(*N*-mesylphenylalanyloxy)-3-nitroxy-2*H*-1-benzopyran (**2**), whose specific rotation was −17.2°, was separated from the resulting mixture of crystalline and oily diastereomers by recrystallization. The C_3-position was determined to have *R* configuration by X-ray analysis.[4)] Hydrolysis of the optically active (3*R*) ester **2** gave the (3*R*)-8-hydroxy compound **4**. Similarly, the (3*S*) ester **3**, whose specific rotation was +17.2°, was produced by using (D)-*N*-mesylphenylalanine instead of (L)-*N*-mesylphenylalanine, and hydrolysis of **3** gave the (3*S*)-8-hydroxy compound

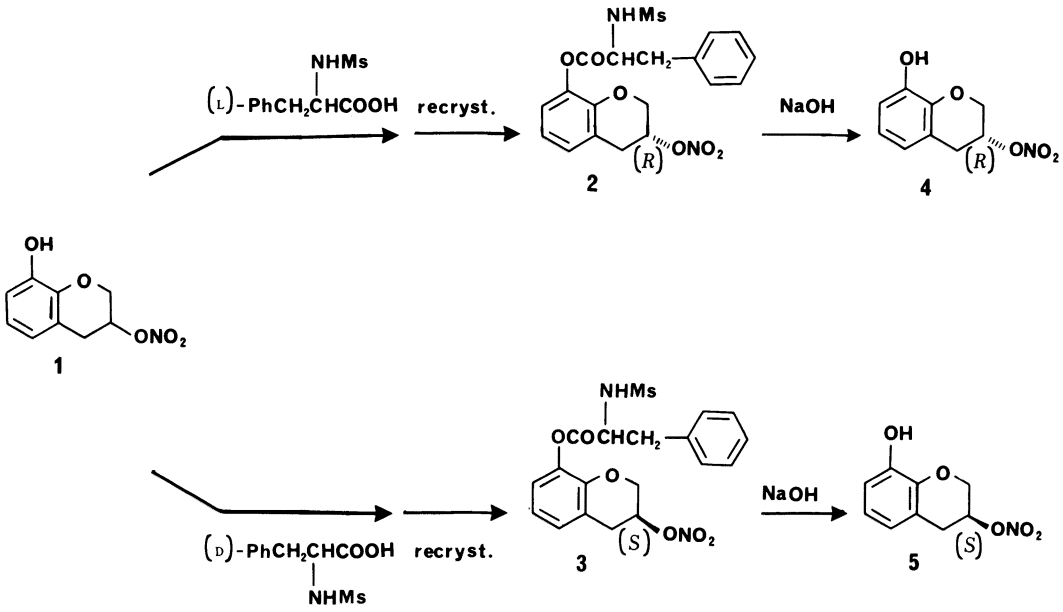
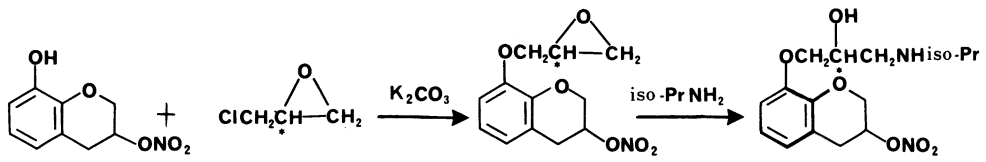


Chart 1



7 : *R*
7′: *S*

6: 2′*S*
8: 2′*R*

9: 2′*S*-NIP
10: 2′*R*-NIP

Chart 2

5. Then, we examined the reaction of **1** with epichlorohydrin to synthesize the glycidyl ether **6** (Chart 2).

In the reaction of (*R*)- and/or (*S*)-epichlorohydrin with phenols, Baldwin *et al.*[5-7] obtained mainly methyloxiranes whose configuration at the C_2-position in the side chain was inverted. On the basis of this result, it was supposed that (2′*S*)-3,4-dihydro-8-(2,3-epoxypropoxy)-3-nitroxy-2*H*-1-benzopyran (**6**) and (2′*R*)-3,4-dihydro-8-(2,3-epoxypropoxy)-3-nitroxy-2*H*-1-benzopyran (**8**) could be obtained as major products from (*R*)-epichlorohydrin (**7**) and (*S*)-epichlorohydrin (**7′**) respectively. The amination of **6** gave (2′*S*)-3,4-dihydro-8-[2-hydroxy-3-(isopropylamino)propoxy]-3-nitroxy-2*H*-1-benzopyran (2′*S*-NIP) (**9**) and that of **8** gave (2′*R*)-3,4-dihydro-8-[2-hydroxy-3-(isopropylamino)propoxy]-3-nitroxy-2*H*-1-benzopyran (2′*R*-NIP) (**10**) (Fig. 1). On the other hands, the glycidylation of **1** with (2*S*)-3-(2-nitrobenzenesulfonyloxy)-1,2-epoxypropane (**11**) and subsequent amination with isopropylamine gave stereoselectively 2′*S*-NIP **9** (Chart 3). Therefore it was supposed that this substitution reaction proceeds with retention of configuration. We synthesized four optical isomers of NIP by utilizing **11** and its optical isomer, (2*R*)-3-(2-nitrobenzenesulfonyloxy)-1,2-epoxypropane (**12**). Thus, the glycidylation of **4** with **11** and subsequent amination with isopropylamine gave (2′*S*), (3*R*)-3,4-dihydro-8-[2-hydroxy-3-(isopropylamino)propoxy]-3-nitroxy-2*H*-1-benzopyran (*S,R*-NIP) (**13**) (Chart 4). The *N,O*-

