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Syntheses of Ring-Hydroxylated Nipradilols and Their Denitro Derivatives

TOSHIHIRO AKASHI, KIYOSHI KAWAMURA, MASAMI SHIRATSUCHI* and HIROSHI ISHIHAMA

Tokyo Research Laboratories, Kowa Co., Ltd., Noguchi-cho, Higashimurayama, Tokyo 189, Japan

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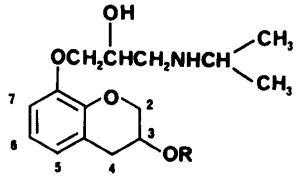
Nipradilol (NIP), 3,4-dihydro-8-(2-hydroxy-3-isopropylamino)propoxy-3-nitroxy-2*H*-1-benzopyran, is extensively metabolized in man and dogs. In order to identify the ring-hydroxylated metabolites we have synthesized *cis*- and *trans*-4-hydroxy-, and 5-hydroxy-NIP, their denitro derivatives and 7-hydroxy-denitro-NIP. As judged from their spectra, *trans*-4-hydroxy- and 5-hydroxy-NIP and their denitro derivatives corresponded to the isolated ring-hydroxylated metabolites. Moreover, a pharmacological study in anesthetized spontaneously hypertensive rat showed that the nitroxy derivatives caused a transient hypotensive response, and both the nitroxy derivatives and the denitro derivatives caused long-lasting bradycardia.

Keywords——nipradilol; 3,4-dihydro-8-(2-hydroxy-3-isopropylamino)propoxy-3-nitroxy-2*H*-1-benzopyran; antihypertensive agent; synthesis; ring-hydroxylated nipradilol; metabolite; structural identification; 5-hydroxy-nipradilol; *trans*-4-hydroxy-nipradilol; stereoselective oxidation

Nipradilol (NIP) is an antihypertensive agent with β-adrenergic blocking and vasodilating actions,[1] and is extensively metabolized in man and dogs by four distinct pathways (denitration, hydroxylation of the ring system, degradation of the side chain and glucuronidation).[2] Two isomeric monohydroxylated metabolites of NIP (M_1, M_2) were detected in the urine of dogs accompanying their denitro derivatives (D_1, D_2) and other metabolites.[2] A nuclear magnetic resonance (NMR) study of D_1 and D_2 suggested that D_1 might be a phenolic type compound, and D_2 might be an alcoholic type. In the NMR spectra, D_1 has an AB quartet with an *ortho*-coupling constant in the aromatic area, and D_2 has no peak corresponding to the 4-position of denitro-NIP (DNIP).[2] Therefore it was suggested that M_1 and D_1 might be oxidized at the 5- or 7-position, and M_2 and D_2 at the 4-position. M_2 and D_2 were also detected in human urine.[2] In some case the ring-hydroxylated β-adrenergic blocking agents have pharmacological activity. For example, 4′-hydroxypropranolol is equipotent with propranolol as a β-receptor antagonist and is believed to contribute to the activity of proparanolol in man.[3] Thus, it is important to investigate the pharmacological activity of ring-hydroxylated NIP. This report describes the syntheses of *cis*- and *trans*-4-hydroxy- and 5-hydroxy-NIP, their denitro derivatives and 7-hydroxy-DNIP, the structural identification of the metabolites, and the pharmacological activities of 5-hydroxy- and *trans*-4-hydroxy-NIP, and the denitro derivatives.



R: NO_2 (nipradilol, NIP)
R: H (denitro-nipradilol, DNIP)

Fig. 1

I. Syntheses of 5-Hydroxy-NIP and 5-Hydroxy-DNIP

We chose compound **1** as a starting material, and planned to convert the formyl moiety into a hydroxy moiety after transformation of the allyl derivative (**1**) into a bromohydrin derivative followed by cyclization to a benzopyran derivative. However, the desired bromohydrin derivative was not obtained in the reaction of **1** with either *N*-bromoacetamide (NBA) or *N*-bromosuccinimide (NBS). In the reaction the major product was the hemiacetal form (**2**), presumably produced by the reaction of the intermediate bromonium cation and the formyl moiety. A minor product was the lactone form (**3**), which might be produced by further oxidation of **2** with NBS (Chart 1).

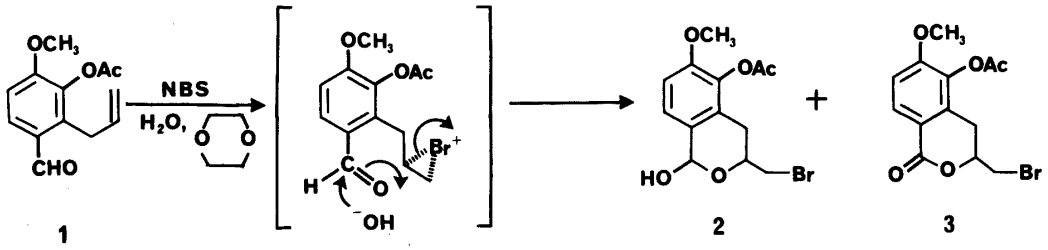


Chart 1

Furthermore, the reaction of an allyl derivative having an acetyl moiety instead of **1** with NBS did not produce the desired bromohydrin derivative, but afforded a complex mixture of products. We next chose a compound having a cyano moiety (**4**) as a starting material (Chart 2). Alkylation of **4** with allyl chloride, followed by Claisen rearrangement gave the phenol **6**. After acetylation of **6** with Ac_2O, oxidation of the resulting acetate having an allyl moiety (**7**) with *m*-chloroperbenzoic acid (*m*-CPBA), followed by treatment with HCl in dioxane, afforded **9** with rearrangement of the acetyl moiety.[4] A benzopyran derivative **10** was obtained on treatment of **9** with K_2CO_3. The transformation of the cyano moiety into a

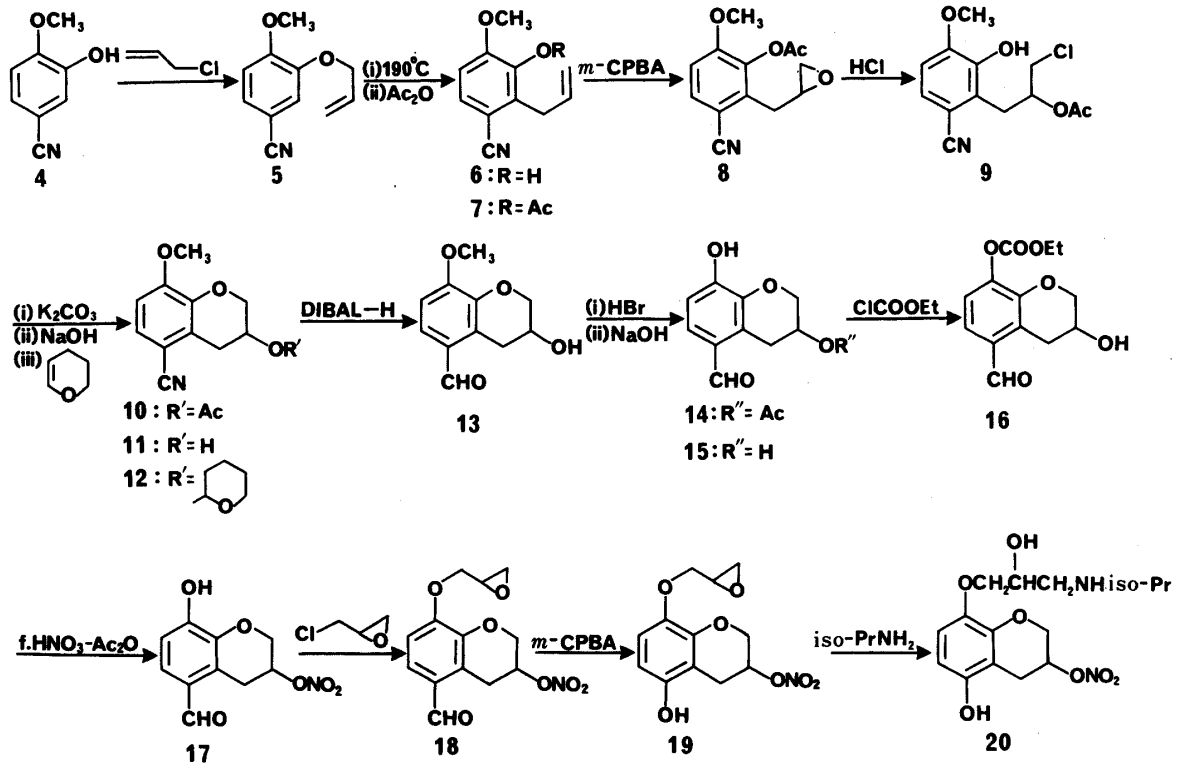


Chart 2. Synthesis of 5-Hydroxy-NIP

formyl moiety was performed with diisobutylaluminum hydride (DIBAL-H).[5] Compound **16**, which was obtained by demethylation of **13** with HBr in AcOH and protection of **15** at the 8-position with ethylchloroformate, was nitrated with fum.HNO_3 in Ac_2O at low temperature. Finally 5-hydroxy-NIP (**20**) was obtained by alkylation of **17** with epichlorohydrin, Baeyer–Villiger oxidation of **18** with *m*-CPBA, and amination of **19** with isopropylamine (Chart 2).

5-Hydroxy-DNIP (**23**) was synthesized by the reaction of **15** with allyl chloride, oxidation of **21** with *m*-CPBA, and amination of **22** with isopropylamine (Chart 3).

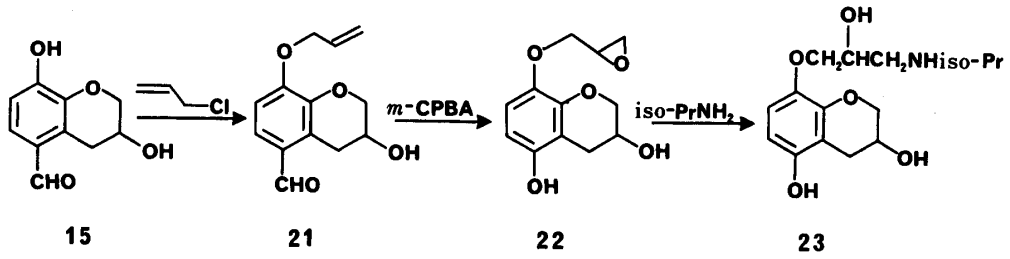


Chart 3. Synthesis of 5-Hydroxy-DNIP

II. Synthesis of 7-Hydroxy-DNIP

Methylation of the starting material **24** with methyl iodide, followed by alkylation with allyl chloride, afforded the allyl ether **26**. Claisen rearrangement of **26** gave the phenol **27**, which was acetylated with Ac_2O. Reaction of the olefin **28** with NBA–H_2O–acetone, followed by treatment with HCl in dioxane,[4] produced a mixture of acetates of the bromohydrins (**31** and **32**). Ring closure of the mixture (**31** and **32**) with K_2CO_3, followed by hydrolysis with NaOH, afforded a mixture of alcohols, which were separated by silica gel column chromatography to give the benzopyran derivative **35** and the benzofuran derivative. Compound **35** was

