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Optical Resolution and Determination of Absolute Configuration of Nipradilol

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It was confirmed that the title compound, a new antihypertensive drug, consists of four optical isomers: two diastereomers and their enantiomers. Separation of the diastereomers was effected by recrystallization. Optical resolution of the enantiomers was carried out by repeated recrystallization of their diastereomeric salts with (+)- or (−)-2-[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl] acetoxy-2-phenylacetic acid or by high performance liquid chromatography of the L-menthoxyacetyl derivatives. The absolute configurations of the separated isomers were determined on the basis of the circular dichroism spectra and proton nuclear magnetic resonance spectra.

Keywords——nipradilol; antihypertensive drug; optical resolution; absolute configuration; CD spectra; ^{1}H-NMR spectra

Nipradilol,[1] 3,4-dihydro-8-(2′-hydroxy-3′-isopropylamino)propoxy-3-nitroxy-2*H*-1-benzopyran, is a newly synthesized antihypertensive drug,[2] in which the presence of four possible optical isomers is expected in view of the existence of two asymmetric centers. It is well known that optical isomers may have extremely different biological activity. For example, such a difference is observed in the case of β-blockers such as propranolol, labetalol and so on.[3] Therefore we wished to determine the absolute configuration of each isomer. In this paper, we describe the separation and structure determination of the four optical isomers.

Results and Discussion

To establish the ratios of optical isomers in nipradilol (**1**), we tried to separate them by high performance liquid chromatography (HPLC) as diastereomeric derivatives. Compound **1** was converted into the *N*,*O*-bis-L-menthoxyacetyl derivative, which showed four peaks on HPLC, the areas of which were all nearly equal (Fig. 1). This result showed that nipradilol is a mixture of four optical isomers.

Separation of two diastereomers (**1A** and **1B**) was effected by repeated recrystallization from ethyl acetate.[1] The *N*,*O*-bis-L-menthoxyacetyl derivatives of **1A** showed two peaks (peak 1 and 2) of longer retention time, and those of **1B**, two peaks (peak 3 and 4) of shorter retention time (Fig. 1).

To resolve **1A** as well as **1B**, the formation of the salts with an optically active acid was necessary. We then searched for a suitable acid for this purpose and were able to obrain salts of **1** with acemetacin[4] (**4**, R′=H in Chart 1), though it lacks an asymmetric center. We therefore synthesized optically active phenyl derivatives ((+)-**4** and (−)-**4**) of acemetacin from indomethacin[4] (**2**). Compound **2** was converted into the corresponding acid chloride (**3**) by reaction with thionyl chloride. The reaction of **3** with (+)-mandelic acid gave (+)-**4** and that with (−)-mandelic acid, (−)-**4** (Chart 1).

