



lactone **2** with diisobutylaluminum hydride (DIBAH) at  $-78^{\circ}\text{C}$  gave **5** in an improved yield. Dehydration of **5** by heating with mesyl chloride and triethylamine in dichloromethane gave **6**<sup>2,3</sup> in 86% yield. Hydroboration of **6** with boran-tetrahydrofuran (THF) complex gave 2,3-dihydronaphtho[1,8-*bc*]pyran-3-ol (**7**). Oxidation of **7** with PCC in dichloromethane afforded a ketone (**8**) in 78% yield. Reaction of **8** with cyanotrimethylsilane in the presence of zinc iodide gave **9**, which was reduced with LAH to 3-aminomethyl-2,3-dihydronaphtho[1,8-*bc*]pyran-

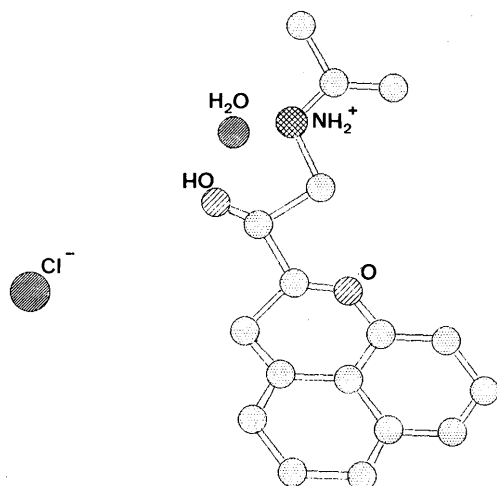


Fig. 1. Crystal Structure of *erythro*-Compound B Hydrochloride<sup>6)</sup>  $\text{C}_{17}\text{H}_{21}\text{NO}_2 \cdot \text{H}_2\text{O} \cdot \text{HCl}$ , monoclinic,  $C2/c$ ,  $a=28.74\text{\AA}$ ,  $b=8.86\text{\AA}$ ,  $c=14.47\text{\AA}$ ,  $\beta=113^{\circ}11'$

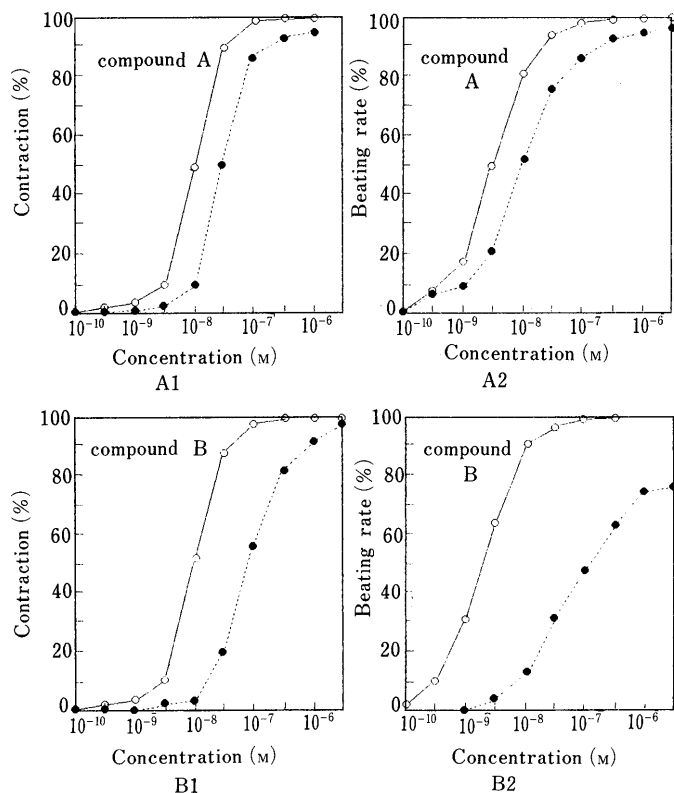


Fig. 2.  $\beta$ -Blocking Actions of Compounds, A and B in Guinea-pig

A1, compound A, contraction of left atrium ( $\text{pA}_2=5.90$ ); A2, compound A, beating rate of right atrium ( $\text{pA}_2=5.83$ ); B1, compound B, contraction of left atrium ( $\text{pA}_2=6.64$ ); B2, compound B, beating rate of right atrium ( $\text{pA}_2=7.46$ ); O, pre- and ●, post-administration of isoproterenol.

3-ol (**10**). Reductive condensation of **10** with acetone by the use of sodium cyanoborohydride gave the desired racemic compound A, which was converted to its hydrochloride, and the sample was subjected to biological assay.