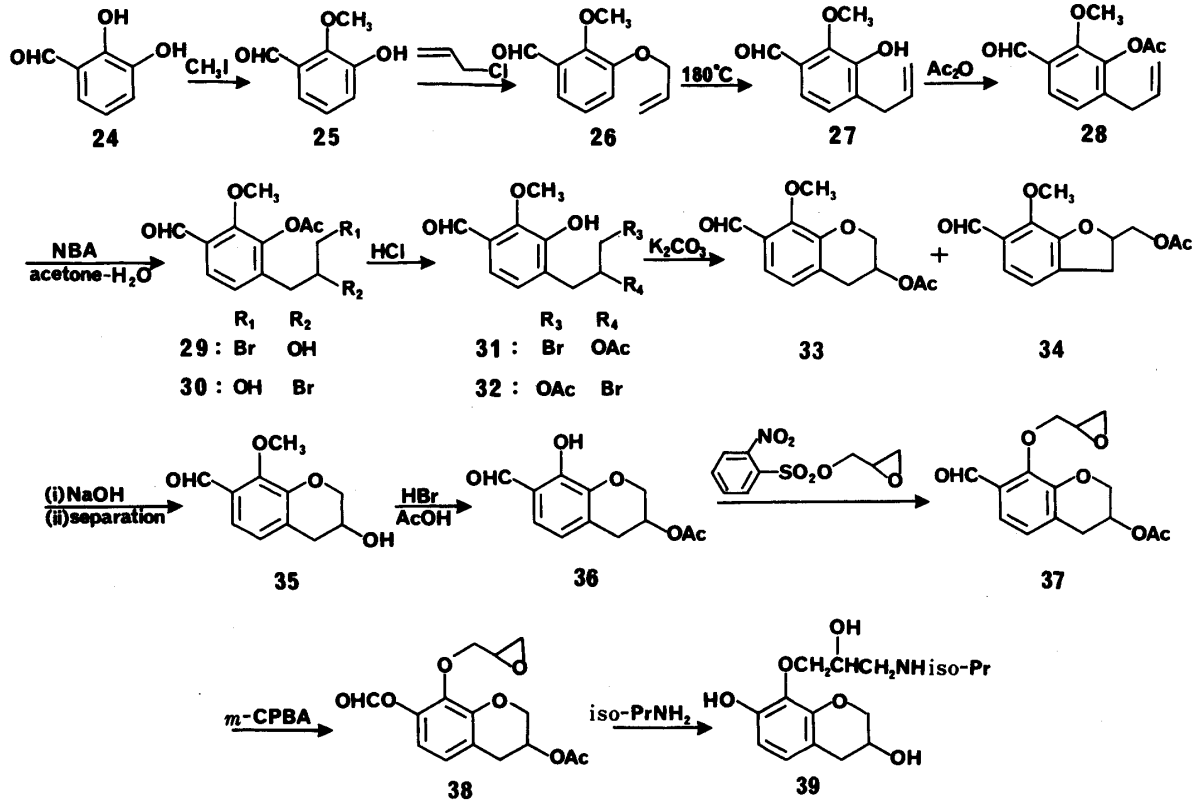
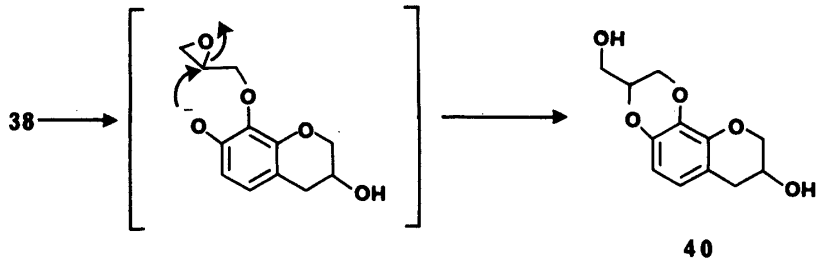


Chart 4. Synthesis of 7-Hydroxy-DNIP

demethylated with HBr in AcOH, and alkylated with glycidol-*o*-nitrobenzenesulfonate[6] to give the epoxide **37**. After Baeyer–Villiger oxidation of **37** with *m*-CPBA, 7-hydroxy-DNIP (**39**) was obtained by amination of the epoxide **38** with isopropylamine (Chart 4). In the last step, the yield was low (10.4%) because of the intramolecular reaction; the phenolate anion attacked the epoxide to form **40** (Chart 5).



40

Chart 5

III. Syntheses of *trans*-, *cis*-4-Hydroxy-NIP and Their Denitro Derivatives

First, compound **41**, which is a key compound in the synthesis of NIP,[7] was protected at the 8-position with ethylchloroformate, and sulfonated at the 3-position with methanesulfonyl chloride to give **43**, which was treated with alkali to give 8-hydroxy-2*H*-1-benzopyran (**44**). Acetylation of **44** with Ac_2O, followed by oxidation of the C_3–C_4 double bond with 40% peracetic acid, afforded a mixture of *cis*- and *trans*-4,8-diacetoxy-3,4-dihydro-3-hydroxy-2*H*-1-benzopyran (**46**) as a pale yellow oil. The mixture was not separated (Chart 6).

The NMR spectrum of the mixture revealed the methyl signals of two acetates (main product $\delta=2.11$ ppm; minor product $\delta=2.16$ ppm) and signals of two protons adjacent to the acetate groups (C_4-H of main product $\delta=5.79$ ppm, d, $J=3.9$ Hz; C_4-H of minor product $\delta=6.03$ ppm, d, $J=3.7$ Hz) in a ratio of 7 : 1. Lap *et al.* reported an NMR study of many *cis*- and *trans*-3,4-dihydro-3,4-disubstituted-2*H*-1-benzopyran derivatives.[8] The protons at the 3- and 4-position in the *trans*-isomers generally gave signals at higher field than those in the *cis*-isomers. The NMR spectra of *cis*- and *trans*-4-acetoxy-3,4-dihydro-3-hydroxy-6-methyl-2*H*-1-benzopyran showed the methyl signals of the acetates (the *trans*-isomer $\delta=2.12$ ppm; the *cis*-isomer $\delta=2.17$ ppm) and the signals of the protons at the 4-position (the *trans*-isomer $\delta=5.75$ ppm, d, $J=4.0$ Hz; the *cis*-isomer $\delta=6.02$ ppm, d, $J=3.0$ Hz).

Therefore we presumed that the main product was the 3,4-*trans*-isomer, and the minor product was the 3,4-*cis*-isomer. Moreover, *cis*-3,4-dihydro-3,4,8-triacetoxy-2*H*-1-benzopyran (**58**) was obtained stereospecifically from compound **45** by Woodward's method,[9] which is a general method to obtain stereospecifically a *cis* diol from an olefin (Chart 7). The NMR spectrum of **58** coincided with that of the minor product in the mixture **46**.

Thus, the stereoselective oxidation of **45** with 40% peracetic acid resulted in a mixture of 3,4-*trans*-isomer and 3,4-*cis*-isomer in a ratio of 7 : 1.

The mixture **46** was deacetylated selectively at the 8-position with piperidine, and protected at the 8-position with trichloroacetyl chloride. After nitration of **48** with fum.HNO_3–Ac_2O, **49** was deprotected with isopropylamine, and separated on a silica gel column to give *trans*- and *cis*-3,4-dihydro-4,8-dihydroxy-3-nitroxy-2*H*-1-benzopyran (**50**, **51**, respectively). Finally, alkylation of **50** and **51** with epichlorohydrin, followed by amination with isopropylamine, afforded *trans*- and *cis*-4-hydroxy-NIP (**54**, **55**), respectively.

Further, *trans*- and *cis*-4-hydroxy-DNIP was obtained by hydrogenation of **54** and **55** on Pd–C, respectively (Chart 6).

Since **50**, **51**, and epichlorohydrin are racemic compounds, **52**—**57** are mixtures of two racemates, and consequently their melting ranges are broad.

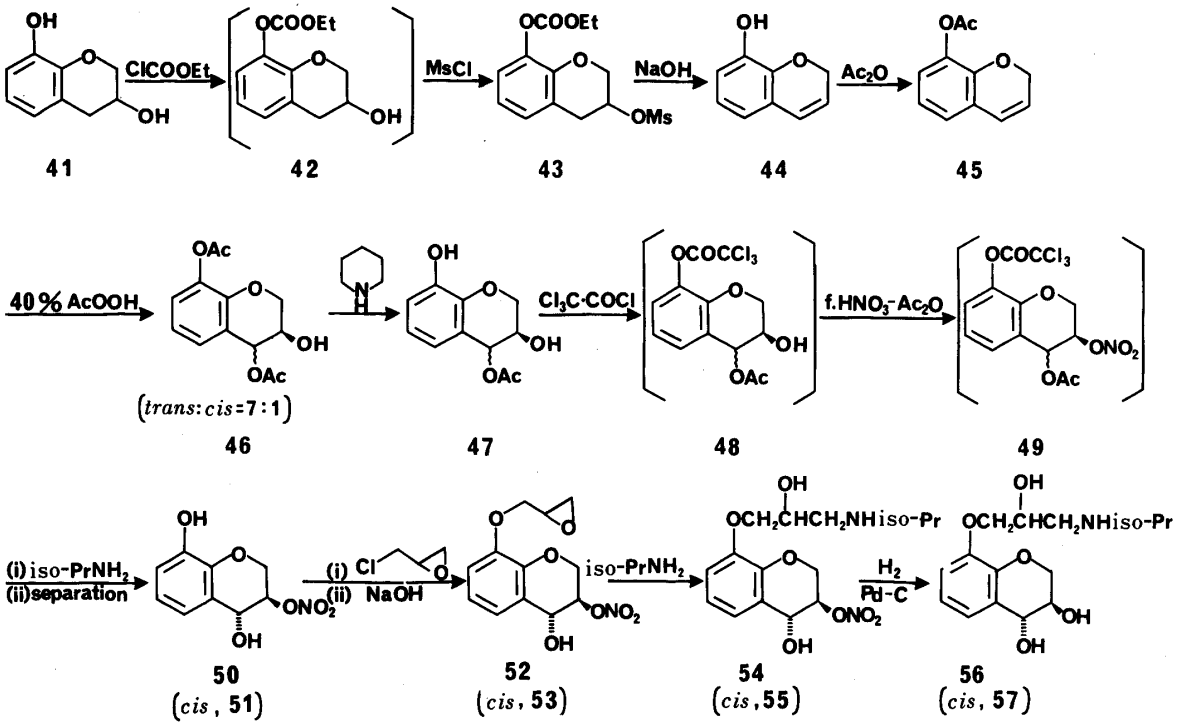


Chart 6[a]. Synthesis of *trans*-4-Hydroxy- and *cis*-4-Hydroxy-NIP, and Their Denitro Derivatives

a) All stereochemical diagrams represent only one enantiomer of racemic compounds.