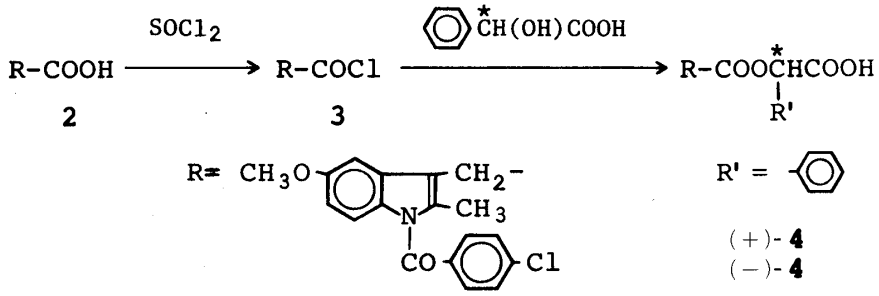

Chart 1. Synthesis of Optically Active Acids

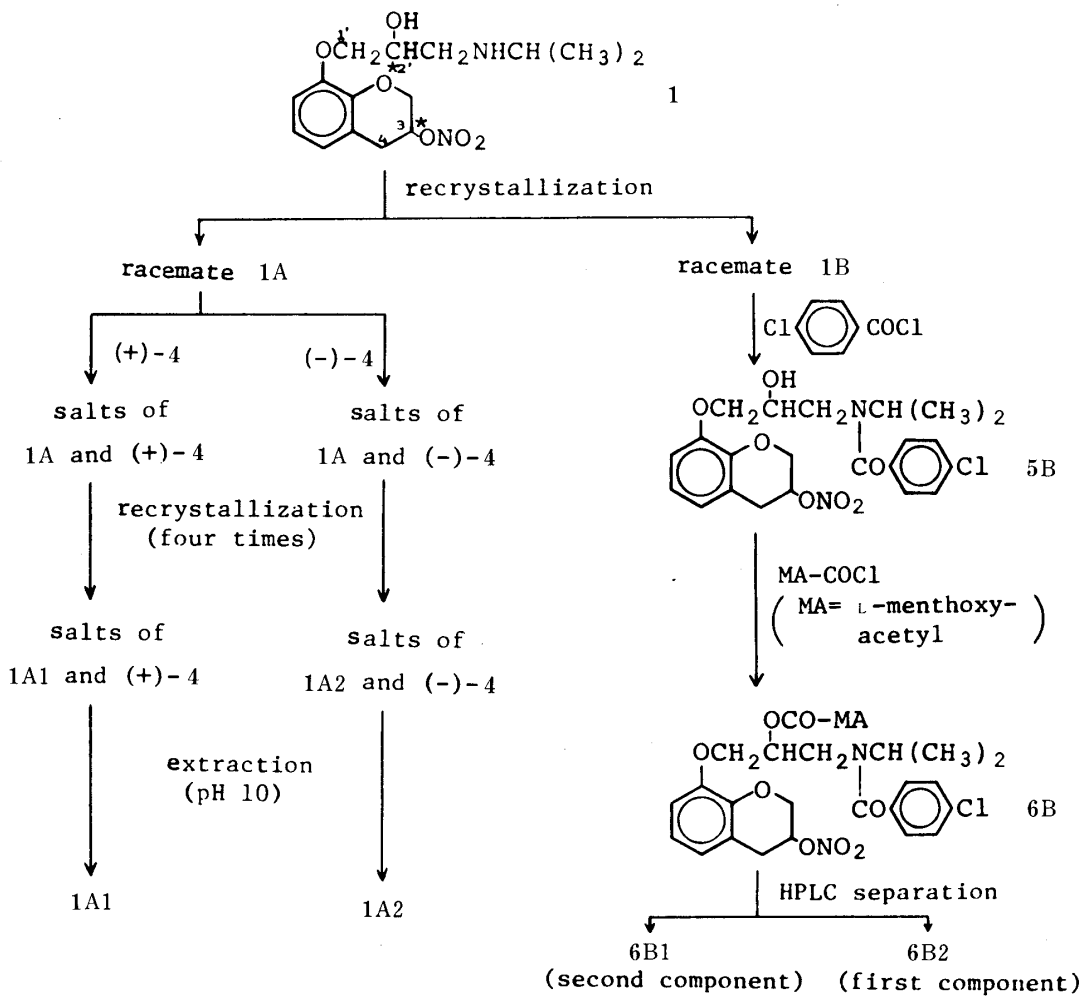

Chart 2. Optical Resolution of the Four Isomers in **1**

Resolution of **1A** was effected through the formation of diastereomeric salts with (+)-**4** and (−)-**4** (Chart 2). Recrystallization of the salts of **1A** and (+)-**4** four times provided the enantiometrically pure salt of **1A1** and (+)-**4**. The purity was checked by HPLC as the *N,O*-bis-L-menthoxyacetyl derivative of **1A1** (Fig. 1). The salt of **1A2** and (−)-**4** was similarly obtained from the salts of **1A** and (−)-**4**, and the purity was also checked by HPLC. A similar procedure was carried out for the resolution of **1B** using (+)-**4**. However, we have not yet isolated pure enantiomer but only a mixture which is rich in **1B1**, because it took more than several months for a single recrystallization. We had planned to determine the absolute configurations of the isomers in **1** on the basis of the dibenzoate chirality rule. We therefore

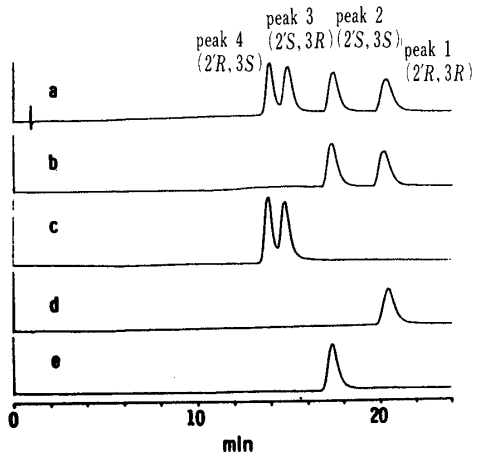

Fig. 1. Chromatograms of *N*,*O*-Bis-L-menthoxyacetyl Derivatives of (a) Nipradilol (**1**), (b) **1A**, (c) **1B**, (d) **1A1** and (e) **1A2**

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

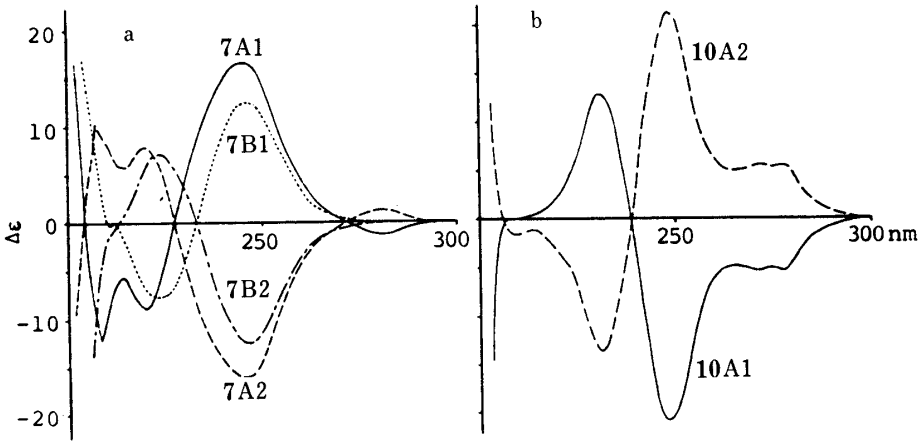

Fig. 2. CD Spectra of (a) 7A1, 7A2, 7B1 and 7B2 and (b) **10**A1 and **10**A2

tried to separate **1B** into its components by HPLC of diastereomeric derivatives which could be converted into *N*,*O*-bis-*p*-chlorobenzoyl derivatives for measurements of circular dichroism (CD) spectra after the separation. Thus, **1B** was converted into *N*-*p*-chlorobenzoyl derivatives (**5B**) and then into *N*-*p*-chlorobenzoyl-*O*-L-menthoxyacetyl derivatives (**6B**). The resulting **6B** could be separated into two components by HPLC. The first component **6B2** was the derivative of the enantiomer **1B2** and the second component, **6B1**, that of the enantiomer **1B1** (Chart 2).