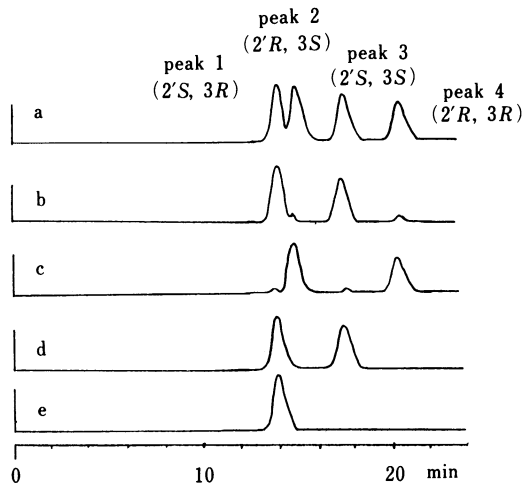


Fig. 1. Chromatogram of *N*,*O*-Bis-L-methoxyacetyl Derivatives of (a) NIP, (b) 2′*S*-NIP Obtained from (*R*)-Epichlorohydrin, (c) 2′*R*-NIP Obtained from (*S*)-Epichlorohydrin, (d) 2′*S*-NIP Obtained from **11**, (e) *S*,*R*-NIP

Column: Partisil-10 (10 μm) (Whatman), 4 × 200 mm. Eluent: hexane–ethyl acetate (5 : 1), 1.5 ml/min. Detection: UV 275 nm.

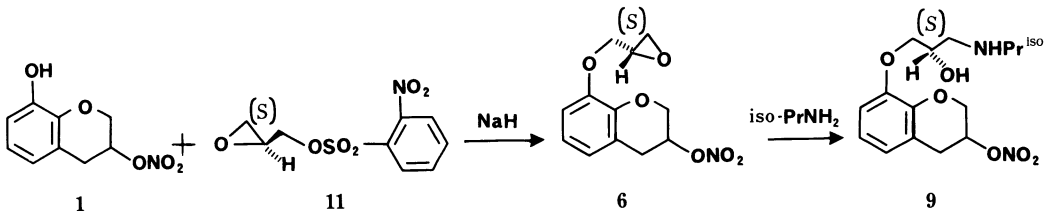


Chart 3

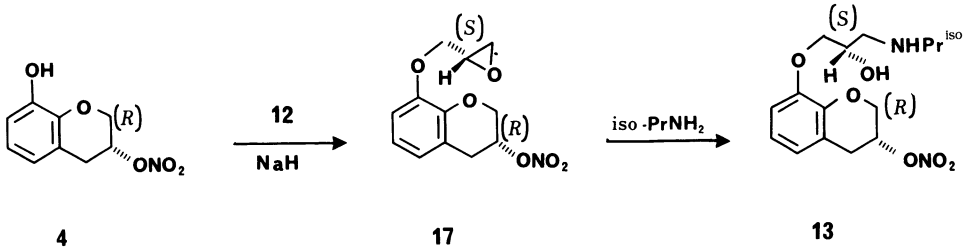


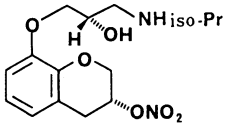
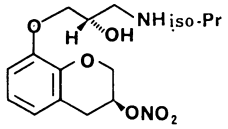
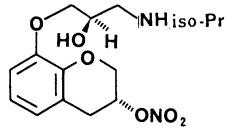
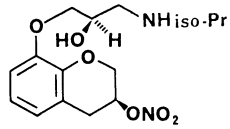
Chart 4

bis-L-methoxyacetyl derivative of **13** gave a single peak on HPLC (Fig. 1). The other isomers of NIP were similarly synthesized, and each gave a single peak on HPLC (Table I). These products were identified by comparison of the circular dichroism spectra and nuclear magnetic resonance (NMR) spectra with those of compounds of known configuration.[3)]