The synthesis of compound B from the intermediate **5** was started by the introduction of a vinyl function into position 2. Reaction of **5** with vinyl magnesium bromide gave an allyl alcohol (**11**), which was treated with acid to give a 2-vinyl derivative (**12**). Attempts to convert **12** to the corresponding epoxide with various agents, *e.g.*, MCPBA, *tert*-butyl peroxide, or hydrogen peroxide, were unsuccessful. Ozonolysis of the vinyl compound **12** gave an aldehyde (**13**). Conversion of **13** to the amino alcohol (**15**) and an attempt to isolate the product in the same manner as described for A were unsuccessful, probably owing to instability of **15**. The aldehyde (**13**) was then allowed to react with nitromethane in the presence of triethylamine, giving a nitro alcohol (**16**) in good yield. The product was proved, by examination of its proton magnetic resonance spectrum, to be a mixture of diastereomers (6:1).<sup>4)</sup> Reduction of the mixture (**16**) with LAH to **15**, followed by reductive condensation with acetone and sodium cyanoborohydride, gave compound B, which was converted to its hydrochloride. The isolated hydrochloride was found to be the *erythro* isomer by X-ray crystallography (Fig. 1). The *threo* compound could not be obtained in a pure state.

**Bioassay** The hydrochlorides of A and B showed  $\beta$ -blocking activities, increasing the contraction and beating rate of excised atriums of guinea-pig. Both compounds shifted the dose-response curves of contraction and beating rate to the right, and are judged to have  $\beta$ -blocking activities; the potency of B is greater than that of A (Fig. 2).

The potency of B is approximately one tenth of that of propranolol.

#### Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The infrared (IR) spectra were measured on a Hitachi EPI-G2 spectrophotometer and mass spectra (MS) were measured with a JEOL JMS-HX 100 instrument. The proton nuclear magnetic resonance ( $^1\text{H-NMR}$ ) spectra were determined on a JEOL FX200 spectrometer using tetramethylsilane as an internal standard. The coupling patterns are indicated as follows: singlet=s, doublet=d, triplet=t, septet=sep, multiplet=m, broad=br, and aromatic protons=arom.

Liquid chromatographies were performed using a silica gel (Merck Kieselgel 60) column. The organic solutions were dried over anhydrous sodium sulfate.

**2,3-Dihydronaphtho[1,8-*bc*]pyran-2-one (**2**)** Anhydrous  $\text{NaHCO}_3$  (47.3 g, 560 mmol) and MCPBA (50.0 g, 230 mmol) were added to a solution of acenaphthenone (1, 25.0 g, 150 mmol) in  $\text{CH}_2\text{Cl}_2$  (750 ml), and the suspension was refluxed for 3 d. During this period, further  $\text{NaHCO}_3$  (15.8 g) and MCPBA (16.2 g) were added at intervals of 12 h (5 times). The precipitate was filtered off and the filtrate was washed with 2%  $\text{Na}_2\text{CO}_3$  and  $\text{H}_2\text{O}$ , then dried. The solvent was removed *in vacuo* and the resulting residue was purified by chromatography (*n*-hexane:AcOEt = 10:1) to provided **2** as yellow crystals (16.7 g, 61%), mp  $101\text{--}102^{\circ}\text{C}$  (from *n*-hexane). *Anal.* Calcd for  $\text{C}_{12}\text{H}_8\text{O}_2$ : C, 78.25; H, 4.38. Found: C, 78.07; H, 4.46. IR  $\nu_{\text{max}}^{\text{Nujol}} \text{ cm}^{-1}$ : 1760 (COO).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 4.27 (2H, s,  $\text{CH}_2$ ), 7.1–7.8 (6H, m, arom).

**8-(2-Hydroxyethyl)-1-naphthol (**3a**)** Compound **2** (16.7 g, 91 mmol) was dissolved in THF (230 ml), and  $\text{LiAlH}_4$  (3.3 g, 87 mmol) was added under an Ar atmosphere. The mixture was stirred for 15 min at room temperature. After addition of  $\text{H}_2\text{O}$  and then of 10% HCl, the whole was extracted with  $\text{CHCl}_3$ . The extract was washed with brine, dried, and evaporated under reduced pressure. Crystals that deposited upon addition

of  $\text{CHCl}_3$  to the residue were recrystallized from benzene to give **3a** as colorless crystals (11.1 g, 65%), mp 131–132 °C (lit.<sup>2</sup>) mp 134–136 °C). *Anal.* Calcd for  $\text{C}_{12}\text{H}_{12}\text{O}_2$ : C, 76.57; H, 6.43. Found: C, 76.41; H, 6.55. IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 3370 (OH).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.42 (1H, br, s, OH), 3.59 (2H, t,  $J=6$  Hz,  $\text{ArCH}_2$ ), 4.10 (2H, t,  $J=6$  Hz,  $\text{CH}_2\text{OH}$ ), 6.85–7.72 (6H, m, arom), 7.83 (1H, brs, ArOH).