For the assignment of the absolute configuration at C2′ in the β-side chain, two enantiomers (**1A1** and **1A2**) were directly converted into *N*,*O*-bis-*p*-chlorobenzoyl derivatives (7A1 and 7A2), and **6B1** and **6B2** were converted into **5B1** and **5B2** by partial hydrolysis and then into *N*,*O*-bis-*p*-chlorobenzoyl derivatives (7B1 and 7B2) (Chart 3). On the other hand, for the assignment of the absolute configuration at C3 in the benzopyran ring, **1A1** and **1A2** were converted into 8-hydroxy-3-nitroxybenzopyrans (**8A1** and **8A2**) by pyrolysis and then into 3,8-dihydroxybenzopyrans (**9A1** and **9A2**) by hydrolysis. Further, the resulting **9A1** and **9A2** were converted into 3,8-bis-*p*-chlorobenzoyloxybenzopyrans (**10A1** and **10A2**) (Chart 3). CD spectra of 7A1, 7A2, 7B1 and 7B2 are shown in Fig. 2a and those of **10A1** and **10A2**, in Fig. 2b.

The dibenzoate chirality rule is now widely accepted for the determination of absolute configurations. It can be applied not only to the benzoate system but also to the benzamide system.[5] Three staggered conformers are possible for 2′*R* configuration in the β-side chain (Fig. 3). It was predicted that conformer i, which would be positive at the longer-wavelength

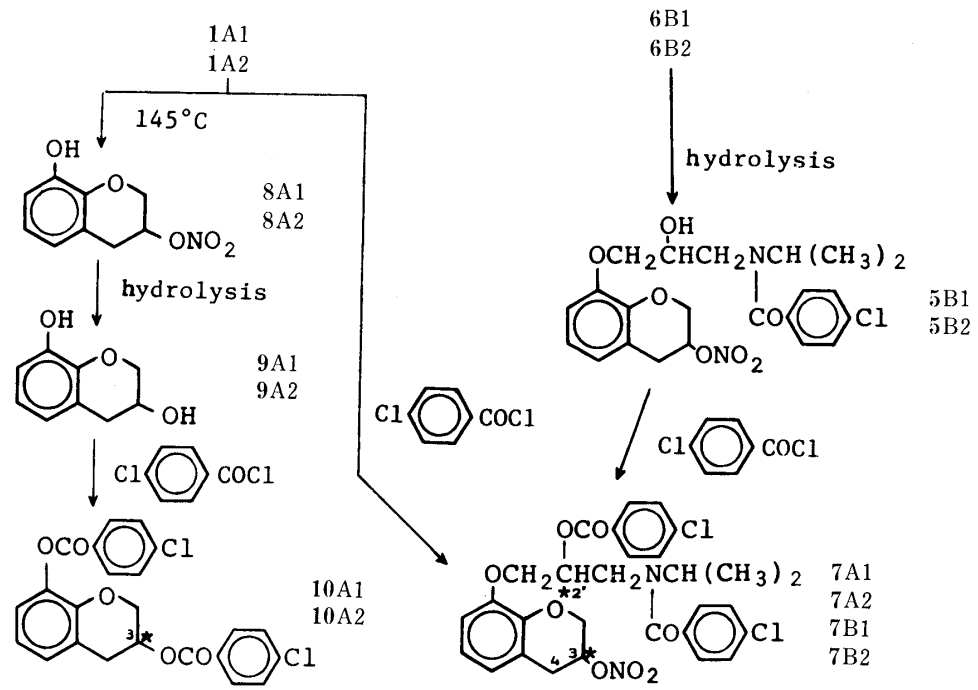

Chart 3. Synthesis of Bis-*p*-chlorobenzoyl Derivatives for Measurements of CD Spectra

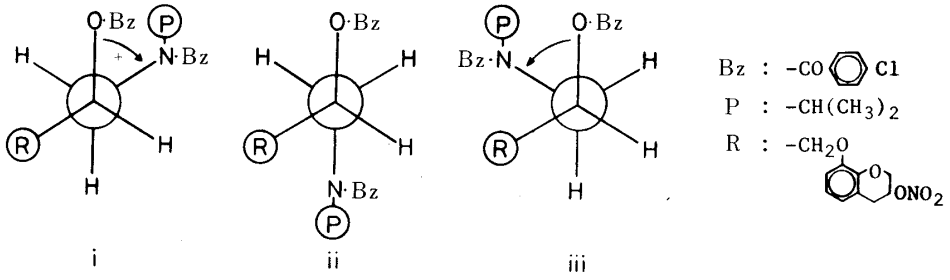

Fig. 3. Three Staggered Conformers for 2′*R* Configuration in the *β*-Side Chain

band and negative at the shorter-wavelength band (positive Cotton effect), would be more stable than conformer iii because of the difference between their steric hindrances, and conformer ii should give little or no Cotton effect because of the symmetric arrangement of the two benzoyl groups. As can be seen in the CD spectra in Fig. 2a, **7A1** and **7B1** showed positive Cotton effects and **7A2** and **7B2**, negative. The configurations at C2′ in **7A1** and **7B1** are therefore *R* and those in **7A2** and **7B2**, *S*. On the other hand, it was predicted that 3*S* configuration in the benzopyran ring would show positive Cotton effect and conversely 3*R*, negative. Since **10A1** showed a negative Cotton effect and **10A2**, positive (Fig. 2b), the configuration at C3 in **10A1** is *R* and that in **10A2**, *S*. Thus, **1A1** and **1A2** were assigned the 2′*R*,3*R* and 2′*S*,3*S* configurations, respectively, and **1A** is therefore the racemate of 2′*R*,3*R* and 2′*S*,3*S*. From these results, **1B** is clearly the racemate of 2′*R*,3*S* and 2′*S*,3*R*. Since the configuration at C2′ in **7B1** is *R* and that in **7B2** is *S*, **1B1** and **1B2** were assigned as 2′*R*,3*S* and 2′*S*,3*R*, respectively.