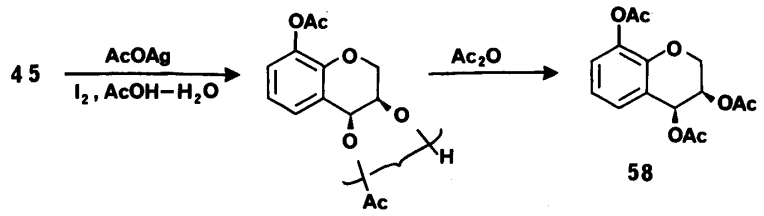


Chart 7[a]. Woodward's Method

a) All stereochemical diagrams represent only one enantiomer of racemic compounds.

IV. Structural Identification of Ring-Hydroxylated NIP

As reported by Yoshimura *et al.*,[2] two isomeric monohydroxylated NIPs (M_1, M_2) and their denitro derivatives (D_1, D_2) were detected in the urine of dogs. M_1 corresponded spectrally to the synthetic 5-hydroxy-NIP (NMR, infrared (IR) and mass spectrum (MS)). The NMR spectrum of the denitro derivative (D_1) had an AB quartet (δ: 6.26 and 6.65 ppm) with an *ortho*-coupling constant ($J=8.6$ Hz) in the aromatic area. The synthetic 5-hydroxy-DNIP and 7-hydroxy-DNIP had AB quartets at δ: 6.26 and 6.65 ppm, $J=8.6$ Hz, and δ: 6.29 and 6.53 ppm, $J=8.3$ Hz, respectively. Thus, it was proved that the aromatic ring of NIP was hydroxylated at the 5-position.

A small amount of another hydroxy-NIP (M_2) was detected by selected ion monitoring (GC-MS), and its denitro derivative (D_2) was isolated in sufficient amount for spectral analysis. The NMR spectrum of D_2, showed a 4-position methine signal (δ: 4.44 ppm). The synthetic *trans*-4-hydroxy-DNIP and *cis*-4-hydroxy-DNIP showed this methine signal at δ: 4.44 and 4.68 ppm, respectively. Moreover, the isolated metabolite (D_2) corresponded to the synthetic *trans*-4-hydroxy-DNIP in the gas chromatogram.[2] Thus, aliphatic hydroxylation occurred at the 4-position with *trans*-configration.

The ring-hydroxylated metabolites in human urine were *trans*-4-hydroxy-NIP (M_2) and its denitro derivative (D_2). Details of this work were reported by Yoshimura *et al.*[2)]

V. Pharmacological Activity of Ring-Hydroxylated Metabolites of NIP

The effects of NIP and its metabolites on blood pressure and heart rate was studied in anesthetized spontaneously hypertensive rats (SHRs).

NIP at a dose of 1 mg/kg caused long-lasting hypotensive response and bradycardia. *trans*-4-Hydroxy-, and 5-hydroxy-NIP at a dose of 1 mg/kg caused a transient hypotensive response and long-lasting bradycardia. *trans*-4-Hydroxy-DNIP at a dose of 1 mg/kg did not produce a hypotensive response, while it caused long-lasting bradycardia.

Experimental

All melting points are uncorrected. IR absorption spectra were obtained with JASCO IRA-1 and Shimadzu IR-435 spectrometers. NMR spectra were measured with 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 low- and high-resolution mass spectra were obtained with JEOL JMS-D100, JEOL JMS-D300 and JEOL JMS-DX300 mass spectrometers in the electron impact mode at an ionization potential of 70 eV. Preparative thin-layer chromatography (TLC) was performed on E. Merck Silica gel 60 PF_{254}, and TLC on E. Merck Silica gel 60 F_{254}. Column chromatography was performed on Wako Silica gel (C-200). All the organic extracts were dried over anhydrous Na_2SO_4 prior to evaporation, which was performed under reduced pressure.

3-Allyloxy-4-methoxy-benzonitrile (5)——Allyl chloride (24.0 g) and K_2CO_3 (36.0 g) were added to a solution of **4** (38.9 g) in *N,N*-dimethylformamide (DMF) (190 ml). The reaction mixture was stirred at 100 °C for 1 h, then poured into water and extracted with ether. The extract was washed with 1 N NaOH, and brine, and evaporated to give a solid (48.2 g), which was recrystallized from ether–petr. ether to give 44.7 g (90.6%) of **5** as pale yellow needles, mp 41—43 °C. IR (KBr): 2220 (CN) cm^{-1}. NMR (CCl_4) δ: 3.86 (3H, s, OCH_3), 4.44—4.62 (2H, m, $-C\underline{H}_2CH=CH_2$), 5.18—5.54 (2H, m, $-OCH_2CH=C\underline{H}_2$), 5.80—6.22 (1H, m, $-OCH_2C\underline{H}=CH_2$), 6.82 (1H, d, J=8 Hz, ArH), 6.96—7.26 (2H, m, ArH). *Anal.* Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.87; H, 5.87; N, 7.33.

2-Allyl-3-hydroxy-4-methoxy-benzonitrile (6)——Compound **5** (44.4 g) was heated at 190 °C for 2.5 h under an atmosphere of nitrogen. Ether was added to the reaction mixture, and the ether solution was extracted with 10% NaOH. After being made acidic with conc. HCl, the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with brine, and evaporated to give a crude solid, which was chromatographed on a silica gel column (benzene). Recrystallization from benzene–hexane gave 40.9 g (92.1%) of **6** as colorless needles, mp 91.5 °C. IR (KBr): 3320 (OH), 2240 (CN) cm^{-1}. NMR ($CDCl_3$) δ: 3.52—3.68 (2H, m, $-C\underline{H}_2CH=CH_2$), 3.94 (3H, s, OCH_3), 4.96—5.24 (2H, m, $-CH_2CH=C\underline{H}_2$), 5.74—6.12 (1H, m, $-CH_2C\underline{H}=CH_2$), 5.86 (1H, s, OH), 6.76 (1H, d, J=8 Hz, ArH), 7.18 (1H, d, J=8 Hz, ArH). *Anal.* Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.72; H, 5.88; N, 7.13.

3-Acetoxy-2-allyl-4-methoxy-benzonitrile (7)——A solution of acetic anhydride (44.1 g) in CH_2Cl_2 (180 ml), and then a solution of triethylamine (43.7 g) in CH_2Cl_2 (180 ml) were added to a solution of **6** (40.9 g) in CH_2Cl_2 (600 ml). The reaction mixture was stirred for 20 h at room temperature, then water was added, and the whole was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with 2 N HCl, satd. $NaHCO_3$, and brine, and evaporated to give a crude solid, which was recrystallized from benzene–hexane to give 47.85 g (95.7%) of **7** as colorless prisms, mp 89 °C. IR (KBr): 2220 (CN), 1770 (C=O) cm^{-1}. NMR ($CDCl_3$) δ: 2.30 (3H, s, $OCOCH_3$), 3.44—3.60 (2H, m, $-C\underline{H}_2CH=CH_2$), 3.86 (3H, s, OCH_3), 4.96—5.22 (2H, m, $-CH_2CH=C\underline{H}_2$), 5.60—6.06 (1H, m, $-CH_2C\underline{H}=CH_2$), 6.88 (1H, d, J=8 Hz, ArH), 7.50 (1H, d, J=8 Hz, ArH). *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.39; H, 5.68; N, 5.89.

3-Acetoxy-2-(2,3-epoxy)propyl-4-methoxy-benzonitrile (8)——*m*-Chloroperbenzoic acid (80%, 121 g) was added portionwise to a solution of **7** (47.85 g) in CH_2Cl_2 (1.0 l) with stirring and ice-cooling. The mixture was stirred for 41 h at room temperature, then 10% Na_2CO_3 was added dropwise. The organic layer was washed with 10% Na_2SO_3, 10% Na_2CO_3, and brine, and evaporated to give a crude product, which was chromatographed on a silica gel column (hexane : AcOEt = 2 : 1). Recrystallization from AcOEt–hexane gave 43.55 g (85.1%) of **8** as colorless prisms, mp 82.5—83.5 °C. IR (KBr): 2220 (CN), 1770 (C=O) cm^{-1}. NMR ($CDCl_3$) δ: 2.34 (3H, s, $OCOCH_3$), 2.54—2.84 (2H, m, $-CH_2-\underset{\backslash O /}{CH}-C\underline{H}_2$), 2.88—3.24 (3H, m, $-C\underline{H}_2C\underline{H}-CH_2$), 3.88 (3H, s, OCH_3), 6.91 (1H, d, J=8 Hz, ArH), 7.54 (1H, d, J=8 Hz, ArH). *Anal.* Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 62.98; H, 5.28; N, 5.48.

2-(2-Acetoxy-3-chloro)propyl-3-hydroxy-4-methoxy-benzonitrile (9)——An 18.5% HCl–dioxane solution (262 g) was added slowly to a solution of **8** (41.05 g) in dioxane (330 g) stirring and ice-cooling. After being stirred for 48 h at room temperature, the reaction mixture was neutralized with satd. $NaHCO_3$, and extracted with AcOEt. The AcOEt layer was washed with brine, and evaporated to give a crude product, which was chromatographed on a silica gel column ($CHCl_3$: hexane = 10 : 1). Recrystallization from AcOEt–hexane gave 37.1 g (78.8%) of **9** as colorless needles,

mp 113—114 °C. IR (KBr): 3240 (OH), 2230 (CN), 1740 (C=O) cm^{-1}. NMR ($CDCl_3$) δ: 2.04 (3H, s, $OCOCH_3$), 3.16—3.32 (2H, m, $-CH_2-CH(OAc)-CH_2Cl$), 3.60—3.76 (2H, m, $-CH_2Cl$), 3.95 (3H, s, OCH_3), 5.27—5.52 (1H, m, $-CH_2CH(OAc)$), 6.08 (1H, s, OH), 6.80 (1H, d, J=8 Hz, ArH), 7.18 (1H, d, J=8 Hz, ArH). *Anal.* Calcd for $C_{13}H_{14}ClNO_4$: C, 55.04; H, 4.97; N, 4.94. Found: C, 55.19; H, 4.96; N, 4.93.

3-Acetoxy-5-cyano-3,4-dihydro-8-methoxy-2*H*-1-benzopyran (10)——A mixture of **9** (37.1 g), K_2CO_3 (23.5 g) and DMF (470 ml) was stirred for 1 h at room temperature. After addition of water, the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with brine, and evaporated to give a solid, which was recrystallized from acetone to give 29.2 g (90.3%) of **10** as colorless prisms, mp 178—180 °C. IR (KBr): 2220 (CN), 1730 (C=O) cm^{-1}. NMR ($CDCl_3$) δ: 2.06 (3H, s, $OCOCH_3$), 2.88—3.46 (2H, m, C_4-H), 3.92 (3H, s, OCH_3), 4.06—4.52 (2H, m, C_2-H), 5.26—5.42 (1H, m, C_3-H), 6.77 (1H, d, J=8 Hz, C_7-H), 7.24 (1H, d, J=8 Hz, C_6-H). *Anal.* Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.00; H, 5.33; N, 5.58.