**1-Benzoyloxy-8-(2-hydroxyethyl)naphthalene (3b)** Anhydrous  $\text{Na}_2\text{CO}_3$  (2.07 g, 15 mmol) and benzyl bromide (1.2 ml, 10 mmol) were added to a solution of **3a** (1.88 g, 10 mmol) in acetone (41 ml), and the mixture was stirred for 24 h in an Ar atmosphere at room temperature. The solid was filtered off and the filtrate was concentrated *in vacuo*. The residue was mixed with  $\text{H}_2\text{O}$  and extracted with  $\text{CHCl}_3$ . The extract was dried and evaporated to leave an oil, which was chromatographed (*n*-hexane:  $\text{AcOEt}=4:1$ ) to give **3a** as colorless crystals (2.39 g, 86%), mp 82.5–83.5 °C (from *n*-hexane). *Anal.* Calcd for  $\text{C}_{19}\text{H}_{18}\text{O}_2$ : C, 81.98; H, 6.52. Found: C, 81.94; H, 6.57. IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 3300 (OH).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.90 (1H, brs, OH), 3.39 (2H, t,  $J=7$  Hz,  $\text{ArCH}_2$ ), 3.69 (2H, t,  $J=7$  Hz,  $\text{CH}_2\text{OH}$ ), 5.13 (2H, s,  $\text{OCH}_2\text{Ar}$ ), 6.9–7.7 (11H, m, arom).

**1-(2-Hydroxyethyl)-8-(methoxyethoxymethoxy)naphthalene (3c)** Methoxyethoxymethyl chloride (0.6 ml, 5.3 mmol) was added to a solution of **3a** (0.94 g, 5 mmol) in acetone (10 ml), and the solution was stirred for 5 h at room temperature. The solid was filtered off and the dried filtrate was concentrated *in vacuo*. The residual oil was chromatographed (*n*-hexane:  $\text{AcOEt}=3:1$  then  $1:1$ ) to give **3c** as an oil (0.75 g, 54%). IR  $\nu_{\text{max}}^{\text{neat}}$   $\text{cm}^{-1}$ : 3380 (OH).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.15 (1H, brs, OH), 3.41 (3H, s,  $\text{OCH}_3$ ), 3.55–3.65, 3.91–3.97 (each 4H, m,  $\text{ArCH}_2\text{CH}_2\text{O}$  and  $\text{OCH}_2\text{CH}_2\text{O}$ ), 5.45 (2H, s,  $\text{OCH}_2\text{O}$ ), 7.05–7.71 (6H, m, arom). HR-MS  $m/z$ : Calcd  $\text{C}_{16}\text{H}_{20}\text{O}_4$ : 276.3324. Found: 276.3341.

**1-Benzoyloxy-8-(formylmethyl)naphthalene (4b)** PCC (3.60 g, 17 mmol) was added to a solution of **3b** (2.35 g, 8.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (9 ml), and the mixture was stirred for 1 h. The mixture was filtered through Florisil and the filtrate was concentrated under reduced pressure. The residue was chromatographed (*n*-hexane:  $\text{AcOEt}=20:1$ – $10:1$ ), giving **4b** as crystals (1.01 g, 44%), mp 75–76 °C (benzene–*n*-hexane). *Anal.* Calcd for  $\text{C}_{19}\text{H}_{16}\text{O}_2$ : C, 82.58; H, 5.84. Found: C, 82.66; H, 5.94. IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 1720 (CHO).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 4.15 (2H, d,  $J=1$  Hz,  $\text{CH}_2\text{CHO}$ ), 5.09 (2H, s,  $\text{OCH}_2\text{Ph}$ ), 6.8–7.75 (11H, m, arom), 9.47 (1H, t,  $J=1$  Hz, CHO).

**1-(Methoxyethoxymethoxy)-8-(formylmethyl)naphthalene (4c)** Pyridinium chlorochromate (1.16 g, 5.4 mmol) was added to a solution of **3c** (0.75 g, 2.7 mmol) in  $\text{CH}_2\text{Cl}_2$  (13.5 ml) and the mixture was stirred for 1 h. The suspension was mixed with Florisil and filtered. The filtrate was concentrated *in vacuo* and the resulting oil was purified by chromatography (*n*-hexane:  $\text{AcOEt}=5:1$ – $3:1$ ) to provide an oil (429.4 mg). The solid left on the filter was extracted with a mixture of  $\text{CHCl}_3$  and MeOH (10:1), and the residue obtained by evaporation of the extract was chromatographed (*n*-hexane:  $\text{AcOEt}=5:1$ ) to give an additional crop of **4c** (112.1 mg, overall yield: 73%). IR  $\nu_{\text{max}}^{\text{neat}}$   $\text{cm}^{-1}$ : 1720 (OH).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.35 (3H, s,  $\text{OCH}_3$ ), 3.55, 3.80 (each 2H, m,  $\text{OCH}_2\text{CH}_2\text{O}$ ), 4.17 (2H, brs,  $\text{OCH}_2\text{O}$ ), 7.1–7.8 (11H, m, arom), 9.79 (1H, t,  $J=2$  Hz, CHO). HR-MS  $m/z$ : Calcd  $\text{C}_{16}\text{H}_{18}\text{O}_4$ : 274.3165. Found: 274.3152.