In order to confirm the above assignments, proton nuclear magnetic resonance (^{1}H-NMR) studies were carried out. There was no appreciable difference between the ^{1}H-NMR spectra of the two diastereomers (**1A** and **1B**). Compounds **1A** and **1B** were therefore converted into dihydroxy compounds (**11A** and **11B**) and then *N*-acetyl derivatives (**12A** and

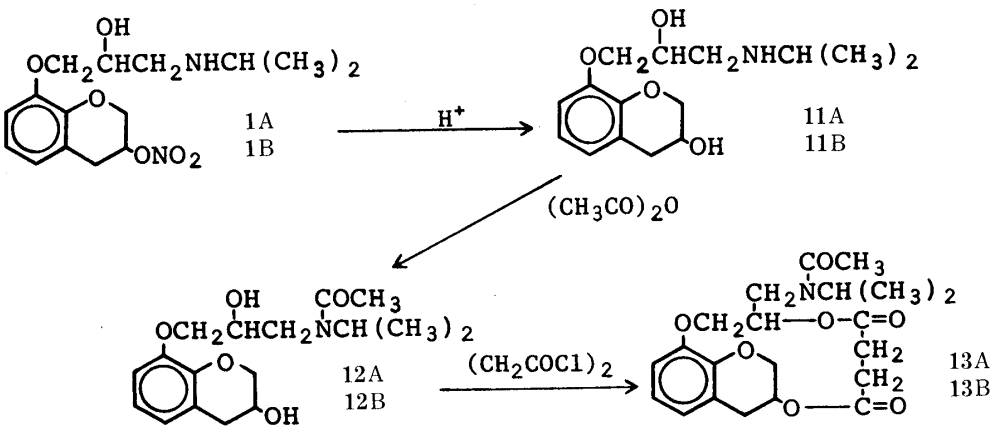

Chart 4. Synthesis of Cyclic Diesters for Measurements of ^{1}H-NMR Spectra

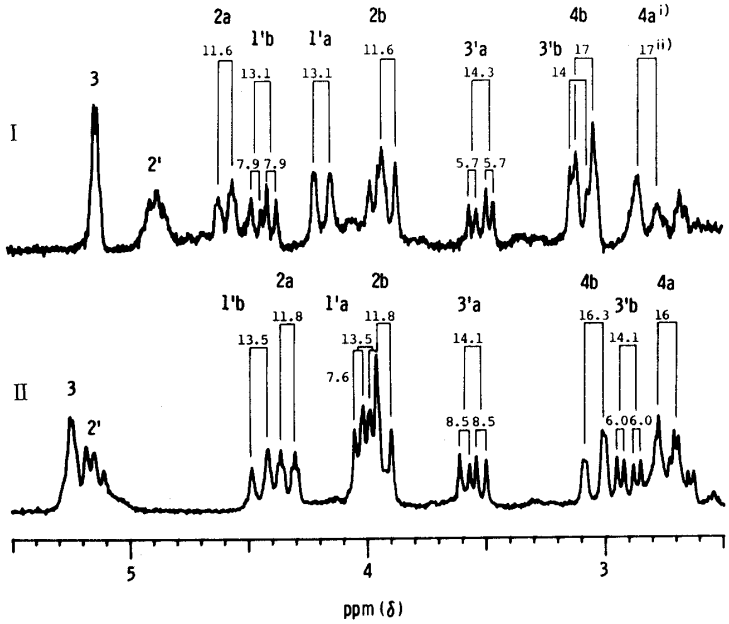

Fig. 4. Partial ^{1}H-NMR Spectra (199.5 MHz, CCl_4) of Cyclic Diesters

I, **13A**; II, **13B**. i) Assignment of proton. ii) Coupling constant.

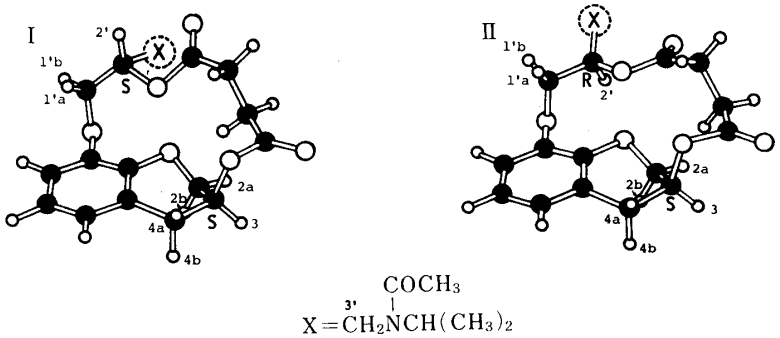

Fig. 5. Stereomodels of Cyclic Diesters Having 3*S* Configuration in the Benzopyran Ring

I, 2′*S*, 3*S* configuration; II, 2′*R*, 3*S* configuration. ●, carbon; o, hydrogen; ○, oxygen.