5-Cyano-3,4-dihydro-3-hydroxy-8-methoxy-2*H*-1-benzopyran (11)——A 10% NaOH solution (19 ml) was added to a solution of **10** (3.121 g) in tetrahydrofuran (THF) (63 ml). The mixture was stirred for 30 min at room temperature, then MeOH (15 ml) was added. The solution was stirred for 40 min at room temperature and neutralized with 2 N HCl. After removal of the organic solvent, the residue was diluted with water, and extracted with AcOEt. The AcOEt layer was washed with brine, and evaporated to give a crude solid, which was recrystallized from benzene to give 2.367 g (91.4%) of **11** as colorless needles, mp 140—142 °C. IR (KBr): 3500 (OH), 2220 (CN) cm^{-1}. NMR ($CDCl_3$) δ: 2.41 (1H, d, J=6 Hz, OH), 2.80—3.36 (2H, m, C_4-H), 3.92 (3H, s, OCH_3), 4.16—4.56 (3H, m, C_2-, C_3-H), 6.78 (1H, d, J=8 Hz, C_7-H), 7.26 (1H, d, J=8 Hz, C_6-H). *Anal.* Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.13; H, 5.41; N, 6.73.

5-Cyano-3,4-dihydro-8-methoxy-3-tetrahydropyranyloxy-2*H*-1-benzopyran (12)——Benzene (40 ml), a solution of dihydropyran (1.098 g) in benzene (20 ml), and then *p*-toluensulfonic acid (100 mg) were added successively to a solution of **11** (2.233 g) in THF (20 ml). The mixture was stirred for 15 h at room temperature, then a solution of dihydropyran (275 mg) in benzene (5 ml) was added. The reaction mixture was stirred for 24 h at room temperature, made alkaline with satd. $NaHCO_3$ to pH 8—9, and extracted with AcOEt. The AcOEt layer was washed with brine, and evaporated to give a crude oil, which was chromatographed on a silica gel column ($CHCl_3$: benzene = 10 : 1) to give 3.14 g (100%) of **12** as a colorless oil. IR (neat): 2220 (CN) cm^{-1}. NMR ($CDCl_3$) δ: 1.40—2.00 (6H, m, dihydropyran ring), 2.92—3.20 (2H, m, C_4-H), 3.38—3.66 (2H, m, dihydropyran ring), 3.88 (3H, s, OCH_3), 4.10—4.44 (3H, m, C_2-, C_3-H), 4.72—4.98 (1H, m, dihydropyran ring), 6.72 (1H, d, J=8 Hz, C_7-H), 7.18 (1H, d, J=8 Hz, C_6-H). MS *m/z*: 289 (M^+).

3,4-Dihydro-5-formyl-3-hydroxy-8-methoxy-2*H*-1-benzopyran (13)——Under an atmosphere of nitrogen, diisobutylaluminum hydride (25% toluene solution, 7.6 ml) was added dropwise through a dry syringe to a solution of **12** (3.055 g) in dry benzene (52 ml). The mixture was stirred for 2 h at room temperature, then cooled in an ice-water bath, and MeOH (6 ml), water (15 ml), and then AcOEt were added slowly. The mixture was filtered on celite, and the organic layer was separated from the filtrate, and evaporated to give a crude oil. A solution of the crude oil in THF (50 ml) was treated with 2 N HCl (50 ml), and the reaction mixture was stirred for 30 min at room temperature. The solution was neutralized with satd. $NaHCO_3$, and extracted with AcOEt. The AcOEt layer was washed with brine, and evaporated to give crude crystals, which were recrystallized from benzene to give 1.641 g (74.6%) of **13** as colorless needles, mp 124—125 °C. IR (KBr): 3500 (OH), 1675 (C=O) cm^{-1}. NMR ($CDCl_3$) δ: 2.60 (1H, br s, OH), 3.08—3.62 (2H, m, C_4-H), 3.82 (3H, s, OCH_3), 4.08—4.36 (3H, m, C_2-, C_3-H), 6.84 (1H, d, J=8 Hz, C_7-H), 7.36 (1H, d, J=8 Hz, C_6-H), 9.88 (1H, s, CHO). *Anal.* Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.15; H, 5.76.

3-Acetoxy-3,4-dihydro-5-formyl-8-hydroxy-2*H*-1-benzopyran (14)——A mixture of **13** (991 mg) and 25% HBr (acetic acid, 57 ml) was heated at 80 °C in a sealed tube for 4 h, then 10% NaOH (90 ml) was added slowly with ice-cooling. The solution was extracted with AcOEt. The AcOEt layer was washed with brine, and evaporated to give a brown oil, which was chromatographed on a silica gel column ($CHCl_3$) to give a solid. Recrystallization from benzene–hexane gave 961 mg (85.5%) of **14** as slightly brown needles, mp 115—117 °C. IR (KBr): 3260 (OH), 1710 (acetate C=O), 1680 (formyl C=O) cm^{-1}. NMR ($CDCl_3$) δ: 2.06 (3H, s, $OCOCH_3$), 3.38—3.56 (2H, m, C_4-H), 4.06—4.50 (2H, m, C_2-H), 5.24—5.44 (1H, m, C_3-H), 6.30 (1H, br s, OH), 6.92 (1H, d, J=8 Hz, C_7-H), 7.35 (1H, d, J=8 Hz, C_6-H), 9.88 (1H, s, CHO). *Anal.* Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 61.07; H, 5.04.

3,4-Dihydro-3,8-dihydroxy-5-formyl-2*H*-1-benzopyran (15)——A mixture of **14** (961 mg) and 1 N NaOH (12 ml) was stirred for 30 min at room temperature, and washed with $CHCl_3$. After acidification with 2 N HCl, the solution was extracted with AcOEt. The AcOEt layer was washed with brine, and evaporated to give a crude solid, which was recrystallized from acetone–hexane to give 464 mg (58.7%) of **15** as pale yellow needles, mp 134—135 °C. IR (KBr): 3325 (OH), 1660 (C=O) cm^{-1}. NMR (DMSO-d_6) δ: 2.82—3.52 (2H, m, C_4-H), 3.74—4.20 (3H, m, C_2-, C_3-H), 5.06 (1H, br s, alcoholic OH), 6.76 (1H, d, J=8 Hz, C_7-H), 7.27 (1H, d, J=8 Hz, C_6-H), 9.83 (1H, s, phenolic OH), 9.89 (1H, s, CHO). *Anal.* Calcd for $C_{10}H_{10}O_4 \cdot 0.1H_2O$: C, 61.28; H, 5.25. Found: C, 61.25; H, 5.16.

3,4-Dihydro-8-ethoxycarbonyloxy-5-formyl-3-hydroxy-2*H*-1-benzopyran (16)——A solution of triethylamine (295 mg) in THF (1 ml), and then a solution of ethylchloroformate (316 mg) in THF (1.5 ml) were added dropwise to a solution of **15** (518 mg) in THF (7 ml) below −5 °C. The reaction mixture was stirred for 2 h below 0 °C. The resulting precipitate was filtered off, and the filtrate was evaporated. The residue was chromatographed on a silica gel column

($CHCl_3$) to give 675 mg (95.0%) of **16** as a colorless oil. IR (neat): 3420 (OH), 1765 (carbonate C=O), 1690 (formyl C=O) cm^{-1}. NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$), 2.98 (1H, br s, OH), 3.20—3.42 (2H, m, C_4-H), 4.02—4.48 (3H, m, C_2-, C_3-H), 4.31 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), 7.14 (1H, d, J=8 Hz, C_7-H), 7.38 (1H, d, J=8 Hz, C_6-H), 9.98 (1H, s, CHO).

3,4-Dihydro-5-formyl-8-hydroxy-3-nitroxy-2*H*-1-benzopyran (17)——A solution of fum. HNO_3 (271 mg) in Ac_2O (439 mg) (prepared below −10 °C) was added dropwise to a solution of **16** (572 mg) in acetonitrile (6 ml) below −10 °C. The mixture was stirred for 30 min below −10 °C, then a solution of fum. HNO_3 (41 mg) in Ac_2O (66 mg) was added dropwise below −10 °C. The whole was stirred for 30 min below −10 °C, then satd. $NaHCO_3$ was added until the mixture was neutralized. The mixture was extracted with AcOEt, and the AcOEt layer was washed with brine, and evaporated to give 689 mg of a yellow oil, which was dissolved in MeOH (5.0 ml). To this solution, 1 N NaOH (4.6 ml) was added, and the mixture was stirred for 20 min at room temperature, then acidified with 2 N HCl. The MeOH was removed, and the residue was extracted with AcOEt. The AcOEt layer was washed with brine, and evaporated to give a crude product, which was chromatographed on a silica gel column ($CHCl_3$). Recrystallization from benzene–hexane gave 319 mg (62.1%) of **17** as yellow prisms, mp 132—136 °C. IR (KBr): 3360 (OH), 1665 (C=O), 1630, 1260 (ONO_2) cm^{-1}. NMR ($CDCl_3$) δ: 3.59 (2H, d, J=5 Hz, C_4-H), 4.16—4.70 (2H, m, C_2-H), 5.40—5.60 (1H, m, C_3-H), 6.12 (1H, br s, OH), 6.94 (1H, d, J=8 Hz, C_7-H), 7.35 (1H, d, J=8 Hz, C_6-H), 9.84 (1H, s, CHO). *Anal.* Calcd for $C_{10}H_9NO_6$: C, 50.21; H, 3.79; N, 5.86. Found: C, 50.38; H, 3.83; N, 5.96.

3,4-Dihydro-8-(2,3-epoxy)propoxy-5-formyl-3-nitroxy-2*H*-1-benzopyran (18)——Epichlorohydrin (439 mg) was added to a solution of **17** (249 mg) in 1 N NaOH (2.08 ml). The mixture was stirred for 21 h at room temperature, then dioxane (2 ml) and 1 N NaOH (0.4 ml) were added. After being stirred for 1 h at room temperature, the reaction mixture was diluted with water, and extracted with AcOEt. The AcOEt layer was washed with brine, and evaporated to give a crude solid, which was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with 1 N NaOH, and brine, and evaporated to give the crystals, which were purified by prep. TLC ($CHCl_3$: acetone = 5 : 1) to give 158 mg (51.5%) of **18** as pale yellow crystals, mp 155—170 °C. IR (KBr): 1685 (C=O), 1620, 1280 (ONO_2) cm^{-1}. NMR ($CDCl_3$) δ: 2.72—3.04 (2H, m, $-C\underline{H}(O)-C\underline{H}_2$), 3.30—3.52 (1H, m, $-C\underline{H}(O)-CH_2$), 3.59 (2H, d, J=5 Hz, C_4-H), 3.80—4.74 (4H, m, C_2-H, $-C\underline{H}_2C\underline{H}(O)-CH_2$), 5.40—5.60 (1H, m, C_3-H), 6.95 (1H, d, J=8 Hz, C_7-H), 7.38 (1H, s, J=8 Hz, C_6-H), 9.88 (1H, s, CHO). MS Calcd for $C_{13}H_{13}NO_7$: M, 295.0690. Found m/z: M^+, 295.0685.