**2,3-Dihydronaphtho[1,8-*bc*]pyran-2-ol (5)** 1) A solution of **2** (920.0 mg, 5 mmol) in dry toluene (15 ml) was stirred with DIBAL (1.0 M in hexane, 6 ml) for 1.5 h at  $-78^\circ\text{C}$ . After addition of  $\text{H}_2\text{O}$  (3.5 ml) at the same temperature, the mixture was warmed to room temperature and stirring was continued for 30 min. The mixture was acidified with 2 N HCl and extracted with  $\text{CH}_2\text{Cl}_2$  and the organic layer was washed with 2%  $\text{NaHCO}_3$  then with  $\text{H}_2\text{O}$ . After drying, the solution was evaporated *in vacuo* and the residue was purified by chromatography (*n*-hexane:  $\text{AcOEt}=10:1$ – $5:1$ ) to provide **5** as crystals (871.7 mg, 94%), mp 69–71 °C (from  $\text{AcOEt}$ –*n*-hexane). *Anal.* Calcd for  $\text{C}_{12}\text{H}_{10}\text{O}_2$ : C, 77.40; H, 5.41. Found: C, 77.45; H, 5.47. IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 3450 (OH).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.24 (1H, dd,  $J=16, 5$  Hz,  $\text{CH}_2$ ), 3.34 (1H, dd,  $J=6, 0.5$  Hz, OH), 3.45 (1H, dd,  $J=16, 3$  Hz,  $\text{CH}_2$ ), 5.79 (1H, ddd,  $J=6, 5, 3$  Hz,  $\text{CHOH}$ ), 7.17–7.74 (6H, m, arom).

2a) A mixture of **4b** (22.1 mg, 0.08 mmol), NaI (24 mg, 0.16 mmol), and chlorotrimethylsilane (20  $\mu\text{l}$ , 0.16 mmol) in MeCN (1 ml) was stirred under an Ar atmosphere for 10 min. The mixture was diluted with  $\text{H}_2\text{O}$  and extracted with  $\text{CH}_2\text{Cl}_2$ . The extract was washed with aqueous 2%  $\text{Na}_2\text{SO}_3$  and  $\text{H}_2\text{O}$ , dried, and evaporated *in vacuo*. The residual oil was purified by preparative thin-layer chromatography (PTLC) ( $R_f$ : 0.2) to give **5** (11.6 mg, 78%), which was identical with that obtained in 1) on the basis of comparison of the spectra data.

2b) Compound **4c** (21.9 mg, 0.08 mmol) was treated in a similar manner to that described for **4b** in 2a) to obtain the same product (15.0 mg,

100%). The spectral data of the sample were identical with those of the authentic sample obtained in 1).

**Naphtho[1,8-*bc*]pyran (6)**  $\text{MeSO}_2\text{Cl}$  (47  $\mu\text{l}$ ) was added to an ice-cooled solution of **5** (93.0 mg, 0.5 mmol) and  $\text{Et}_3\text{N}$  (174.2  $\mu\text{l}$ ) in  $\text{CH}_2\text{Cl}_2$  (1.5 ml) with stirring over a 15-min period, and the mixture was refluxed for 3.5 h, then diluted with  $\text{CH}_2\text{Cl}_2$  and washed with  $\text{H}_2\text{O}$  and with 10% HCl. The solution was dried and evaporated to leave crystals, which were chromatographed (*n*-hexane) to obtain **6** as yellow crystals (71.9 mg, 86%), 62–63 °C (lit.<sup>2</sup>) 44–54 °C, lit.<sup>3</sup>) 50–55 °C). IR  $\nu_{\text{max}}^{\text{CHCl}_3}$   $\text{cm}^{-1}$ : 1648 ( $\text{C}=\text{C}$ ) (lit.<sup>3</sup>) 1640).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 5.94 (1H, d,  $J=6$  Hz,  $\text{ArCH}=\text{C}$ ), 6.69 (1H, d,  $J=6$  Hz,  $\text{C}=\text{CH}-\text{O}$ ), 6.64–7.34 (6H, m, arom).

**2,3-Dihydronaphtho[1,8-*bc*]pyran-3-ol (7)** Compound **6** (33.6 mg, 0.2 mmol) was dissolved in THF (0.5 ml) and the solution was cooled in an ice-bath. To the stirred solution,  $\text{BH}_3$ –THF complex (1.0 M in THF, 0.4 ml) was added, and stirring was continued for 2.5 h under an atmosphere of Ar at room temperature. Usual work up and purification by chromatography (*n*-hexane:  $\text{AcOEt}=10:1$ – $5:1$ ) gave **7** (24.3 mg, 65%). IR  $\nu_{\text{max}}^{\text{neat}}$   $\text{cm}^{-1}$ : 3350 (OH).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.07 (1H, brs, OH), 4.34 (1H, dd,  $J=11, 2.5$  Hz,  $\text{CH}_2\text{O}$ ), 4.42 (1H, dd,  $J=11, 4$  Hz,  $\text{CH}_2\text{O}$ ), 5.00 (1H, dd,  $J=4, 2.5$  Hz, HOCH), 6.99–7.82 (6H, m, arom). HR-MS  $m/z$ : Calcd for  $\text{C}_{12}\text{H}_{10}\text{O}_2$ : 186.0678. Found: 186.0672.