12B). Further, the resulting **12A** and **12B** were converted into cyclic diesters (**13A** and **13B**) by reaction with succinyl chloride (Chart 4).

The ^{1}H-NMR spectra of **13A** and **13B** are shown in Fig. 4. It was observed that the H1′a, H1′b and H2′ signals of **13A**, in comparison to those of **13B**, were 0.13 ppm downfield, at nearly the same position, and 0.30 ppm upfield, respectively. We estimated the influence of the circular current in the benzene ring[6] on the chemical shifts of H1′a, H1′b and H2′ in 2′*S*,3*S* configuration as well as in 2′*R*,3*S* configuration on the basis of molecular models of the cyclic diesters, and could predict that the H2′ signal in 2′*S*,3*S* would appear at higher field than in 2′*R*,3*S*, in spite of various available conformers of the 14-membered ring in the diester. This analysis suggested that 2′*S*,3*S* is a component of **13A** and 2′*R*,3*S* is a component of **13B**. As regards the split patterns, H1′a and H1′b in **13A** were a doublet (J_{gem}=13.1 (Hz), J_{vic}= approximately 0) and double doublet (J_{gem}=13.1, J_{vic}=7.6), respectively, and in **13B**, a double doublet (J_{gem}=13.5, J_{vic}=7.6) and doublet (J_{gem}=13.5, J_{vic}=approximately 0), respectively. The approximative dihedral angles between the C1′–H1′a and C2′–H2′ bonds and between the C1′–H1′b and C2′–H2′ bonds in **13A** were estimated to be 90 and 30°, respectively, and those in **13B**, 150 and 90°, respectively. The molecular models I (2′*S*,3*S*) and II (2′*R*,3*S*) having the above-mentioned torsion angles (Fig. 5) could be easily constructed without severe steric hindrance assuming that 2′*S*,3*S* is a component of **13A** and 2′*R*,3*S* is a component of **13B**. Further, the above-mentioned differences between the chemical shifts of protons in **13A** and in **13B** could be explained on the basis of models I and II. Thus, the results of ^{1}H-NMR studies supported the results of CD spectroscopic studies. Figure 1 shows the assignment of each peak on HPLC.

We can now assign the isomers in nipradilol (**1**). The biological behavior of the diastereomers (**1A** and **1B**) and the optical pure compounds (**1A1**, **1A2**, **1B1** and **1B2**) are being investigated at present, and the results will be reported elsewhere.

Experimental

HPLC was performed with a JASCO TRI ROTAR-II equipped with a UVIDEC-100II detector. Analytical and preparative thin-layer chromatographies (TLC) were performed on E. Merck Silica gel $60F_{254}$ plates (20×20 cm; thickness, 0.25 or 2 mm). ^{1}H-NMR spectra were recorded on a JEOL JNM-FX200 spectrometer (199.5 MHz). Chemical shifts are reported in ppm (δ) from internal tetramethylsilane. In the case of measurement in CCl_4, $CDCl_3$ was used to provide an external lock signal. Low-resolution mass spectra (LRMS) and high-resolution mass spectra (HRMS) were recorded on JEOL JMS-D300 and JMS-DX300 mass spectrometers. CD spectra were recorded on a JASCO J-500A spectrophotometer. Optical rotations were recorded on a JASCO DIP-4 polarimeter.

Preparation of Diacyl Compounds——General Procedure: An acid chloride (L-menthoxyacetyl chloride or *p*-chlorobenzoyl chloride) (50 μl) was added to a solution of the precursor (**1**, **5B**, **1A1**, **1A2**, **6B1**, **6B2**, **9A1** or **9A2**) (5—10 mg) of a diacyl compound in dry pyridine (0.5 ml) at room temperature. After 30 min, water (50 μl) was added to the solution and the solvent was removed *in vacuo*. The residue was dissolved in chloroform (5 ml) and washed with 1 N HCl (3 ml×2), saturated $NaHCO_3$ solution (3 ml) and then water (3 ml). After being dried (Na_2SO_4), the solution was evaporated *in vacuo* and the residue was purified by preparative TLC with hexane–ethyl acetate (1 : 1) as the developing solvent.

3,4-Dihydro-8-[3′-(*N*-isopropyl-*N*-L-menthoxyacetyl)amino-2′-L-menthoxyacetyl]propoxy-3-nitroxy-2*H*-1-benzopyran (*N*,*O*-Bis-L-menthoxyacetyl Derivative)——Reaction of **1** (5 mg) with L-menthoxyacetyl chloride according to the general procedure gave the *N*,*O*-bis-L-menthoxyacetyl derivatives (oil, 7 mg), which were analyzed by HPLC under the conditions described in Fig. 1. LRMS (FAB) *m/z*: 719 (MH^+), 674, 508, 478, 460. HRMS (EI): Calcd for $C_{39}H_{63}N_2O_{10}$: 719.4479. Found: 719.4469.