3,4-Dihydro-8-(2,3-epoxy)propoxy-5-hydroxy-3-nitroxy-2*H*-1-benzopyran (19)——*m*-Chloroperbenzoic acid (80%, 384 mg) was added portionwise to a solution of **18** (175 mg) in CH_2Cl_2 (11 ml) with stirring and ice-cooling. The mixture was stirred for 18 h at room temperature, then MeOH (4 ml) and 1 N NaOH (4 ml) were added. After further stirring for 1 h at room temperature, the solution was acidified with 1 N HCl to pH 5, made alkaline with satd. $NaHCO_3$ to pH 8, and extracted with AcOEt. The organic layer was washed with brine, and evaporated to give a crude solid, which was purified by prep. TLC (AcOEt : hexane = 1 : 1) to give 104 mg (62.1%) of **19** as pale yellow crystals, mp 120—126 °C. IR (KBr): 3425 (OH), 1620, 1280 (ONO_2) cm^{-1}. NMR ($CDCl_3$) δ: 2.60—2.96 (2H, m, $-CH(O)-C\underline{H}_2$), 2.96—3.14 (2H, m, C_4-H), 3.28—3.44 (1H, m, $-C\underline{H}(O)-CH_2$), 3.80—4.56 (4H, m, C_2-H, $-C\underline{H}_2CH(O)-CH_2$), 4.56—5.32 (1H, m, OH), 5.32—5.52 (1H, m, C_3-H), 6.26 (1H, d, J=8 Hz, C_6-H), 6.70 (1H, d, J=8 Hz, C_7-H). MS Calcd for $C_{12}H_{13}NO_7$: M, 283.0692. Found m/z: M^+, 283.0692.

3,4-Dihydro-5-hydroxy-8-(2-hydroxy-3-isopropylamino)propoxy-3-nitroxy-2*H*-1-benzopyran (20)——A mixture of **19** (40 mg), isopropylamine (84 mg), and MeOH (2 ml) was heated at reflux for 30 min, then evaporated to dryness. The residue was purified by prep. TLC ($CHCl_3$: 16% NH_3 in MeOH = 5 : 1) to give 27.5 mg (56.9%) of **20** as an amorphous material. IR (KBr): 1625, 1280 (ONO_2) cm^{-1}. NMR (CD_3OD) δ: 1.11 (6H, d, J=6 Hz, $-CH(C\underline{H}_3)_2$), 2.56—3.14 (5H, m, $-C\underline{H}_2NHC\underline{H}$, C_4-H), 3.82—4.60 (5H, m, $-OC\underline{H}_2C\underline{H}OH$, C_2-H), 5.42—5.60 (1H, m, C_3-H), 6.30 (1H, d, J=8 Hz, C_6-H), 6.69 (1H, d, J=8 Hz, C_7-H). *Anal.* Calcd for $C_{15}H_{22}N_2O_7$: C, 52.63; H, 6.48; N, 8.18. Found: C, 52.34; H, 6.61; N, 7.72.

8-Allyloxy-3,4-dihydro-5-formyl-3-hydroxy-2*H*-1-benzopyran (21)——A mixture of **15** (404 mg), K_2CO_3 (290 mg), allyl chloride (191 mg) and DMF (7 ml) was heated at 100 °C for 1 h. Water was added to the mixture, and the solution was extracted with AcOEt. The AcOEt layer was washed with brine, and evaporated to give the crude crystals, which were recrystallized from $CHCl_3$–hexane to give 470 mg (96.4%) of **21** as pale yellow needles, mp 108—109.5 °C. IR (KBr): 3410 (OH), 1670 (C=O) cm^{-1}. NMR ($CDCl_3$) δ: 3.08—3.62 (2H, m, C_4-H), 4.10—4.40 (3H, m, C_2-, C_3-H), 4.67 (2H, d, J=6 Hz, $-C\underline{H}_2CH=CH_2$), 5.22—5.58 (2H, m, $-CH_2CH=C\underline{H}_2$), 5.86—6.28 (1H, m, $-CH_2C\underline{H}=CH_2$), 6.84 (1H, d, J=8 Hz, C_7-H), 7.34 (1H, d, J=8 Hz, C_6-H), 9.90 (1H, s, CHO). *Anal.* Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.82; H, 5.98.

3,4-Dihydro-3,5-dihydroxy-8-(2,3-epoxy)propoxy-2*H*-1-benzopyran (22)——*m*-Chloroperbenzoic acid (80%, 307 mg) was added portionwise to a solution of **21** (70 mg) in CH_2Cl_2 (2 ml) with stirring and ice-cooling. The mixture was stirred for 20 h at room temperature, then MeOH (2 ml) and 1 N NaOH (3 ml) were added. After being stirred for 30 min at room temperature, the solution was acidified with 2 N HCl to pH 5, made alkaline with satd. $NaHCO_3$ to pH 8, and extracted with AcOEt. The organic layer was washed with brine, and evaporated to give the crude product,

which was purified by prep. TLC ($CHCl_3$: AcOEt = 2 : 3) to give 30 mg (42.1%) of **22** as a pale yellow oil. NMR ($CDCl_3 + CD_3OD$) δ: 2.44—3.12 (4H, m, C_4-H, –CH(O)–CH$_2$(O)), 3.76—4.28 (5H, m, C_2-, C_3-H, –OCH$_2$CH(O)–CH$_2$(O)), 6.26 (1H, d, J = 8 Hz, C_6-H), 6.65 (1H, d, J = 8 Hz, C_7-H).

3,4-Dihydro-3,5-dihydroxy-8-(2-hydroxy-3-isopropylamino)propoxy-2*H*-1-benzopyran (23)——A mixture of **22** (50 mg), isopropylamine (124 mg) and MeOH (3 ml) was heated to reflux for 40 min. After evaporation, the residue was purified by prep. TLC ($CHCl_3$: 16% NH_3 in MeOH = 5 : 1) to give 27 mg (43.3%) of **23** as a pale yellow oil. IR (neat): 3280 (OH) cm^{-1}. NMR (CD_3OD) δ: 1.11 (6H, d, J = 6.3 Hz, –NHCH(CH$_3$)$_2$), 2.40—3.10 (5H, m, C_4-H, –CH$_2$NHCH), 3.76—4.24 (6H, m, C_2-, C_3-H, –OCH$_2$CHOH), 6.26 (1H, d, J = 8.6 Hz, C_6-H), 6.65 (1H, d, J = 8.6 Hz, C_7-H). MS Calcd for $C_{15}H_{23}NO_5$: M, 297.1576. Found m/z: M^+, 297.1589.

3-Hydroxy-2-methoxy-benzaldehyde (25)——A mixture of **24** (8.963 g), methyl iodide (9.21 g), K_2CO_3 (4.48 g) and acetone (90 ml) was heated at reflux for 5 h. The resulting precipitate was filtered off, and the filtrate was evaporated. Water was added to the residue, and the solution was extracted with AcOEt. The AcOEt layer was washed with brine, and evaporated to give a mixture, which was chromatographed on a silica gel column ($CHCl_3$: hexane = 5 : 1) to give the crude crystals. Recrystallization from benzene–hexane gave 2.26 g (22.9%) of **25** as colorless needles, mp 108—110 °C (Lit.[10] 113—115 °C). IR (KBr): 3200 (OH), 1656 (C=O) cm^{-1}. NMR ($CDCl_3$) δ: 3.98 (3H, s, OCH_3), 6.00 (1H, s, OH), 7.04—7.46 (3H, m, ArH), 10.27 (1H, s, CHO).

3-Allyloxy-2-methoxy-benzaldehyde (26)——A mixture of **25** (2.24 g), allyl chloride (1.69 g), K_2CO_3 (3.05 g) and DMF (40 ml) was heated at 100 °C for 1.5 h, then allowed to cool. Water was added to the mixture, and the solution was extracted with ether. The ether layer was washed with brine, and evaporated to give 2.83 g (100%) of **26** as a yellow oil. IR (neat): 1675 (C=O) cm^{-1}. NMR ($CDCl_3$) δ: 4.01 (3H, s, OCH_3), 4.57—4.72 (2H, m, –OCH$_2$CH=CH$_2$), 5.23—5.60 (2H, m, –CH=CH$_2$), 5.90—6.30 (1H, m, –CH=CH$_2$), 7.06—7.24 (2H, m, C_4-, C_5-H), 7.42 (1H, dd, J = 2 Hz, J' = 6 Hz, C_6-H), 10.42 (1H, s, CHO). MS m/z: 192 (M^+).

4-Allyl-3-hydroxy-2-methoxy-benzaldehyde (27)——Compound **26** (2.80 g) was heated at 180 °C for 3.5 h under an atmosphere of nitrogen. After cooling of the reaction mixture, ether was added and the ether solution was extracted with 1 N NaOH. After being made acidic with conc. HCl, the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with brine, and evaporated to give a crude oil, which was chromatographed on a silica gel column (benzene) to give 1.37 g (48.9%) of **27** as a yellow oil. The ether layer was evaporated to recover 1.01 g of **26**. IR (neat): 3400 (OH), 1675 (C=O) cm^{-1}. NMR ($CDCl_3$) δ: 3.42—3.58 (2H, m, –CH$_2$CH=CH$_2$), 3.96 (1H, s, OCH_3), 5.00—5.32 (2H, m, –CH=CH$_2$), 5.80—6.20 (1H, m, –CH=CH$_2$), 6.27 (1H, s, OH), 7.04 (1H, d, J = 8 Hz, C_5-H), 7.35 (1H, d, J = 8 Hz, C_6-H), 10.22 (1H, s, CHO). MS m/z: 192 (M^+).

3-Acetoxy-4-allyl-2-methoxy-benzaldehyde (28)——A solution of acetic anhydride (1.45 g) in CH_2Cl_2 (6.7 ml), and a solution of triethylamine (1.43 g) in CH_2Cl_2 (6.7 ml) were added to a solution of **27** (1.36 g) in CH_2Cl_2 (34 ml). The whole was stirred for 17 h at room temperature, then water was added. The mixture was stirred for 30 min at room temperature, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with 2 N HCl, satd. $NaHCO_3$ and brine, and evaporated to give 1.57 g (95.0%) of **28** as a pale yellow oil. IR (neat): 1770 (acetate C=O), 1688 (formyl C=O) cm^{-1}. NMR ($CDCl_3$) δ: 2.36 (3H, s, $OCOCH_3$), 3.28—3.44 (2H, m, CH$_2$CH=CH$_2$), 3.92 (3H, s, OCH_3), 4.99—5.26 (2H, m, –CH=CH$_2$), 5.66—6.10 (1H, m, –CH=CH$_2$), 7.12 (1H, d, J = 8 Hz, C_5-H), 7.68 (1H, d, J = 8 Hz, C_6-H), 10.32 (1H, s, CHO). MS m/z: 234 (M^+).

3-Acetoxy-4-(3-bromo-2-hydroxy)propyl-2-methoxy-benzaldehyde (29) and 3-Acetoxy-4-(2-bromo-3-hydroxy)-propyl-2-methoxy-benzaldehyde (30)——A solution of *N*-bromoacetamide (1.84 g) in water (13 ml) was added portionwise to a solution of **28** (1.57 g) in acetone (40 ml) with ice-cooling. The mixture was stirred for 6 h at room temperature, then water was added and the whole was extracted with AcOEt. The AcOEt layer was washed with satd. $NaHCO_3$ and brine, and evaporated to give a mixture of **29** and **30** (about 1 : 1, 2.23 g) as a pale brown oil. NMR ($CDCl_3$) δ: 2.39 (3H, s, $OCOCH_3$), 2.55—3.35 (3H, m, OH, benzylic position H), 3.40—3.52 (about 0.5 × 2H, m, –CHBr–CH$_2$OH), 3.79 (about 0.5 × 2H, d, J = 5 Hz, –CH(OH)–CH$_2$Br), 3.93 (3H, s, OCH_3), 3.85—4.43 (1H, m, methine H), 7.21 (1H, d, J = 8 Hz, C_5-H), 7.71 (1H, d, J = 8 Hz, C_6-H), 10.31 (1H, s, CHO). MS m/z: 330 and 332 (M^+).