**2,3-Dihydronaphtho[1,8-*bc*]pyran-3-one (8)** PCC (86.2 mg, 0.4 mmol) was added to a solution of **7** (37.2 mg, 0.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 ml), and the mixture was stirred for 3.5 h at room temperature. The suspension was filtered through Florisil and the filtrate was evaporated *in vacuo*. The residue was chromatographed (*n*-hexane:  $\text{AcOEt}=50:1$ ) to isolate **8** as yellow crystals (28.8 mg, 78%), mp 103–104 °C (from EtOH) (lit.<sup>5</sup>) 104 °C). *Anal.* Calcd for  $\text{C}_{12}\text{H}_8\text{O}_2$ : C, 78.25; H, 4.38. Found: C, 78.65; H, 4.33. IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 1680 ( $\text{C}=\text{O}$ ) (lit.<sup>5</sup>) 1667).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 4.93 (2H, s,  $\text{CH}_2$ ), 7.13–8.18 (6H, m, arom).

**3-Aminomethyl-2,3-dihydronaphtho[1,8-*bc*]pyran-3-ol (10)** A mixture of **8** (500.0 mg, 2.72 mmol), a catalytic amount of  $\text{ZnI}_2$ , and trimethylsilyl cyanide (0.68 ml, 5.40 mmol) was stirred for 2 h under an Ar atmosphere. THF (15 ml) was added, and then  $\text{LiAlH}_4$  (4.7 mg, 12.5 mmol) was added. The mixture was stirred for an additional 2 h at room temperature. The excess  $\text{LiAlH}_4$  was destroyed by addition of  $\text{H}_2\text{O}$  and aqueous NaOH, and the mixture was extracted with  $\text{Et}_2\text{O}$ . After drying of the extract, the solvent was removed *in vacuo* and the residue was chromatographed ( $\text{CHCl}_3$ :  $\text{MeOH}=10:1$ – $5:1$ ) to obtain **10** as crystals (303.0 mg, 52%), mp 81–82 °C. *Anal.* Calcd for  $\text{C}_{13}\text{H}_{13}\text{NO}_2$ : C, 72.54; H, 6.09; N, 6.51. Found: C, 72.33; H, 6.23; N, 6.70. IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 2500–3300 (OH and  $\text{NH}_2$ ).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.30 (3H, brs, OH and  $\text{NH}_2$ ), 2.74, 3.13 (each 1H, d,  $J=13$  Hz,  $\text{CH}_2\text{NH}_2$ ), 3.98, 4.31 (each 1H, d,  $J=11$  Hz,  $\text{CH}_2-\text{O}$ ), 6.9–7.8 (6H, m, arom).

**3-(*N*-Isopropylaminomethyl)-2,3-dihydronaphtho[1,8-*bc*]pyran-3-ol (A)** 1)  $\text{NaBH}_3\text{CN}$  (16.0 mg, 0.25 mmol) was added to a mixture of **10** (54.0 mg, 0.25 mmol),  $\text{AcOH}$  (14 ml) and  $\text{Me}_2\text{CO}$  (20  $\mu\text{l}$ , 0.28 mmol) in MeOH (1 ml), and the mixture was stirred for 40 min at room temperature, then diluted with  $\text{H}_2\text{O}$  and extracted with  $\text{CHCl}_3$ . The extract was dried and evaporated *in vacuo*, leaving the crude product, which was chromatographed ( $\text{CHCl}_3$ :  $\text{MeOH}=20:1$ – $10:1$ ) to provide A as an oil (49.0 mg, 77%). IR  $\nu_{\text{max}}^{\text{neat}}$   $\text{cm}^{-1}$ : 3200–3400 (OH and NH).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.09 (6H, d,  $J=6$  Hz,  $\text{CH}_3 \times 2$ ), 2.57 (1H, dd,  $J=13, 1$  Hz,  $\text{N}-\text{CH}_2$ ), 2.70 (2H, brs, OH and NH), 2.84 (1H, sep,  $J=6$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 3.14 (1H, d,  $J=13$  Hz,  $\text{N}-\text{CH}_2$ ), 4.00 (1H, dd,  $J=11, 1$  Hz,  $\text{OCH}_2$ ), 4.27 (1H, d,  $J=11$  Hz,  $\text{OCH}_2$ ), 6.9–7.8 (6H, m, arom).

The product was dissolved in ether and gaseous HCl was passed through the solution, precipitating the hydrochloride. The crystalline salt was recrystallized from ethanol–ether. mp 196–198 °C. *Anal.* Calcd for  $\text{C}_{16}\text{H}_{20}\text{ClNO}_2$ : C, 65.41; H, 6.86; N, 4.77. Found: C, 65.38; H, 6.91; N, 4.81.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.45, 1.48 (each 3H, d,  $J=7$  Hz,  $\text{CH}_3 \times 2$ ), 3.17, 3.46 (each 1H, brd,  $J=13$  Hz,  $\text{CH}_2\text{N}$ ), 3.48 (1H, brs,  $\text{CH}(\text{CH}_3)_2$ ), 4.14, 5.07 (each 1H, d,  $J=11$  Hz,  $\text{CH}_2-\text{O}$ ), 5.99 (1H, brs, OH), 6.9–7.8 (6H, m, arom), 8.66, 9.42 (each 1H, brs,  $\text{NH}_2^+$ ).