2-[1-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetoxy-2-phenylacetic Acid ((+)-4 and (−)-4)——A mixture of **2** (2 g), dry dioxane (1 ml) and thionyl chloride (0.28 ml) was refluxed. After 30 min, (+)-mandelic acid (0.8 g) and dry dioxane (10 ml) were added to the solution, and the mixture was further refluxed for 30 min then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (40 ml) and isopropylamine (3 ml) was added to the solution. The salts that separated were collected by suction and then shaken in 0.5 N HCl (40 ml) and ethyl acetate (20 ml). The organic layer was washed with water, treated with charcoal and dried (Na_2SO_4). Isopropylamine (0.5 ml) was added to the solution and the salts that separated were treated once more as above. The organic layer was then

concentrated to dryness *in vacuo* to give (+)-**4** (yellow solid, 1.2 g). Compound (−)-**4** was prepared in the same manner using (−)-mandelic acid instead of (+)-mandelic acid. $[\alpha]_D^{25}$ ($c=0.1$, $CHCl_3$): (+)-**4**, 66.2°; (−)-**4**, −65.9°. *Anal.* Calcd for $C_{27}H_{22}ClNO_6 \cdot C_{15}H_{22}N_2O_6$ (as salts with **1**): C, 61.65; H, 5.42; N, 5.14. Found: (+)-**4**, C, 61.41; H, 5.48; N, 5.07. (−)-**4**, C, 61.48; H, 5.60; N, 4.89. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (s, 3H, 2-C$\underline{H}_3$), 3.75 (s, 3H, 5-OC$\underline{H}_3$), 3.81 (s, 2H, 3-C$\underline{H}_2$–), 5.92 (s, 1H, 3-CH$_2$COOC$\underline{H}$–), 6.6—7.0 (m, 3H, indol-$\underline{H}$), 7.3—7.7 (m, 9H, benzoyl-$\underline{H}$ and phenyl-$\underline{H}$).

Optical Resolution of Racemate 1A——A solution of (+)-**4** (300 mg) and **1A** (200 mg) in hot ethyl acetate (15 ml) was mixed with hot hexane (15 ml), and allowed to stand overnight at room temperature. After removal of the mother liquid by decantation, the salts were dissolved in hot ethyl acetate (17 ml). The solution was mixed with hot hexane (15 ml) and left overnight at room temperature. This recrystallization procedure was repeated four times. The salts which were optically resolved were dissolved in chloroform (5 ml) and shaken with 1 N HCl (5 ml). The aqueous layer was transferred to another container, made alkaline with NH_3–NH_4Cl buffer solution (5 M, pH 10) (4 ml) and extracted with chloroform (10 ml). The organic layer was dried (Na_2SO_4) and concentrated to dryness *in vacuo*. The residue was recrystallized from ethyl acetate to give enantiomer **1A1** (white crystals, 40 mg). Enantiomer **1A2** was obtained in the same manner using (−)-**4** instead of (+)-**4**. The purity of each enantiomer was checked by HPLC as the *N*,*O*-bis-L-menthoxyacetyl derivative under the conditions described in Fig. 1. $[\alpha]_D^{25}$ ($c=0.1$, $CHCl_3$): **1A1**, 14.4°; **1A2**, −14.2°. *Anal.* Calcd for $C_{15}H_{22}N_2O_6$: C, 55.21; H, 6.79; N, 8.58. Found: **1A1**, C, 55.08; H, 6.68; N, 8.47. **1A2**, C, 55.30; H, 6.66; N, 8.51. NMR ($CDCl_3$) δ: 1.08 (d, 6H, –CH(C$\underline{H}_3$)$_2$), 2.7—2.9 (m, 3H, 3′-C$\underline{H}_2$, –C$\underline{H}$(CH$_3$)$_2$), 3.03 and 3.28 (br d, dd, 2H, 4-C$\underline{H}_2$), 3.9—4.1 (m, 3H, 1′-C$\underline{H}_2$, 2′-C$\underline{H}$), 4.28 and 4.42 (br d, dq, 2H, 2-C$\underline{H}_2$), 5.45 (m, 1H, 3-C$\underline{H}$), 6.6—6.9 (m, 3H, Ar-$\underline{H}$).

3,4-Dihydro-8-[3′-(*N*-*p*-chlorobenzoyl-*N*-isopropyl)amino-2′-hydroxy]propoxy-3-nitroxy-2*H*-1-benzopyran (5B)——Triethylamine (0.1 ml) and a solution of *p*-chlorobenzoyl chloride (25 mg) in benzene (10 ml) were added to a solution of **1B** (50 mg) in benzene (15 ml) at room temperature. After standing for 30 min, the solution was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by preparative TLC with hexane–AcOEt (1 : 1) as the developing solvent to give **5B** (oil, 60 mg). ^{1}H-NMR ($CDCl_3$) δ: 1.20 (q, 6H, –CH(C$\underline{H}_3$)$_2$), 3.03 and 3.31 (br d, dd, 2H, 4-C$\underline{H}_2$), 3.71 (br s, 2H, 3′-C$\underline{H}_2$), 3.8—4.5 (m, 6H, 2-C$\underline{H}_2$, 1′-C$\underline{H}_2$, 2′-C$\underline{H}$, –C$\underline{H}$(CH$_3$)$_2$), 5.48 (m, 1H, 3-C$\underline{H}$), 6.7—7.0 (m, 3H, Ar-$\underline{H}$), 7.3—7.5 (m, 4H, benzoyl-$\underline{H}$). LRMS (EI) *m/z*: 465 (MH^+), 446, 254, 139 (base). HRMS (EI): Calcd for $C_{22}H_{26}ClN_2O_7$: 465.1425. Found: 465.1415.