Biological Activity and Discussion

β-Blocking Activity——The compounds listed in Table I were tested for antagonistic action towards isoproterenol, *i.e.* β-blocking action, using isolated atrium and trachea of guinea pigs. The results are shown in Tables II and III. In the tables, pA_2 is the reciprocal logarithm of the molar concentration of each test compound required to shift the dose–response curve of isoproterenol in parallel to 2-fold higher dose. The parenthesized figures are efficacy ratios based on NIP. The results demonstrate that the β-blocking activity of *R*,*R*-NIP is about one-tenth of that of NIP, while that of *S*,*R*-NIP is about 3 to 8 times as strong as

TABLE I. Optical Isomers of NIP

Compd. No.	Structure		Yield[a] (%)	mp (°C)	$[\alpha]_D^{25}$ (°)
13		(*S,R*-NIP)	74.4	105.3—105.8	+16.2
14		(*S,S*-NIP)	63.1	140.5—141.0	−15.8
15		(*R,R*-NIP)	70.3	140.3—141.0	+15.5
16		(*R,S*-NIP)	71.1	105.3—106.1	−16.7

a) Overall yield of glycidylation and amination.

TABLE II. Effects of NIP and Its Isomers on β-Adrenoceptors in Guinea-pig

Antagonist	Right atrium (β_1-Adrenoceptors)			Left atrium (β_1-Adrenoceptors)		
	n[a]	$pA_2 \pm$S.E. (Ratio)	Slope ± S.E.	n[a]	$pA_2 \pm$S.E. (Ratio)	Slope ± S.E.
NIP	5	9.07 ± 0.12 (1.00)	−0.98 ± 0.05	5	8.72 ± 0.10 (1.00)	−1.17 ± 0.04
S,R-NIP	5	9.56 ± 0.08 (3.09)	−0.99 ± 0.03	5	9.60 ± 0.12 (7.59)	−1.05 ± 0.03
S,S-NIP	5	8.14 ± 0.20 (0.12)	−1.08 ± 0.06	5	8.17 ± 0.09 (0.28)	−1.04 ± 0.06
R,R-NIP	6	7.64 ± 0.15 (0.037)	−0.91 ± 0.05	5	7.65 ± 0.11 (0.085)	−0.93 ± 0.06
R,S-NIP	5	5.83 ± 0.07[b] (0.0006)	—	6	5.48 ± 0.10[b] (0.0006)	—
Propranolol	3	8.70 ± 0.11 (0.43)	−0.99 ± 0.01	4	8.57 ± 0.17 (0.71)	−0.99 ± 0.07

pA_2 and slope were calculated as described by Arunlakshana and Schild.[8] The agonist used was isoprotenol. *a*) Number of guinea-pigs. *b*) pA_2 estimated from the shift produced in the presence of 10^{-5} M antagonist.[9]

that of NIP, and that of *S,S*-NIP is about 3 times as strong as that of *R,R*-NIP. Previous reports have shown that β-blockers possessing the *S* configuration are more potent than those of *R* configuration among compounds of the aryloxypropanolamine type [propranolol, practolol and timolol].[10-13] This finding is in accordance with our results. Furthermore, the β-blocking activity of *S,R*-NIP is about 26 times as strong as that of *S,S*-NIP. Therefore, it

TABLE III. Effects of NIP and Its Isomers on β-Adrenoceptors in Guinea-pig

Antagonist	Tracheal strip (β_2-Adrenoceptors)		
	n	$pA_2 \pm$S.E. (Ratio)	Slope $\pm$S.E.
NIP	6	8.49 ± 0.11 (1.00)	-0.95 ± 0.05
S,R-NIP	6	9.18 ± 0.15 (4.90)	-1.09 ± 0.11
S,S-NIP	6	7.60 ± 0.09 (0.13)	-0.95 ± 0.06
R,R-NIP	6	7.39 ± 0.23 (0.079)	-0.85 ± 0.09
R,S-NIP	6	5.84 ± 0.11 (0.002)	-0.80 ± 0.06
Propranolol		—	—

TABLE IV. Effects of NIP and Its Isomers on K^+-Induced Contracture and NE Induced Contraction in Canine Mesenteric Arteries