4-(2-Acetoxy-3-bromo)propyl-3-hydroxy-2-methoxy-benzaldehyde (31) and 4-(3-Acetoxy-2-bromo)propyl-3-hydroxy-2-methoxy-benzaldehyde (32)——An 18.5% HCl sclution (dioxane, 15 g) was added slowly to a solution of a mixture of **29** and **30** (about 1 : 1, 2.23 g) in dioxane (60 ml). The mixture was stirred for 16 h at room temperature, then water was added, and the whole was extracted with AcOEt. The AcOEt layer was washed with satd. $NaHCO_3$ and brine, and evaporated to give a mixture of **31** and **32** (about 1 : 1, 2.20 g) as a pale brown oil. NMR ($CDCl_3$) δ: 2.06 (about 0.5 × 3H, s, $OCOCH_3$ of **32**), 2.12 (about 0.5 × 3H, s, $OCOCH_3$ of **31**), 3.04—3.64 (2H, about 0.5 × 2H, m, benzylic position H, CH_2Br of **31**), 3.96 (3H, s, OCH_3), 4.37 (about 0.5 × 2H, d, J = 5 Hz, CH$_2$OCOCH$_3$ of **32**), 4.44—4.72 (about 0.5 × 1H, m, methine H of **32**), 5.20—5.46 (about 0.5 × 1H, m, methine H of **31**), 7.04 (1H, d, J = 8 Hz, C_5-H), 7.30, 7.32 (1H, 2 × d, each J = 8 Hz, C_6-H), 10.18 (1H, s, CHO). MS m/z: 330 and 332 (M^+).

3-Acetoxy-3,4-dihydro-7-formyl-8-methoxy-2*H*-1-benzopyran (33) and 2-Acetoxymethyl-2,3-dihydro-6-formyl-7-methoxy-1-benzofuran (34)——K_2CO_3 (1.21 g) was added to a solution of a mixture of **31** and **32** (about 1 : 1, 2.20 g) in DMF (60 ml). The mixture was stirred for 1.5 h at room temperature, then water was added, and the solution was

extracted with AcOEt. The AcOEt layer was washed with brine, and evaporated to give a mixture of **33** and **34** (about 1 : 1, 1.55 g) as a pale brown oil. NMR ($CDCl_3$) δ: 2.09 (3H, s, $OCOCH_3$), 2.72—3.52 (2H, m, benzylic position H), 4.04 (about 0.5 × 3H, s, OCH_3 of **33**), 4.12 (about 0.5 × 3H, s, OCH_3 of **34**), 4.20—4.55 (2H, m, C_2-H of **33**, CH_2OCOCH_3 of **34**), 4.96—5.24 (about 0.5 × 1H, m, C_2-H of **34**), 5.24—5.44 (about 0.5 × 1H, m, C_3-H of **33**), 6.95, 7.00 (1H, 2 × d, each J=8 Hz, ArH), 7.42 (1H, d, J=8 Hz, ArH), 10.44 (1H, s, CHO). MS m/z: 250 (M^+).

3,4-Dihydro-7-formyl-3-hydroxy-8-methoxy-2*H*-1-benzopyran (35)——A solution of a mixture of **33** and **34** (about 1 : 1, 1.55 g) in MeOH (23 ml) was treated with 10% NaOH (4.6 ml). After being stirred for 1 h at room temperature, the reaction mixture was acidified with 2 N HCl. After removal of the MeOH, the residue was diluted with water, and extracted with AcOEt. The AcOEt layer was washed with brine, and evaporated to give the mixture, which was chromatographed on a silica gel column ($CHCl_3$: hexane = 5 : 1) to give 429 mg of benzofuran derivative as a yellow oil and 487 mg of **35** as crude crystals. Recrystallization of the crude crystals from benzene–hexane gave 374 mg of **35** (yield from **28**, 26.8%) as colorless needles, mp 84—85 °C. IR (KBr): 3380 (OH), 1665 (C=O) cm^{-1}. NMR ($CDCl_3$) δ: 2.16 (1H, br s, OH), 2.69—3.31 (2H, m, C_4-H), 3.99 (3H, s, OCH_3), 4.15—4.45 (3H, m, C_2-, C_3-H), 6.87 (1H, d, J=8 Hz, C_5-H), 7.34 (1H, d, J=8 Hz, C_6-H), 10.33 (1H, s, CHO). MS m/z: 208 (M^+). *Anal.* Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.32; H, 5.83.

3-Acetoxy-3,4-dihydro-7-formyl-8-hydroxy-2*H*-1-benzopyran (36)——A mixture of **35** (374 mg) and 25% HBr (acetic acid, 7 ml) was heated at 60 °C in a sealed tube for 1.5 h. Then 10% NaOH was added slowly with ice-cooling, and the pH was adjusted to about 2. The solution was extracted with AcOEt. The AcOEt layer was washed with brine, and evaporated to give 470 mg of a mixture, which was chromatographed on a silica gel column ($CHCl_3$) to give 407 mg of crude crystals. Recrystallization from benzene–hexane gave 354 mg (83.5%) of **36** as pale yellow needles, mp 105—109 °C. IR (KBr): 3400 (OH), 1730 (acetate C=O), 1649 (formyl C=O) cm^{-1}. NMR ($CDCl_3$) δ: 2.06 (3H, s, $OCOCH_3$), 2.76—3.40 (2H, m, C_4-H), 4.06—4.55 (2H, m, C_2-H), 5.22—5.42 (1H, m, C_3-H), 6.72 (1H, d, J=8 Hz, C_5-H), 7.12 (1H, d, J=8 Hz, C_6-H), 9.84 (1H, s, CHO), 11.14 (1H, s, OH). MS m/z: 236 (M^+). *Anal.* Calcd for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 61.24; H, 5.21.

3-Acetoxy-3,4-dihydro-8-(2,3-epoxy)propoxy-7-formyl-2*H*-1-benzopyran (37)——A solution of **36** (320 mg) in dry THF (3.6 ml) was added dropwise through a dry syringe to a suspension of 50% NaH (78 mg) in dry THF (0.8 ml). The mixture was stirred for 10 min at room temperature, then a solution of glycidol-*o*-nitrobenzenesulfonate (421 mg) in dry THF (4.4 ml) was added dropwise through a dry syringe. The whole was stirred at 60 °C for 13 h, the resulting precipitate was filtered off, and the filtrate was evaporated. The residue was dissolved in $CHCl_3$, and the $CHCl_3$ solution was washed with brine, and evaporated to give 511 mg of a mixture. Purification by prep. TLC ($CHCl_3$: MeOH = 40 : 1) gave 173 mg (59.7%) of **37** as a colorless oil. IR (neat): 1735 (acetate C=O), 1680 (formyl C=O) cm^{-1}. NMR ($CDCl_3$) δ: 2.04 (3H, s, $OCOCH_3$), 2.63—3.52 (5H, m, C_4-H, $-CH\underset{\diagdown O \diagup}{-}CH_2$), 4.00—4.52 (4H, m, C_2-H, $-OCH_2CH\underset{\diagdown O \diagup}{-}CH_2$), 5.20—5.40 (1H, m, C_3-H), 6.87 (1H, d, J=8 Hz, C_5-H), 7.36 (1H, d, J=8 Hz, C_6-H), 10.40 (1H, s, CHO). MS Calcd for $C_{15}H_{16}O_6$: M, 292.0946. Found m/z: M^+, 292.0951.

3-Acetoxy-3,4-dihydro-8-(2,3-epoxy)propoxy-7-formyloxy-2*H*-1-benzopyran (38)——*m*-Chloroperbenzoic acid (80%, 356 mg) was added portionwise with stirring and ice-cooling to a solution of **37** (160 mg) in CH_2Cl_2 (2.0 ml). After stirring had continued for 15 h at room temperature, $CHCl_3$ was added to the reaction mixture. The organic layer was washed with 10% Na_2CO_3 and brine, and evaporated to give 124 mg (73.5%) of **38** as a colorless oil. IR (neat): 1735 (C=O) cm^{-1}. NMR ($CDCl_3$) δ: 2.05 (3H, s, $OCOCH_3$), 2.58—3.42 (5H, m, C_4-H, $-CH\underset{\diagdown O \diagup}{-}CH_2$), 3.90—4.56 (4H, m, C_2-H, $-OCH_2CH\underset{\diagdown O \diagup}{-}CH_2$), 5.12—5.36 (1H, m, C_3-H), 6.64 (1H, d, J=8 Hz, ArH), 6.80 (1H, d, J=8 Hz, ArH), 8.26 (1H, s, OCHO). MS Calcd for $C_{15}H_{16}O_7$: M, 308.0893. Found m/z: M^+, 308.0876.

3,4-Dihydro-3,7-dihydroxy-8-(2-hydroxy-3-isopropylamino)propoxy-2*H*-1-benzopyran (39)——A mixture of **38** (90 mg), isopropylamine (87 mg) and MeOH (3.0 ml) was heated at reflux for 40 min, then evaporated. The residue was purified by prep. TLC ($CHCl_3$: 16% NH_3 in MeOH = 5 : 1) to give 9 mg (10.4%) of **39** as a colorless oil. NMR (CD_3OD) δ: 1.10 (6H, d, J=6.4 Hz, $-NHCH(CH_3)_2$), 2.46—3.10 (5H, m, C_4-H, $-CH_2NHCH$), 3.72—4.13 (6H, m, C_2-, C_3-H, $-OCH_2CH(OH)-$), 6.29 (1H, d, J=8.3 Hz, C_6-H), 6.53 (1H, d, J=8.3 Hz, C_5-H). MS Calcd for $C_{15}H_{23}NO_5$: M, 297.1574. Found m/z: M^+, 297.1568.

3,4-Dihydro-8-ethoxycarbonyloxy-3-methanesulfonyloxy-2*H*-1-benzopyran (43)——A solution of ethylchloroformate (5.14 g) in THF (20 ml) was added dropwise to a mixture of **41** (7.50 g), triethylamine (5.03 g) and THF (60 ml) below 10 °C. The mixture was stirred for 30 min at the same temperature, and a solution of triethylamine (7.31 g) in THF (60 ml) was added. Then a solution of methanesulfonyl chloride (7.76 g) in THF (20 ml) was added dropwise below 20 °C. The whole was stirred for 1 h at room temperature, the resulting precipitate was filtered off, and the filtrate was evaporated. AcOEt was added to the residue. The AcOEt layer was washed with satd. $NaHCO_3$ and brine, and evaporated to give a crude solid, which was recrystallized from AcOEt–hexane to give 13.8 g (96.5%) of **43** as colorless prisms, mp 118—119 °C. NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz, $-CO_2CH_2CH_3$), 3.06 (3H, s, $-OSO_2CH_3$), 3.04—3.30 (2H, m, C_4-H), 4.10—4.58 (4H, m, C_2-H, $-CO_2CH_2CH_3$), 5.16—5.36 (1H, m, C_3-H), 6.90—7.16 (3H, m,

ArH). MS *m/z*: 316 (M^+).