3,4-Dihydro-8-[3′-(*N*-*p*-chlorobenzoyl-*N*-isopropyl)amino-2′-L-menthoxyacetyloxy]propoxy-3-nitroxy-2*H*-1-benzopyran (6B) and HPLC Separation of 6B into Two Components (6B1 and 6B2)——Reaction of **5B** (10 mg) with L-menthoxyacetyl chloride according to the general procedure gave **6B** (oil, 12 mg). The separation of **6B** into two components was achieved by preparative HPLC on a 10-μm silica gel column (4 × 400 mm, packing: Partisil-10 (Whatman)) eluted with hexane–AcOEt (7 : 1) at a flow rate of 1 ml/min. The first component was **6B2** and the second, **6B1**. LRMS (FAB) *m/z*: 661 (MH^+), 616, 465, 450, 420.

Partial Hydrolysis of 6B1 and 6B2——Compound **6B1** (10 mg) was dissolved in isopropylamine (2 ml). After 24 h at room temperature, the solvent was removed *in vacuo*. The residue was purified by preparative TLC with hexane–AcOEt (1 : 1) as the developing solvent to give **5B1** (oil, 5 mg). The same treatment of **6B2** gave **5B2**. Spectral data of **5B1** and **5B2** were identical with those of **5B**.

3,4-Dihydro-8-[2′-*p*-chlorobenzoyloxy-3′-(*N*-*p*-chlorobenzoyl-*N*-isopropyl)amino]propoxy-3-nitroxy-2*H*-1-benzopyran (7A1, 7A2, 7B1 and 7B2)——Reaction of **1A1**, **1A2**, **6B1** or **6B2** (5 mg) with *p*-chlorobenzoyl chloride according to the general procedure gave **7A1**, **7A2**, **7B1** or **7B2** (colorless crystals, 5—7 mg), respectively. ^{1}H-NMR (acetone-d_6) δ: 1.15 and 1.20 (d, d, 6H, –CH(C$\underline{H}_3$)$_2$), 3.09 and 3.30 (br d, dt, 2H, 4-C$\underline{H}_2$), 3.8—4.1 (m, 3H, 3′-C$\underline{H}_2$, –C$\underline{H}$(CH$_3$)$_2$), 4.2—4.6 (m, 4H, 2-C$\underline{H}_2$, 1′-C$\underline{H}_2$), 5.68 (m, 1H, 3-C$\underline{H}$), 5.89 (m, 1H, 2′-C$\underline{H}$), 6.8—7.0 (m, 3H, Ar-$\underline{H}$), 7.3—8.1 (m, 8H, benzoyl-$\underline{H}$). LRMS (EI) *m/z*: 602 (M^+), 539, 446, 393, 139 (base). HRMS (EI): Calcd for $C_{29}H_{28}Cl_2N_2O_8$: 602.1220. Found: **7A1**, 602.1200; **7A2**, 602.1180; **7B1**, 602.1187; **7B2**, 602.1241.

3,4-Dihydro-8-hydroxy-3-nitroxy-2*H*-1-benzopyran (8A1 and 8A2)——Compound **1A1** (300 mg) was heated at 145 °C for 30 min. The resulting mixture was separated by preparative TLC with chloroform–acetone–isopropylamine (10 : 5 : 1) as the developing solvent to give **8A1** (colorless crystals, 20 mg, *Rf*: about 0.7). Similar treatment of **1A2** gave **8A2**. ^{1}H-NMR ($CDCl_3$) δ: 3.04 and 3.28 (br d, dd, 2H, 4-C$\underline{H}_2$), 4.29 and 4.45 (br d, dq, 2H, 2-C$\underline{H}_2$), 5.47 (m, 1H, 3-C$\underline{H}$), 6.6—6.9 (m, 3H, Ar-$\underline{H}$). LRMS (EI) *m/z*: 211 (M^+, base), 147, 135, 122, 107, 91, 77.

3,4-Dihydro-3,8-dihydroxy-2*H*-1-benzopyran (9A1 and 9A2)——A solution of **8A1** (10 mg) in 2 N HCl (2 ml) was heated at 105 °C for 3 h. After cooling, the solution was neutralized and extracted with ethyl acetate (5 ml). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative TLC with chloroform–isopropyl ether–methanol–triethylamine (12 : 3 : 3 : 2) as the developing solvent to give **9A1** (colorless crystals, 7 mg). Similar treatment of **8A2** gave **9A2**. ^{1}H-NMR ($CDCl_3$) δ: 2.83 and 3.10 (br d, dd, 2H, 4-C$\underline{H}_2$), 4.2 (m, 2H, 2-C$\underline{H}_2$), 5.30 (m, 1H, 3-C$\underline{H}$), 6.6—6.9 (m, 3H, Ar-$\underline{H}$). LRMS (EI) *m/z*: 166 (M^+, base), 147, 135, 122, 107, 91, 77.

3,4-Dihydro-3,8-bis(*p*-chlorobenzoyloxy)-2*H*-1-benzopyran (10A1 and 10A2)——Reaction of **9A1** (5 mg) and *p*-chlorobenzoyl chloride according to the general procedure gave **10A1** (colorless crystals, 5 mg). Similar treatment of **9A2** gave **10A2**. ^{1}H-NMR (acetone-d_6) δ: 3.14 and 3.41 (br d, dd, 2H, 4-C$\underline{H}_2$), 4.33 and 4.41 (d, dq, 2H, 2-C$\underline{H}_2$), 5.59 (m, 1H, 3-C$\underline{H}$), 6.9—7.2 (m, 3H, Ar-$\underline{H}$), 7.5—8.3 (m, 8H, benzoyl-$\underline{H}$). LRMS (EI) *m/z*: 442 (M^+), 286, 139 (base),