2)  $\text{Me}_2\text{CO}$  (34 l, 0.47 mmol) and  $\text{NaBH}_3\text{CN}$  (62.8 mg, 0.23 mmol) were added to a solution of **10** (50.0 mg, 0.23 mmol) in MeOH (5 ml). The mixture was stirred at room temperature for 30 min, concentrated, diluted with  $\text{H}_2\text{O}$ , and extracted with ether. The ethereal layer was washed with brine and dried. After removal of the solvent, the residue was fractionated by PTLC ( $\text{AcOEt}$ :  $\text{EtOH}=10:1$ ) and the fraction of  $R_f=0.4$  gave A (10.0 mg, 16%). This was identical in terms of the spectral data with the authentic sample prepared by procedure 1.

**8-(2-Hydroxy-3-butenyl)-1-naphthol (11)** Compound **5** (2.05 g, 11 mmol) was dissolved in THF (33 ml), and vinyl magnesium bromide (1.0 M in THF, 24.2 ml, 24.2 mmol) was added to the solution under an atmosphere

of Ar. The mixture was stirred for 2 d at room temperature. During this period, additional portions (10 ml, and 17 ml) of the Grignard reagent were added at 16 and 24 h after the start of stirring. A saturated aqueous  $\text{NH}_4\text{Cl}$  solution was added to the mixture and the THF layer was evaporated *in vacuo*. Then  $\text{H}_2\text{O}$  was added to the residue. The mixture was extracted with  $\text{CH}_2\text{Cl}_2$ , and the extract was washed with 2%  $\text{NaHCO}_3$  and  $\text{H}_2\text{O}$ , dried and evaporated. The resulting residue was chromatographed (*n*-hexane:AcOEt = 10:1—5:1) to give **11** as colorless crystals (1.97 g, 84%), mp 100.5—101.5°C (from AcOEt-*n*-hexane). *Anal.* Calcd for  $\text{C}_{14}\text{H}_{14}\text{O}_2$ : C, 78.48; H, 6.59. Found: C, 78.43; H, 6.66. IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 3350, 3550 (OH).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.78 (1H, brs,  $\text{CHOH}$ ), 3.45 (1H, dd, 14, 3.5 Hz, Ar- $\text{CH}_2$ ), 3.64 (1H, dd,  $J$  = 14, 8.5 Hz, Ar- $\text{CH}_2$ ), 4.55—4.66 (1H, m,  $\text{HOCH}$ ), 5.18 (1H, dt,  $J$  = 10.5, 1.5 Hz,  $\text{C}=\text{CH}_2$ ), 5.31 (1H, dt,  $J$  = 17, 1.5 Hz,  $\text{C}=\text{CH}_2$ ), 6.04 (1H, ddd,  $J$  = 17, 10.5 Hz,  $\text{H}_2\text{C}=\text{CH}$ ), 6.92—7.72 (6H, m, arom), 8.12 (1H, brs, Ar-OH). EI-MS  $m/z$ : 214 ( $\text{M}^+$ ).

**2-Vinyl-2,3-dihydronaphtho[1,8-*bc*]pyran (12)** Concentrated  $\text{H}_2\text{SO}_4$  (8 ml) was added to a solution of **11** (1.71 g, 8 mmol) in MeOH (40 ml). The mixture was stirred for 30 min, then diluted with  $\text{H}_2\text{O}$  and the MeOH was distilled off under reduced pressure. The resulting residue was taken up in  $\text{H}_2\text{O}$  and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$ . The extract was washed with 2%  $\text{NaHCO}_3$  and  $\text{H}_2\text{O}$ . The dried solution was evaporated *in vacuo* and the residue was chromatographed (*n*-hexane) to provide **12** as an oil (1.43 g, 91%). IR  $\nu_{\text{max}}^{\text{neat}}$   $\text{cm}^{-1}$ : 1600 ( $\text{C}=\text{C}$ ).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.22 (2H, d,  $J$  = 6.5 Hz,  $\text{CH}_2$ ), 4.781—4.79 (1H, m,  $\text{CH}-\text{O}$ ), 5.32 (1H, dt,  $J$  = 10.5, 1 Hz,  $\text{C}=\text{CH}_2$ ), 5.50 (1H, dt,  $J$  = 17, 1 Hz,  $\text{C}=\text{CH}_2$ ), 6.13 (1H, ddd,  $J$  = 17, 10.5, 6 Hz,  $\text{H}_2\text{C}=\text{CH}$ ), 6.60—7.71 (6H, m, arom). HR-MS  $m/z$ : Calcd  $\text{C}_{14}\text{H}_{12}\text{O}$ : 196.0885. Found: 196.0893.