8-Hydroxy-2*H*-1-benzopyran (44)——A mixture of **43** (7.90 g), 10% NaOH (60 ml) and MeOH (40 ml) was stirred for 40 min at 80 °C, then acidified with 2 N HCl. The MeOH was removed, and the residue was extracted with benzene. The benzene layer was washed with satd. $NaHCO_3$ and brine, and evaporated to give the crude oil (3.27 g), which was chromatographed on a silica gel column ($CHCl_3$: hexane = 10 : 1) to give 3.13 g (84.6%) of **44** as a pale yellow oil. IR (neat): 3404 (OH) cm^{-1}. NMR ($CDCl_3$) δ: 4.80—4.96 (2H, m, C_2-H), 5.40 (1H, s, OH), 5.68—5.88 (1H, m, C_3-H), 6.36—6.90 (4H, m, C_4-H, ArH). MS Calcd for $C_9H_8O_2$; M, 148.0524. Found *m/z*: M^+, 148.0509.

8-Acetoxy-2*H*-1-benzopyran (45)——A solution of Ac_2O (4.31 g) in CH_2Cl_2 (10 ml) was added dropwise to a mixture of **44** (3.13 g), triethylamine (4.28 g) and CH_2Cl_2 (40 ml). The whole was stirred for 4 h at room temperature, then water was added. The reaction mixture was stirred for 1 h at room temperature, and extracted with $CHCl_3$. The organic layer was washed with 2 N HCl, satd. $NaHCO_3$ and brine, and evaporated to give 3.82 g (95.0%) of **45** as a pale yellow oil. IR (neat): 1770 (C=O) cm^{-1}. NMR ($CDCl_3$) δ: 2.27 (3H, s, $OCOCH_3$), 4.74—4.89 (2H, m, C_2-H), 5.66—5.87 (1H, m, C_3-H), 6.33—6.53 (1H, m, C_4-H), 6.83 (3H, s, ArH). MS *m/z*: 190 (M^+).

4,8-Diacetoxy-3,4-dihydro-3-hydroxy-2*H*-1-benzopyran (46, a Mixture of *trans*-, and *cis*-Isomers)——A 40% peracetic acid solution (7.64 g) was added slowly to a mixture of **45** (3.82 g), AcONa (3.80 g) and AcOH (38 ml) with ice-cooling. The whole was stirred for 6 h at room temperature, then 10% $Na_2S_2O_3$ (50 ml) was added slowly with ice-cooling. The reaction mixture was stirred for 10 min, then extracted with AcOEt. The AcOEt layer was washed with satd. $NaHCO_3$ and brine, and evaporated to give a crude oil (5.04 g), which was chromatographed on a silica gel column ($CHCl_3$) to give 3.86 g (72.2%) of **46** (*trans*-isomer : *cis*-isomer = 7 : 1) as a pale yellow oil. IR (neat): 3423 (OH), 1732 (C=O) cm^{-1}. NMR ($CDCl_3$) δ: 2.11 (7/8 × 3H, s, $OCOCH_3$ for *trans*-isomer), 2.16 (1/8 × 3H, s, $OCOCH_3$ for *cis*-isomer), 2.32 (3H, s, phenol acetate), 2.68 (1H, br s, OH), 3.98—4.12 (1H, m, C_3-H), 4.24 (2H, d, J = 3.2 Hz, C_2-H), 5.79 (7/8 × 1H, d, J = 3.9 Hz, C_4-H for *trans*-isomer), 6.03 (1/8 × 1H, d, J = 3.7 Hz, C_4-H for *cis*-isomer), 6.90—7.08 (2H, m, C_5-, C_6-H), 7.19—7.25 (1H, m, C_7-H). MS Calcd for $C_{13}H_{14}O_6$: M, 266.0901. Found *m/z*: M^+, 266.0846.

4-Acetoxy-3,4-dihydro-3,8-dihydroxy-2*H*-1-benzopyran (47, a Mixture of *trans*-, and *cis*-Isomers)——A mixture of **46** (3.86 g), piperidine (1.24 g), and $CHCl_3$ (40 ml) was heated at reflux for 1 h, then evaporated, and the residue was chromatographed on a silica gel column ($CHCl_3$) to give 2.97 g (91.4%) of **47** (*trans*-isomer : *cis*-isomer = 7 : 1) as a colorless oil. IR (neat): 3355 (OH), 1718 (C=O) cm^{-1}. NMR ($CDCl_3$) δ: 2.11 (7/8 × 3H, s, $OCOCH_3$ for *trans*-isomer), 2.16 (1/8 × 3H, s, $OCOCH_3$ for *cis*-isomer), 4.02—4.10 (1H, m, C_3-H), 4.14—4.40 (2H, m, C_2-H), 5.76 (7/8 × 1H, d, J = 3.7 Hz, C_4-H for *trans*-isomer), 6.04 (1/8 × 1H, d, J = 4.2 Hz, C_4-H for *cis*-isomer), 6.80—6.98 (3H, m, ArH). MS Calcd for $C_{11}H_{12}O_5$: M, 224.0695. Found *m/z*: M^+, 224.0690.

***trans*-, and *cis*-3,4-Dihydro-4,8-dihydroxy-3-nitroxy-2*H*-1-benzopyran (50, 51)**——A solution of trichloroacetyl chloride (2.23 g) in dry THF (11 ml) was added dropwise to a mixture of **47** (2.70 g), triethylamine (1.24 g), and dry THF (27 ml) below −5 °C. The whole was stirred at the same temperature for 30 min, the precipitate was filtered off, and the filtrate was evaporated to give 4.58 g of **48** as a yellow oil, which was dissolved in acetonitrile (35 ml). A solution of fum. HNO_3 (1.56 g) in Ac_2O (2.53 g) was added dropwise to the above solution below −10 °C. The mixture was stirred for 30 min below −10 °C, and a solution of fum. HNO_3 (1.56 g) in Ac_2O (2.53 g) was added dropwise below −10 °C. Stirring was continued for 30 min below −10 °C, then a solution of fum. HNO_3 (391 mg) in Ac_2O (631 mg) was added dropwise to the mixture below −10 °C. The whole was stirred for 30 min below −10 °C, satd. $NaHCO_3$ was added, stirring was continued for 30 min, and the mixture was extracted with AcOEt. The AcOEt layer was washed with satd. $NaHCO_3$ and brine, and evaporated to give 4.56 g of **49** as a yellow oil, which was dissolved in MeOH (47 ml). Isopropylamine (5.8 ml) was added to the above solution, and the mixture was stirred for 3.5 h at room temperature, then evaporated to give a crude oil, which was chromatographed on a silica gel column ($CHCl_3$) to give 935 mg of **50** and 95 mg of **51**. Each crude solid was recrystallized from AcOEt–hexane to give 818 mg (29.9%) of **50** and 78 mg (2.86%) of **51**, as colorless needles.

50: mp 126—128 °C. IR (KBr): 3445 (OH), 1637, 1270 (ONO_2) cm^{-1}. NMR (CD_3OD) δ: 4.40 (1H, dd, J = 2.1 Hz, J' = 12.7 Hz, C_2-H_{ax}), 4.51 (1H, ddd, J = 1.2 Hz, J' = 3.3 Hz, J'' = 12.7 Hz, C_2-H_{eq}), 4.67 (1H. dd, J = 1.2 Hz, J' = 3.4 Hz, C_4-H), 5.22—5.30 (1H, m, C_3-H), 6.71—6.86 (3H, m, ArH). *Anal.* Calcd for $C_9H_9NO_6$: C, 47.58; H, 3.99; N, 6.17. Found: C, 47.78; H, 3.99; N, 6.06.

51: mp 138—143 °C. IR (KBr): 3380 (OH), 1618, 1280 (ONO_2) cm^{-1}. NMR (CD_3OD) δ: 4.27—4.50 (2H, m, C_2-H), 5.08 (1H, d, J = 3.9 Hz, C_4-H), 5.45—5.55 (1H, m, C_3-H), 6.71—6.96 (3H, m, ArH). *Anal.* Calcd for $C_9H_9NO_6$: C, 47.58; H, 3.99; N, 6.17. Found: C, 47.53; H, 4.04; N, 5.92.

***trans*-3,4-Dihydro-8-(2,3-epoxy)propoxy-4-hydroxy-3-nitroxy-2*H*-1-benzopyran (52)**——A mixture of **50** (731 mg), epichlorohydrin (889 mg) and tetramethylammonium chloride (40 mg) was stirred for 17 h at room temperature, then $CHCl_3$ was added. The $CHCl_3$ layer was washed with brine, and evaporated to give a colorless oil (1.20 g). This was dissolved in dioxane (6.1 ml), and 1 N NaOH (4.14 ml) was added to the solution. After stirring for 1 h at room temperature, $CHCl_3$ and water were added to the mixture. The $CHCl_3$ layer was separated, washed with 1 N NaOH and brine, and evaporated to give a mixture (974 mg). The mixture was chromatographed on a silica gel column ($CHCl_3$: AcOEt = 30 : 1) to give a solid (483 mg), which was recrystallized from $CHCl_3$–AcOEt to give 354 mg (38.8%) of **52** as colorless needles, mp 106—110 °C. IR (KBr): 3280 (OH), 1630, 1280 (ONO_2) cm^{-1}. NMR

(CDCl$_3$) δ: 2.64—3.06 (3H, m, –CH(O)–CH$_2$, OH), 3.20—3.50 (1H, m, –CH(O)–CH$_2$), 3.84—4.34 (2H, m, –OCH$_2$–), 4.36—4.60 (2H, m, C_2-H), 4.70 (1H, d, J=4 Hz, C_4-H), 5.13—5.30 (1H, m, C_3-H), 6.80—7.08 (3H, m, ArH). *Anal.* Calcd for $C_{12}H_{13}NO_7$: C, 50.88; H, 4.63; N, 4.95. Found: C, 50.56; H, 4.63; N, 4.86.

***trans*-3,4-Dihydro-4-hydroxy-8-(2-hydroxy-3-isopropylamino)propoxy-3-nitroxy-2*H*-1-benzopyran (54)**——A mixture of **52** (312 mg), isopropylamine (325 mg) and MeOH (11 ml) was heated to reflux for 40 min. After evaporation, the residue was purified by prep. TLC ($CHCl_3$: 16% NH_3 in MeOH = 8 : 1) to give a solid (270 mg), which was recrystallized from AcOEt–Et_2O–hexane to give 225 mg (59.7%) of **54** as colorless needles, mp 97—110 °C. (Additional recrystallizations of 100 mg of this compound twice from AcOEt–hexane gave 51 mg of colorless needles, mp 131—132 °C.) IR (KBr): 3264 (OH), 1635, 1270 (ONO_2) cm^{-1}. NMR (CD_3OD) δ: 1.17 (6H, d, J=6.6 Hz, –CH(CH$_3$)$_2$), 2.75—3.05 (3H, m, –CH$_2$NHCH), 3.92—4.19 (3H, m, –OCH$_2$CH(OH)–), 4.35—4.56 (2H, m, C_2-H), 4.69 (1H, dd, J=1.2 Hz, J'=3.4 Hz, C_4-H), 5.24—5.31 (1H, m, C_3-H), 6.90—7.05 (3H, m, ArH). *Anal.* Calcd for $C_{15}H_{22}N_2O_7$: C, 52.62; H, 6.48; N, 8.18. Found: C, 52.27; H, 6.34; N, 7.88.