	K^+-Contracture		Norepinephrine contraction (α-Adrenoceptors)		
	n	$pD_2 \pm$S.E. (Ratio)	n	$pA_2 \pm$S.E. (Ratio)	Slope $\pm$S.E.
NIP	7	6.17 ± 0.07 (1.00)	6	6.81 ± 0.09 (1.00)	-0.85 ± 0.07
S,R-NIP	7	6.24 ± 0.07 (1.17)	6	7.12 ± 0.10 (2.04)	-0.94 ± 0.07
R,R-NIP	6	6.35 ± 0.03 (1.51)	6	6.75 ± 0.12 (0.87)	-0.90 ± 0.09
S,S-NIP	7	4.69 ± 0.15 (0.03)	6	5.65 ± 0.12 (0.07)	-0.66 ± 0.06
R,S-NIP	7	4.77 ± 0.10 (0.04)	6	5.44 ± 0.06 (0.04)	-0.78 ± 0.03

pD_2 = concentration of antagonist required to produce an agonist dose/ratio of 2. pA_2 and slope were calculated as described by Arunlakshana and Schild.[8]

is suggested that the 3*R* configuration (at the nitroxy moiety) is superior to the 3*S* configuration with regard to approach to the receptor.

Vasodilating activity: The compounds indicated in Table I were tested for antagonistic action on potassium contracture (direct vasorelaxing activity) and their antagonistic action on the contractile activity of norepinephrine (NE) (α-blocking activity) in the isolated superior mesentric artery of dogs. The results are shown in Table IV. In the table, pD_2 represents the reciprocal logarithm of the molar concentration of each test compound required to inhibit the maximum reaction to potassium (25 mM K^+) by 50%. The parenthesized figures have the same meanings as in Table II. The above results demonstrate that the vasodilating activity of *R,R*-NIP is nearly equivalent to that of NIP, and the vasodilating activity of *S,R*-NIP is about 1.1 to 2 times that of NIP, while the vasodilating activities of *S,S*-NIP and *R,S*-NIP are weaker than that of NIP. Therefore, it is suggested that the 3*R* configuration at the nitroxy

moiety has higher pharmacological activity than the 3*S* configuration.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were measured with JASCO IRA-1 and Shimadzu IR-435 spectrometers. NMR spectra were taken at 60 MHz with a Varian EM-360 spectrometer and at 100 MHz with a JEOL JNM-MH-100 spectrometer. Chemical shifts are expressed in δ (ppm) values. The following abbreviations are used: s = singlet, d = doublet, q = quartet, dd = double doublet, m = multiplet and br = broad. Mass spectra (MS) were measured with JEOL JMS-D-300 and JMS-D-100 mass spectrometers.

(3*R*)-3,4-Dihydro-8-(*N*-mesyl-L-phenylalanyloxy)-3-nitroxy-2*H*-1-benzopyran (2)——Compound **1** (31.8 g, 150 mmol) was dissolved in CH_2Cl_2 (500 ml) and *N*-mesyl-L-phenylalanine (36.6 g, 150 mmol) and 4-dimethylaminopyridine (DMAP) (3.7 g, 30 mmol) were added. A solution of dicyclohexylcarbodiimide (40 g, 194 mmol) in CH_2Cl_2 (130 ml) was added with stirring at room temperature, and the mixture was stirred for 12 h at the same temperature. The precipitate was removed from the reaction mixture by filtration. The filtrate was concentrated, and the residue was dissolved in AcOEt. This solution was washed successively with 5% HCl, 5% aqueous NaOH and H_2O, then evaporated, and the residue was dissolved in tetrahydrofuran (THF). The insoluble materials were removed by filtration. Hexane was added, and the solution was left to stand. The precipitated crystals were collected by filtration, and recrystallized from acetone to give 12.8 g (yield, 19.4%) of the desired product as colorless prisms, mp 191—195 °C (dec.), $[\alpha]_D^{25} -17.2°$ ($c=3$, THF). NMR ($CDCl_3$) δ: 2.74 (3H, s, CH_3), 3.08—3.50 (4H, m, C_4-H, CH_2-Ar), 4.24—4.36 (2H, m, C_2-H), 4.60—4.80 (1H, m, >CHNH), 4.92 (1H, d, $J=9$ Hz, NH), 5.36—5.56 (1H, m, C_3-H), 6.80—7.10 (3H, m, Ar-H), 7.32 (5H, s, Ar-H). IR ν_{max}^{KBr} cm^{-1}: 3240 (NH), 1778 (COO), 1635, 1272 (ONO_2), 1325, 1150 (SO_2NH). MS *m/z* 436 (M^+). *Anal.* Calcd for $C_{19}H_{20}N_2O_8S$: C, 52.29; H, 4.62; N, 6.42. Found: C, 52.51; H, 4.74; N, 6.27.