**2-Formyl-2,3-dihydronaphtho[1,8-*bc*]pyran (13)** A solution of **12** (294.0 mg, 1.5 mmol) in MeOH (15 ml) was cooled to  $-78^\circ\text{C}$ , and  $\text{O}_3$  was passed into the solution with stirring until the spot of **12** was no longer observed on TLC (4.5 h). The ozonide was decomposed by addition of  $\text{Me}_2\text{S}$  (0.5 ml). After addition of  $\text{H}_2\text{O}$ , the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  and the extract was washed with  $\text{H}_2\text{O}$  and dried. The solution was evaporated *in vacuo* and the residue was chromatographed (*n*-hexane: $\text{CH}_2\text{Cl}_2$  = 1:1), giving **13** as an oil (177.7 mg, 60%). IR  $\nu_{\text{max}}^{\text{neat}}$   $\text{cm}^{-1}$ : 1740 ( $\text{CHO}$ ).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.36 (1H, dd,  $J$  = 16, 8 Hz, Ar- $\text{CH}_2$ ), 3.45 (1H, dd,  $J$  = 16, 5 Hz, Ar- $\text{CH}_2$ ), 4.75 (1H, dd,  $J$  = 8, 5 Hz,  $\text{CH}-\text{CHO}$ ), 7.10—7.75 (6H, m, arom), 9.92 (1H, s,  $\text{CHO}$ ). HR-MS  $m/z$ : Calcd  $\text{C}_{13}\text{H}_{10}\text{O}_2$ : 198.1497. Found: 198.1485.

**Attempt to Obtain 2-(2-Amino-1-hydroxyethyl)-2,3-dihydronaphtho[1,8-*bc*]pyran (15)** A mixture of **13** (29.7 mg, 0.15 mmol), a catalytic amount of  $\text{ZnI}_2$ , and  $\text{Me}_3\text{SiCN}$  (81  $\mu\text{l}$ , 0.60 mmol) was stirred for 30 min, followed by addition of THF (1 ml) and  $\text{LiAlH}_4$  (25.0 mg, 0.66 mmol). The mixture was stirred for 10 min at room temperature. A small amount of  $\text{H}_2\text{O}$  and 30% NaOH (35  $\mu\text{l}$ ) was added to the mixture and the resulting mixture was extracted with ether. The extract was washed with brine, dried, and evaporated. The residue was subjected to PTLC ( $\text{CHCl}_3$ :MeOH = 1:1) and the fraction of  $R_f$  = 0.1 gave an amino alcohol (8.3 mg, 24%). However, it was too unstable for further purification to be possible, and decomposed during the period of spectral measurement.

**2-(1-Hydroxy-2-nitroethyl)-2,3-dihydronaphtho[1,8-*bc*]pyran (16)** A mixture of **13** (639.5 mg, 3.23 mmol) and nitromethane (1.8 ml, 33 mmol) was cooled in an ice-bath and  $\text{Et}_3\text{N}$  (93  $\mu\text{l}$ , 0.66 mmol) was added. The mixture was stirred for 15 min under cooling and then for 2 h at room temperature. After addition of  $\text{H}_2\text{O}$ , the mixture was extracted with  $\text{CH}_2\text{Cl}_2$ . The extract was washed with  $\text{H}_2\text{O}$ , 2% HCl, and brine, dried, and evaporated to leave an oil, which was chromatographed (*n*-hexane:AcOEt = 10:1) to provide **16** (832.7 mg, 100%). IR  $\nu_{\text{max}}^{\text{neat}}$   $\text{cm}^{-1}$ : 3470 (OH), 1550 ( $\text{NO}_2$ ).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.60 (1H, brs, OH), 3.23 (1H, dd,  $J$  = 16, 10 Hz, Ar- $\text{CH}_2$ ), 3.39 (1H, dd,  $J$  = 16, 3.5 Hz, Ar- $\text{CH}_2$ ), 4.22 (1H, ddd,  $J$  = 10, 7.5, 3.5 Hz,  $-\text{O}-\text{CH}-$ ), 4.54 (1H, ddd,  $J$  = 9, 7.5, 2.5 Hz,  $\text{HOCH}$ ), 4.66 (1H, dd,  $J$  = 13.5, 9 Hz,  $\text{O}_2\text{N}-\text{CH}_2$ ), 4.91 (1H, dd,  $J$  = 13.5, 2.5 Hz,  $\text{O}_2\text{N}-\text{CH}_2$ ), 6.91—7.72 (6H, m, arom). HR-MS  $m/z$ : Calcd

$\text{C}_{14}\text{H}_{13}\text{O}_4\text{N}$ : 259.0841. Found: 259.0862.