***cis*-3,4-Dihydro-8-(2,3-epoxy)propoxy-4-hydroxy-3-nitroxy-2*H*-1-benzopyran (53)**——A mixture of **51** (300 mg), epichlorohydrin (366 mg) and tetramethylammonium chloride (15 mg) was stirred for 16 h at room temperature, then AcOEt was added. The AcOEt layer was washed with brine, and evaporated to give colorless solid (411 mg). This was dissolved in dioxane (3 ml), and 1 N NaOH (1.71 ml) was added to the solution. The whole was stirred for 2 h at room temperature, then $CHCl_3$ and water were added to the mixture. The $CHCl_3$ layer was separated, washed with 1 N NaOH and brine, and evaporated to give a mixture (264 mg), which was purified by prep. TLC ($CHCl_3$: AcOEt = 2 : 1) to give 53 mg (14.2%) of **53** as colorless crystals, mp 145—155 °C. IR (KBr): 3300 (OH), 1623, 1269 (ONO_2) cm^{-1}. NMR ($CDCl_3$ + CD_3OD) δ: 2.72—3.00 (2H, m, –CH(O)–CH$_2$), 3.88—4.68 (4H, m, –OCH$_2$–, C_2-H), 5.10 (1H, d, J=4 Hz, C_4-H), 5.38—5.60 (1H, m, C_3-H), 6.80—7.18 (3H, m, ArH). MS Calcd for $C_{12}H_{13}NO_7$: M, 283.0692. Found m/z: M^+, 283.0698.

***cis*-3,4-Dihydro-4-hydroxy-8-(2-hydroxy-3-isopropylamino)propoxy-3-nitroxy-2*H*-1-benzopyran (55)**——A mixture of **53** (51 mg), isopropylamine (54 mg) and MeOH (1.5 ml) was heated to reflux for 30 min. After evaporation, the residue was purified by prep. TLC ($CHCl_3$: 16% NH_3 in MeOH = 8 : 1) to give 33 mg (53.6%) of **55** as colorless crystals, mp 104—116 °C. IR (KBr): 3350 (OH), 1629, 1275 (ONO_2) cm^{-1}. NMR (CD_3OD) δ: 1.15 (6H, d, J=6 Hz, –CH(CH$_3$)$_2$), 2.64—3.12 (3H, m, –CH$_2$NHCH), 3.88—4.24 (3H, m, –OCH$_2$CH(OH)–), 4.28—4.50 (2H, m, C_2-H), 5.10 (1H, d, J=4 Hz, C_4-H), 5.42—5.64 (1H, m, C_3-H), 6.80—7.12 (3H, m, ArH). MS Calcd for $C_{15}H_{22}N_2O_7$: M, 342.1427. Found m/z: $(M+H)^+$, 343.1506 (343.1506).

***trans*-3,4-Dihydro-3,4-dihydroxy-8-(2-hydroxy-3-isopropylamino)propoxy-2*H*-1-benzopyran (56)**——A solution of **54** (100 mg) in MeOH (1 ml) was hydrogenated over 10% Pd–C (25 mg) at atmospheric pressure and room temperature for 1 h. The catalyst was filtered off, and the filtrate was evaporated to give a crude oil, which was purified by prep. TLC ($CHCl_3$: 16% NH_3 in MeOH = 5 : 1) to give 54 mg (62.2%) of **56** as colorless crystals, mp 96—102 °C. IR (KBr): 3263 (OH) cm^{-1}. NMR (CD_3OD) δ: 1.10 (6H, d, J=6 Hz, –CH(CH$_3$)$_2$), 2.57—3.01 (3H, m, –CH$_2$NHCH), 3.83—4.33 (6H, m, –OCH$_2$CH(OH)–, C_2-, C_3-H), 4.44 (1H, d, J=4 Hz, C_4-H), 6.89—7.15 (3H, m, ArH). *Anal.* Calcd for $C_{15}H_{23}NO_5 \cdot 0.1H_2O$: C, 60.23; H, 7.82; N, 4.68. Found: C, 60.03; H, 7.70; N, 4.68.

***cis*-3,4-Dihydro-3,4-dihydroxy-8-(2-hydroxy-3-isopropylamino)propoxy-2*H*-1-benzopyran (57)**——A solution of **55** (25 mg) in MeOH (0.2 ml) was hydrogenated over 10% Pd–C (7 mg) at atmospheric pressure and room temperature for 1.5 h. The catalyst was filtered off, and filtrate was evaporated to give a mixture, which was purified by prep. TLC ($CHCl_3$: 16% NH_3 in MeOH = 5 : 1) to give crude crystals. Recrystallization from AcOEt gave 12 mg (55.3%) of **57** as colorless needles, mp 85—92 °C. (An additional recrystallization of 4 mg of this compound from AcOEt gave 2.5 mg of colorless needles, mp 89—91 °C.) IR (KBr): 3350 (OH) cm^{-1}. NMR (CD_3OD) δ: 1.10 (6H, d, J=6 Hz, –CH(CH$_3$)$_2$). 2.58—3.03 (3H, m, –CH$_2$NHCH), 3.85—4.26 (6H, m, –CH$_2$CH(OH)–, C_2-, C_3-H), 4.68 (1H, d, J=3 Hz, C_4-H), 6.84—7.09 (3H, m, ArH). *Anal.* Calcd for $C_{15}H_{23}NO_5 \cdot 0.25H_2O$: C, 59.69; H, 7.85; N, 4.64. Found: C, 59.45; H, 7.63; N, 4.45.

Reaction of 1 with NBS——NBS (152 mg) was added portionwise to a mixture of 3-acetoxy-2-allyl-4-methoxybenzaldehyde (**1**, 200 mg), dioxane (4 ml) and water (2 ml) with stirring and ice-cooling. The mixture was stirred for 40 min with ice-cooling, then water was added. The solution was extracted with Et_2O. The Et_2O layer was washed with satd. $NaHCO_3$ and brine, and evaporated to give a mixture (283 mg), which was purified by prep. TLC ($CHCl_3$: AcOEt = 5 : 1) to give 207 mg (73.2%) of **2** and 45 mg (16.0%) of **3** as colorless needles.

2: mp 66—86 °C. IR (KBr): 3390 (OH), 1765 (acetate C=O) cm^{-1}. NMR ($CDCl_3$) δ: 2.36 (3H, s, OCOCH$_3$), 2.44—2.92 (2H, m, –CH$_2$–), 3.58 (2H, d, J=5 Hz, –CH$_2$Br), 3.84 (3H, s, OCH$_3$), 4.24—4.56 (1H, m, CHCH$_2$Br), 6.08 (1H, d, J=5 Hz, CHOH), 6.95 (1H, d, J=9 Hz, ArH), 7.25 (1H, d, J=9 Hz, ArH). MS Calcd for $C_{13}H_{15}BrO_5$: M, 332.0081 and 330.0104. Found m/z: M^+, 332.0025 and 330.0144.

3: mp 150—152 °C ($CHCl_3$-hexane). IR (KBr): 1765 (acetate C=O), 1725 (lactone C=O) cm^{-1}. NMR ($CDCl_3$) δ: 2.37 (3H, s, OCOCH$_3$), 2.76—3.26 (2H, m, –CH$_2$–), 3.66 (2H, d, J=5 Hz, –CH$_2$Br), 3.94 (3H, s, OCH$_3$), 4.58—4.89 (1H, m, CHCH$_2$Br), 7.07 (1H, d, J=9 Hz, ArH), 8.11 (1H, d, J=9 Hz, ArH). MS Calcd for $C_{13}H_{13}BrO_5$: M, 329.9925 and 327.9944. Found m/z: M^+, 329.9915 and 327.9907.

Woodward's Method——AcOAg (822 mg) and then I_2 (585 mg) were added portionwise to a solution of **45** (417 mg) in AcOH (10 ml) with vigorous stirring at room temperature under an atmosphere of nitrogen. The mixture was stirred for 30 min at room temperature, then heated at 95 °C for 3 h, and allowed to cool. NaCl and AcOEt were added to the mixture. The resulting precipitate was filtered off, and the filtrate was washed with water, satd. $NaHCO_3$ and brine, and evaporated to give a yellow-brown oil (450 mg), which was dissolved in pyridine (4.5 ml). Ac_2O (347 mg) was added to this solution, and the mixture was stirred for 3 h at room temperature. After addition of water, the reaction mixture was stirred for 5 min at room temperature, acidified with 2 N HCl, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with satd. $NaHCO_3$ and brine, and evaporated to give 446 mg (66.1%) of **58** as a yellow-brown oil. NMR ($CDCl_3$) δ: 2.08 (3H, s, $-OCOCH_3$ of C_3-), 2.13 (3H, s, $OCOCH_3$ of C_4-), 2.32 (3H, s, phenol acetate), 4.22—4.32 (2H, m, C_2-H), 5.34—5.45 (1H, m, C_3-H), 6.18 (1H, d, J=3.6 Hz, C_4-H), 6.88—7.18 (3H, m, ArH).

Acetylation of 46——Acetylation of **46** was performed with Ac_2O in pyridine. A mixture of *cis*-, and *trans*-triacetates was obtained as a pale yellow oil in a yield of 95.9%. NMR ($CDCl_3$) δ: 2.05 (7/8 × 3H, s, $-OCOCH_3$ for *trans*-isomer), 2.08 (1/8 × 3H, s, $-OCOCH_3$ for *cis*-isomer), 2.10 (7/8 × 3H, s, $-OCOCH_3$ for *trans*-isomer), 2.13 (1/8 × 3H, s, $-OCOCH_3$ for *cis*-isomer), 2.32 (1/8 × 3H, s, phenol acetate for *cis*-isomer), 2.33 (7/8 × 3H, s, phenol acetate for *trans*-isomer), 4.18—4.48 (2H, m, C_2-H), 5.05—5.13 (7/8 × 1H, m, C_3-H for *trans*-isomer), 5.34—5.45 (1/8 × 1H, m, C_3-H for *cis*-isomer), 5.88 (7/8 × 1H, br dd, J=3.17 Hz, J'=1.46 Hz, C_4-H for *trans*-isomer), 6.18 (1/8 × 1H, d, J=3.6 Hz, C_4-H for *cis*-isomer), 6.86—7.28 (3H, m, ArH).

Pharmacological Method——Male SHRs were anesthetized with thiobutabarbital Na. Blood pressure was measured with a pressure transducer (P 23 ID Statham) connected to a catheter inserted into the femoral artery. Heart rate was measured with cardiotachometer (AT 600G Nihon Kohden) triggered by pulse pressure. Nipradilol and its metabolites were administered intravenously.

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