(3*S*)-3,4-Dihydro-8-(*N*-mesyl-L-phenylalanyloxy)-3-nitroxy-2*H*-1-benzopyran (3)——In the same manner as described for **2**, crude **3** was prepared from **1** (31.8 g, 150 mmol), *N*-mesyl-D-phenylalanine (36.6 g, 150 mmol) and DMAP (3.7 g, 30 mmol). Recrystallization of crude **3** from acetone gave 11.2 g (yield, 17.0%) of the pure product as colorless prisms, mp 192—195 °C (dec.), $[\alpha]_D^{25} +17.2°$ ($c=3$, THF). The NMR spectrum and IR spectrum of **3** were identical with those of **2**.

(3*R*)-3,4-Dihydro-8-hydroxy-3-nitroxy-2*H*-1-benzopyran (4)——Compound **2** (21.6 g, 49.5 mmol) was dissolved in THF (200 ml) at room temperature and MeOH (100 ml) and a 10% aqueous solution (40 ml) of NaOH were added. The mixture was stirred for 1 h, then adjusted to a pH of about 4 with cold HCl, and concentrated. The residue was taken up in $CHCl_3$, the pH of the aqueous layer was adjusted to pH 2 with dilute HCl, and the $CHCl_3$ layer was separated. The organic layer was washed with an aqueous solution of $NaHCO_3$ and also with H_2O, and the solvent was evaporated. Recrystallization of the residue from AcOEt–hexane gave 9.2 g (yield, 88.0%) of the desired product as colorless prisms, mp 129.0—130.5 °C, $[\alpha]_D^{25} +40.8°$ ($c=3$, $CHCl_3$). 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). IR ν_{max}^{KBr} cm^{-1}: 3330 (OH), 1620, 1290 (ONO_2). *Anal.* Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 51.13; H, 4.30; N, 6.56.

(3*S*)-3,4-Dihydro-8-hydroxy-3-nitroxy-2*H*-1-benzopyran (5)——In the same manner as described for **4**, crude **5** was prepared from **3** (21.6 g, 49.5 mmol) and a 10% aqueous solution (40 ml) of NaOH. Recrystallization of crude **5** from AcOEt–hexane gave 9.0 g (yield, 86.3%) of the pure product as colorless prisms, mp 129.0—130.5 °C, $[\alpha]_D^{25} -41.3°$ ($c=3$, $CHCl_3$). The NMR spectrum and IR spectrum of **5** were identical with those of **4**.

(2*R*)-3-(2-Nitrobenzenesulfonyloxy)-1,2-epoxypropane (12)——(*R*)-Glycerol acetonide[14] [bp 88—106 °C (18 mmHg), $[\alpha]_D^{25} -12.10°$ ($c=5.64$, MeOH)] (8.6 g, 65 mmol) was dissolved in $CHCl_3$ (70 ml), and Et_3N (10.0 g, 99 mmol) was added. A solution of tosyl chloride (13.8 g, 72 mmol) in $CHCl_3$ (30 ml) was added dropwise with stirring and ice cooling and the whole was stirred for 12 h, then washed with an aqueous solution of $KHCO_3$ and H_2O. The solvent was evaporated off, the residue (18.7 g) was dissolved in acetone (75 ml), and 1 N HCl (225 ml) was added. The mixture was stirred at 80 °C for 30 min, then concentrated and extracted with AcOEt (450 ml). The extract was washed with H_2O, and the solvent was evaporated off. The residue was purified by silica gel column chromatography [solvent: $CHCl_3$–MeOH (40 : 1)] to give 10.86 g (yield, 67.8%) of (*S*)-3-tosyloxy-1,2-propanediol as colorless needles, mp 57—60 °C, $[\alpha]_D^{25} +9.66°$ ($c=7.35$, MeOH). NMR ($CDCl_3$) δ: 2.40 (3H, s, CH_3), 3.68—4.08 (5H, m, HO–CH_2–CH–CH_2–O–), 7.25 (2H, d, $J=7.5$ Hz, Ar-H), 7.70 (2H, d, $J=7.5$ Hz, Ar-H). (*S*)-3-Tosyloxy-1,2-propanediol (14.90 g, 60.5 mmol) was dissolved in THF (140 ml), and MeONa (6.49 g, 120 mmol) was added with ice cooling. The mixture was stirred for 2 h. Then Et_3N (27.8 ml, 300 mmol) was added, and a solution of 2-nitrobenzenesulfonyl chloride (66.5 g, 300 mmol) in THF (150 ml) was added dropwise. The reaction mixture was stirred for 12 h, then filtered, and the filtrate was concentrated. The residue was purified by silica gel column chromatography [solvent: benzene–$CHCl_3$ (2 : 1)] to give 7.31 g (yield, 46.6%) of the desired compound as a pale yellow viscous oil, $[\alpha]_D^{25} +2.8°$ ($c=15.2$, $CHCl_3$), NMR ($CDCl_3$) δ: 2.60—2.90 (2H, m, –$\underset{O}{CH}$–CH_2), 3.16—3.36 (1H,

m, –CH(O)–CH$_2$), 4.00—4.66 (2H, m, –O–CH$_2$–S–), 7.62—8.16 (4H, m, Ar-H). IR ν_{max}^{film} cm^{-1}: 3000 (⟨O⟩), 1365, 1180 (SO_2). *Anal.* Calcd for $C_9H_9NO_6S$: C, 41.70; H, 3.50; N, 5.40. Found: C, 41.66; H, 3.52; N, 5.18.