111. HRMS (EI): Calcd for $C_{23}H_{16}Cl_2O_5$: 442.0374. Found: **10**A1, 442.0397; **10**A2, 442.0374.

3,4-Dihydro-3-hydroxy-8-(2′-hydroxy-3′-isopropylamino)propoxy-2*H*-1-benzopyran (11A and 11B)——Compound **1**A (500 mg) in 0.3 N H_2SO_4 (80 ml) was refluxed for 24 h. After cooling, the solution was washed with chloroform (40 ml × 2), made alkaline with 5 N NaOH and then extracted with chloroform (50 ml × 2). The combined extracts were washed with a small amount of water, dried (Na_2SO_4) and concentrated *in vacuo* to give **11**A (colorless solid, 350 mg). Similar treatment of **1**B gave **11**B. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (d, 6H, $-CH(CH_3)_2$), 2.6—2.9 (m, 3H, 3′-CH_2, $-CH(CH_3)_2$), 2.8 and 3.05 (br d, dd, 2H, 4-CH_2), 3.9—4.1 (m, 3H, 1′-CH_2, 2′-CH), 4.14 (m, 2H, 2-CH_2), 4.23 (m, 1H, 3-CH), 6.6—6.9 (m, 3H, Ar-H). LRMS (EI) *m/z*: 281 (M^+) 237, 166, 91, 77, 72.

3,4-Dihydro-8-[3′-(*N*-acetyl-*N*-isopropyl)amino-2′-hydroxy]propoxy-3-hydroxy-2*H*-1-benzopyran (12A and 12B)——Acetic anhydride (0.2 ml) was added to a solution of **11**A (200 mg) in dry pyridine (20 ml) at room temperature. The mixture was allowed to stand for 1 h, then water (0.5 ml) was added and the solvent was removed *in vacuo*. The residue was dissolved in chloroform (20 ml) and the solution was washed with 1 N HCl (10 ml × 2), saturated $NaHCO_3$ solution (10 ml) and then water (10 ml). After being dried (Na_2SO_4), the organic layer was concentrated *in vacuo* to give **12**A (oil, 190 mg). Similar treatment of **11**B gave **12**B. ^{1}H-NMR ($CDCl_3$) δ: 1.21 and 1.28 (d, d, 6H, $-CH(CH_3)_2$), 2.19 (s, 3H, $-COCH_3$), 2.82 and 3.09 (dd, dd, 2H, 4-CH_2), 3.56 (m, 2H, 3′-CH_2), 3.83 (t, 1H, one of 1′-CH_2), 4.05 (m, 1H, $-CH(CH_3)_2$), 4.1—4.2 (m, 4H, one of 1′-CH_2, 2′-CH, 2-CH_2), 4.25 (m, 1H, 3-CH), 6.6—7.0 (m, 3H, Ar-H). LRMS (EI) *m/z*: 323 (M^+), 308, 305, 200, 158 (base).

2′,3-Succinyloxy-3,4-dihydro-8-[3′-(*N*-acetyl-*N*-isopropyl)amino]propoxy-2*H*-1-benzopyran (13A and 13B)——Succinyl chloride (50 μl) was added to a solution of **12**A (100 mg) in ethanol-free dry chloroform (10 ml) in a sealed tube, and the solution was heated at 80 °C for 4 h, then cooled. Methanol (0.5 ml) was added and the solution was concentrated *in vacuo*. The residue was purified by preparative TLC with hexane–AcOEt (2 : 1) as the developing solvent to give **13**A (colorless crystals, 40 mg, *Rf*: about 0.25). Similar treatment of **12**B gave **13**B. ^{1}H-NMR (CCl_4) δ: **13**A, 1.16 (m, 6H, $-CH(CH_3)_2$), 2.30 (s, 3H, $-COCH_3$), 2.2—2.7 (m, 4H, $-COCH_2CH_2CO-$), 2.82 (br d, 1H, one of 4-CH_2), 3.0—3.2 (m, 2H, one of 4-CH_2, one of 3′-CH_2), 3.50 (dd, 1H, one of 3′-CH_2), 3.88 and 4.56 (br d, br dt, 2H, 2-CH_2), 3.9 (1H, $-CH(CH_3)_2$), 4.16 and 4.41 (br d, dd, 2H, 1′-CH_2), 4.85 (m, 1H, 2′-CH), 5.11 (m, 1H, 2-CH), 6.6—6.8 (m, 3H, Ar-H); **13**B, 1.22 and 1.32 (dd, dd, 6H, $-CH(CH_3)_2$), 2.06 (s, 3H, $-COCH_3$), 2.0—2.8 (m, 4H, $-COCH_2CH_2CO-$), 2.75 and 3.05 (br d, br d, 2H, 4-CH_2), 2.90 and 3.56 (dd, dd, 2H, 3′-CH_2), 3.85—4.1 (m, 3H, one of 2-CH_2, one of 1′-CH_2, $-CH(CH_3)_2$), 4.33 (br dt, 1H, one of 2-CH_2), 4.45 (br d, 1H, one of 1′-CH_2), 5.15 (m, 1H, 2′-CH), 5.24 (m, 1H, 3-CH), 6.5—6.9 (m, 3H, Ar-H). LRMS (EI) *m/z*: 405 (M^+, base), 362, 320, 258, 216, 148, 140. HRMS (EI): Calcd for $C_{21}H_{27}NO_7$: 405.1785. Found: **13**A, 405.1753; **13**B, 405.1785.

References and Notes

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