**2-[1-Hydroxy-2-(*N*-isopropylamino)ethyl]-2,3-dihydronaphtho[1,8-*bc*]pyran (B)**  $\text{LiAlH}_4$  (398.5 mg, 10.5 mmol) was added to a solution of **15** (906.5 mg, 3.5 mmol) in THF (3 ml), and the mixture was refluxed for 3.5 h. Small amounts of  $\text{H}_2\text{O}$  and 30% NaOH were added and the mixture was extracted with  $\text{Et}_2\text{O}$ . The extract was washed with brine, dried, and evaporated to leave an oil, which was dissolved in  $\text{Me}_2\text{CO}$  (18 ml). AcOH (0.2 ml, 3.5 mmol) and  $\text{NaBH}_3\text{CN}$  (439.9 mg, 7 mmol) were added to this solution and the reaction mixture was stirred for 1.5 h at room temperature, then diluted with  $\text{H}_2\text{O}$  and extracted with  $\text{CH}_2\text{Cl}_2$ . The extract was washed with brine, dried, and evaporated *in vacuo*. The residue was chromatographed ( $\text{CHCl}_3$ :MeOH = 50:1—30:1) to obtain B as an oil (671.1 mg, 71%). IR  $\nu_{\text{max}}^{\text{neat}}$   $\text{cm}^{-1}$ : 2950, 3300 (OH and NH).  $^1\text{H-NMR}$  ( $(\text{CD}_3)_2\text{CO}$ )  $\delta$ : 1.45, 1.46 (each 3H, d,  $J$  = 6.5 Hz,  $\text{CH}_3 \times 2$ ), 3.23 (1H, dd,  $J$  = 17, 10 Hz, Ar- $\text{CH}_2$ ), 3.23 (1H, dd,  $J$  = 13, 9 Hz, N- $\text{CH}_2$ ), 3.40 (1H, dd,  $J$  = 17, 3 Hz, Ar- $\text{CH}_2$ ), 3.53 (1H, sep,  $J$  = 6.5 Hz,  $\text{CH}(\text{CH}_3)_2$ ), 3.61 (1H, dd,  $J$  = 13, 2.5 Hz, N- $\text{CH}_2$ ), 4.18 (1H, ddd,  $J$  = 10, 7, 3 Hz,  $-\text{O}-\text{CH}-$ ), 4.30 (1H, ddd,  $J$  = 9, 7, 2.5 Hz,  $\text{HO}-\text{CH}$ ), 4.0—4.7 (2H, brs, OH and NH), 6.88—7.73 (6H, m, arom). EI-MS  $m/z$ : 271 ( $\text{M}^+$ ).

The product was converted to its hydrochloride by passing gaseous HCl into a solution of the base in ether. The precipitate was recrystallized from  $\text{CHCl}_3$ - $\text{Me}_2\text{CO}$  to give crystals, mp 157—158°C. *Anal.* Calcd for  $\text{C}_{17}\text{H}_{22}\text{ClNO}_2$ : C, 66.33; H, 7.20; N, 4.55. Found: C, 66.08; H, 7.16; N, 4.62. IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 3150 (OH and  $\text{NH}_2$ ).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.49, 1.52 (each 3H, d,  $J$  = 6.5 Hz,  $\text{CH}_3 \times 2$ ), 2.36 (1H, brs, OH), 3.17 (1H, dd,  $J$  = 13, 9 Hz, N- $\text{CH}_2$ ), 3.19 (1H, dd,  $J$  = 17, 10 Hz, Ar- $\text{CH}_2$ ), 3.41 (1H, dd,  $J$  = 17, 3 Hz, Ar- $\text{CH}_2$ ), 3.42—3.69 (2H, m,  $\text{CH}(\text{CH}_3)_2$  and N- $\text{CH}_2$ ), 4.14 (1H, ddd,  $J$  = 10, 7.5, 3 Hz,  $-\text{O}-\text{CH}-$ ), 4.41 (1H, ddd,  $J$  = 9, 7.5, 2 Hz,  $\text{HO}-\text{CH}$ ), 6.86—7.66 (6H, m, arom), 8.54, 9.58 (each 1H, brs,  $\text{NH}_2^+$ ). EI-MS  $m/z$ : 271 ( $\text{M}^+ - \text{HCl}$ ).

**Bioassay** Hearts excised from male guinea-pigs luxated at the cervical vertebrae were used. The right and left atria were fixed vertically in Krebs-Henseleit solution. The contractile force was recorded on applying a shock (50 V, 10 ms, 1 Hz) to the right atrium, and the beating rate was observed on the left one. Various doses of isoproterenol ( $10^{-10}$ — $3 \times 10^{-5}$  M) were applied and the maximum level of response was taken as 100%. Then, the hydrochloride of A or B (initial concentration:  $3 \times 10^{-6}$  M) was applied. Competitive inhibitions in the case of A were  $pA_2$  = 5.90 for contraction and  $pA_2$  = 5.83 for beating rate, and those in the case of B were  $pA_2$  = 6.64 for contraction and (though the maximum response was depressed),  $pA_2$  = 7.46 for beating rate. The  $pA_2$  values of propranolol were 7.52 for contraction and 8.33 for beating rate.

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## References and Notes

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