(2*S*)-3-(2-Nitrobenzenesulfonyloxy)-1,2-epoxypropane (11)——(*R*)-3-Tosyloxy-1,2-propanediol [mp 60—62 °C, $[\alpha]_D^{24}$ −9.25° (*c*=2.12, MeOH)] (24.4 g, 99 mmol) was dissolved in a mixture of MeOH (30 ml) and Et_2O (15 ml). With ice cooling and stirring, MeONa (6.5 g, 120 mmol) was added in four portions at intervals of 1 h. The insoluble materials were then removed by filtration from the reaction mixture, and the solvent was evaporated at below 30 °C to give the crude (*R*)-glycidol (8.4 g). The crude product (8.4 g, 99 mmol) was dissolved in THF (120 ml), and Et_3N (11.1 g, 109 mmol) was added. Then, 2-nitrobenzenesulfonyl chloride (24.2 g, 109 mmol) was added with cooling and stirring, and the mixture was stirred for 2 h. The insoluble materials were removed from the reaction mixture by filtration, and the solvent was evaporated off. The residue was purified by silica gel column chromatography [solvent: benzene–$CHCl_3$ (2:3)] to give 15.45 g (yield, 60.1%) of the desired product. $[\alpha]_D^{25}$ −2.8° (*c*=10.0, $CHCl_3$). NMR ($CDCl_3$) δ: 2.60—2.92 (2H, m, –CH(O)–CH$_2$) 3.16—3.36 (1H, m, –CH(O)–CH$_2$), 4.00—4.66 (2H, m, –CH$_2$–O–S–), 7.60—8.16 (4H, m, Ar-H). IR ν_{max}^{film} cm^{-1}: 3000 (⟨O⟩), 1365, 1180 (SO_2). *Anal.* Calcd for $C_9H_9NO_6S$: C, 41.70; H, 3.50; N, 5.40. Found: C, 41.76; H, 3.51; N, 5.29.

(2′*R*),(3*R*)-3,4-Dihydro-8-(2,3-epoxypropoxy)-3-nitroxy-2*H*-1-benzopyran (18)——Compound **4** (3.75 g, 17.7 mmol) was dissolved in anhydrous THF (30 ml), and a suspension of 50% NaH (0.85 g, 17.7 mmol) in THF (9 ml) was added with ice cooling. The mixture was stirred for 15 min. A solution of **12** (4.6 g, 17.7 mmol) in THF (25 ml) was added, and the whole was stirred at a bath temperature of 70—75 °C for 1.5 h. The precipitate was removed by filtration, and the solvent was evaporated off. The residue was dissolved in $CHCl_3$ (50 ml), and this solution was washed with 5% aqueous NaOH and then with H_2O. The solvent was evaporated off. Recrystallization of the residue from acetone–MeOH gave 3.89 g (yield, 82.0%) of the desired product as colorless needles, mp 141.0—142.5 °C, $[\alpha]_D^{25}$ +34.0° (*c*=2, $CHCl_3$). NMR ($CDCl_3$) δ: 2.64—2.92 (2H, m, –CH(O)–CH$_2$), 2.96—3.44 (3H, m, C_4, –CH(O)–CH$_2$), 3.84—4.52 (4H, m, C_2-H, –OCH$_2$CH), 5.26—5.48 (1H, m, C_3-H), 6.52—6.88 (3H, m, Ar-H). IR ν_{max}^{KBr} cm^{-1}: 1620, 1280 (ONO_2). *Anal.* Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.70; H, 4.82; N, 5.13.

(2′*S*),(3*R*)-3,4-Dihydro-8-(2,3-epoxypropoxy)-3-nitroxy-2*H*-1-benzopyran (17)——In the same manner as described for **18**, crude **17** was prepared from **4** (3.75 g, 17.7 mmol) and **11** (4.6 g, 17.7 mmol). Recrystallization of crude **17** from acetone–MeOH gave 4.3 g (yield, 90.6%) of the pure product as colorless needles, mp 131.5—132.0 °C, $[\alpha]_D^{25}$ +25.3° (*c*=2, $CHCl_3$). NMR ($CDCl_3$) δ: 2.68—2.96 (2H, m, –CH(O)–CH$_2$), 3.00—3.44 (3H, m, C_4-H, –CH(O)–CH$_2$), 3.92—4.52 (4H, m, C_2-H, –OCH$_2$CH), 5.28—5.52 (1H, m, C_3-H), 6.57—6.92 (3H, m, Ar-H). IR ν_{max}^{KBr} cm^{-1}: 1620, 1280 (ONO_2). *Anal.* Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.71; H, 4.85; N, 5.12.

(2′*S*),(3*S*)-3,4-Dihydro-8-(2,3-epoxypropoxy)-3-nitroxy-2*H*-1-benzopyran (19)——In the same manner as described for **18**, crude **19** was prepared from **5** (3.75 g, 17.7 mmol) and **11** (4.6 g, 17.7 mmol). Recrystallization of crude **19** from acetone–MeOH gave 4.0 g (yield, 85.7%) of the pure product as colorless needles, mp 141.0—142.5 °C, $[\alpha]_D^{25}$ −32.8° (*c*=2, $CHCl_3$). NMR ($CDCl_3$) δ: 2.64—2.92 (2H, m, –CH(O)–CH$_2$) 2.96—3.44 (3H, m, C_4-H, –CH(O)–CH$_2$), 3.84—4.52 (4H, m, C_2-H, –OCH$_2$–CH), 5.26—5.48 (1H, m, C_3-H), 6.52—6.88 (3H, m, Ar-H). IR ν_{max}^{KBr} cm^{-1}: 1620, 1280 (ONO_2). *Anal.* Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.76; H, 4.90; N, 5.12.

(2′*R*),(3*S*)-3,4-Dihydro-8-(2,3-epoxypropoxy)-3-nitroxy-2*H*-1-benzopyran (20)——In the same manner as described for **18**, crude **20** was prepared from **5** (3.75 g, 17.7 mmol) and **12** (4.6 g, 17.7 mmol). Recrystallization of crude **20** from acetone–MeOH gave 4.1 g (yield, 86.0%) of the pure product as colorless needles, mp 131.5—132.0 °C, $[\alpha]_D^{25}$ −24.8° (*c*=2, $CHCl_3$). NMR ($CDCl_3$) δ: 2.68—2.96 (2H, m, –CH(O)–CH$_2$), 3.00—3.44 (3H, m, C_4-H, –CH(O)–CH$_2$), 3.92—4.52 (4H, m, C_2-H, –OCH$_2$CH), 5.28—5.52 (1H, m, C_3-H), 6.57—6.92 (3H, m, Ar-H). IR ν_{max}^{KBr} cm^{-1}: 1620, 1280 (ONO_2). *Anal.* Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.80; H, 4.87; N, 5.13.

(2′*R*),(3*R*)-3,4-Dihydro-8-[2-hydroxy-3-(isopropylamino)propoxy]-3-nitroxy-2*H*-1-benzopyran (*R*,*R*-NIP) (15)——Isopropylamine (40 ml, 470 mmol) and EtOH (80 ml) were mixed, and **18** (3.9 g, 14.6 mmol) was added. The mixture was stirred at a bath temperature of 70 °C for 1 h, then evaporated to dryness. The residue was dissolved in $CHCl_3$ (40 ml) and extracted with 1.8% aqueous AcOH (80 ml). The extract was washed with benzene (20 ml), made alkaline with 2 N NaOH and extracted with $CHCl_3$ (100 ml). The extract was washed with H_2O, and the solvent was evaporated off. The residue was purified by alumina column chromatography (solvent: $CHCl_3$), and then recrystallized from benzene–hexane to give 4.08 g (yield, 85.7%) of the desired product as colorless needles, mp 140.3—141.0 °C, $[\alpha]_D^{25}$ +15.5° (*c*=2, $CHCl_3$). NMR ($CDCl_3$) δ: 1.07 (6H, d, *J*=6 Hz, CH_3), 2.20—3.44 (7H, m, C_4-

H, $-CH_2NHCH$, OH), 3.92—4.16 (3H, m, $-OCH_2CH$), 4.16—4.54 (2H, m, C_2-H), 5.33—5.53 (1H, m, C_3-H), 6.58—6.92 (3H, m, Ar-H). IR ν_{max}^{KBr} cm^{-1}: 1620, 1278 (ONO_2). *Anal.* Calcd for $C_{15}H_{22}N_2O_6$: C, 55.21; H, 6.79; N, 8.58. Found: C, 55.13; H, 6.81; N, 8.43.

(2′*S*),(3*R*)-3,4-Dihydro-8-[2-hydroxy-3-(isopropylamino)propoxy]-3-nitroxy-2*H*-1-benzopyran (*S*,*R*-NIP) (13) ——In the same manner as described for **15**, crude **13** was prepared from **17** (3.9 g, 14.6 mmol) and isopropylamine (40 ml, 470 mmol). Recrystallization from benzene–hexane gave 3.91 g (yield, 82.1%) of the pure product as colorless needles, mp 105.3—105.8 °C, $[\alpha]_D^{25}$ +16.2° (c=2, $CHCl_3$). NMR ($CDCl_3$)$\gamma\delta$: 1.07 (6H, d, J=6 Hz, CH_3), 2.20—3.44 (7H, m, C_4-H, $-CH_2NHCH$, OH), 3.88—4.12 (3H, m, $-OCH_2CH$), 4.12—4.52 (2H, m, C_2-H), 5.32—5.52 (1H, m, C_3-H), 6.56—6.92 (3H, m, Ar-H). IR ν_{max}^{KBr} cm^{-1}: 1620, 1278 (ONO_2). *Anal.* Calcd for $C_{15}H_{22}N_2O_6$: C, 55.21; H, 6.79; N, 8.58. Found: C, 55.19; H, 6.76; N, 8.53.

(2′*S*),(3*S*)-3,4-Dihydro-8-[2-hydroxy-3-(isopropylamino)propoxy]-3-nitroxy-2*H*-1-benzopyran (*S*,*S*-NIP) (14) ——In the same manner as described for **15**, crude **14** was prepared from **19** (3.9 g, 14.6 mmol) and isopropylamine (40 ml, 470 mmol). Recrystallization from AcOEt gave 3.51 g (yield, 73.6%) of the pure product as colorless needles, mp 140.5—141.0 °C, $[\alpha]_D^{25}$ −15.8° (c=2, $CHCl_3$). The NMR spectrum and IR spectrum of **14** were identical with those of **15**. *Anal.* Calcd for $C_{15}H_{22}N_2O_6$: C, 55.21; H, 6.79; N, 8.58. Found: C, 55.32; H, 6.82; N, 8.55.

(2′*R*),(3*S*)-3,4-Dihydro-8-[2-hydroxy-3-(isopropylamino)propoxy]-3-nitroxy-2*H*-1-benzopyran (*R*,*S*-NIP) (16) ——In the same manner as describerd for **15**, crude **16** was prepared from **20** (3.9 g, 14.6 mmol) and isopropylamine (40 ml, 470 mmol). Recrystallization from benzene–hexane gave 3.93 g (yield, 82.6%) of the pure product as colorless needles, mp 105.3—106.0 °C, $[\alpha]_D^{25}$ −16.7° (c=2, $CHCl_3$). The NMR spectrum and IR spectrum of **16** were identical with those of **13**. *Anal.* Calcd for $C_{15}H_{22}N_2O_6$: C, 55.21; H, 6.79; N, 8.58. Found: C, 55.27; H, 6.76; N, 8.70.

(2′*R*)-3,4-Dihydro-8-[2-hydroxy-3-(isopropylamino)propoxy]-3-nitroxy-2*H*-1-benzopyran (2′*R*-NIP) (10)—— Compound **1** (106 mg, 0.5 mmol) was dissolved in acetone (1 ml), and K_2CO_3 (69 mg, 0.5 mmol) and (*S*)-epichlorohydrin (93 mg, 1.0 mmol) were added. The mixture was stirred at 70 °C for 17 h. Purification of the reaction mixture by preparative thin layer chromatography (pTLC) gave **8** (31 mg) as colorless needles. This product (31 mg) was dissolved in EtOH (1.1 ml), and isopropylamine (1.1 ml, 12.9 mmol) was added. The mixture was stirred at 90 °C for 1 h, then purification by pTLC gave 34 mg (total yield, 20.1%) of **10** as a colorless viscous oil. $[\alpha]_D^{25}$ +2.6° (c=1.5, MeOH).

(2′*S*)-3,4-Dihydro-8-[2-hydroxy-3-(isopropylamino)propoxy]-3-nitroxy-2*H*-1-benzopyran (2′*S*-NIP) (9)——In the same manner as described for **10**, crude **9** was prepared from **1** (106 mg, 0.5 mmol), (*R*)-epichlorohydrin (93 mg, 1.0 mmol) and isopropylamine (1.1 ml, 12.9 mmol). Purification by pTLC gave 38 mg (total yield, 23.3%) of **9** as a colorless viscous oil. $[\alpha]_D^{25}$ 0° (c=1.9, MeOH).

Acknowledgement The authors wish to thank Prof. Toshio Kawasaki for X-ray crystal analysis and Mr. Akiyoshi Ohhira, Mr. Jiro Matsumoto and Miss Hatsumi Kato for technical assistance.

References and Notes

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