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Synthesis of enantiomeric 4-hydroxypropranolols from 1,4-dihydroxynaphthalene

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Abstract—Both (*R*)- and (*S*)-enantiomers of 4-hydroxypropranolol were effectively prepared from 1,4-dihydroxynaphthalene in eight steps. The overall yields were around 30%.

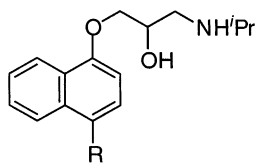
1. Introduction

Propranolol (PL) **1** is a typical adrenoceptor blocking agent that is often prescribed for the treatment of hypertension and arrhythmia. It is known that repeated oral administration of **1** to rats causes deactivation of P-450 mono-oxygenase in liver.[1] Covalent bond formation between 4-hydroxypropranolol (4-OHPL) **2**, a primary metabolite of **1**, and hepatic microsomal proteins could be supposed to be the deactivation mechanism, in which the stereochemistry of **2** should play an important role. Therefore, both enantiomers of 4-OHPL **2** were required for a definitive approach to the question of PL **1**'s metabolic deactivation.

Although (±)-**2** has been prepared,[2] only the enantioselective synthesis of its related aminoalcohols[3] has been reported. Thus, (*S*)-**1** was prepared by regioselective nucleophilic substitution of 1-naphthol with a homochiral glycidol,[3a] Henry reaction of (1-naphthyloxy)acetaldehyde,[3b] dihydroxylation of 1-naphthyl ally ether,[3c] catalytic hydrogenation of aminoketone,[3d] and kinetic resolution of 3-(1-naphthyloxy)propylene oxide[3e] as key asymmetric reactions in the synthesis. Application of the glycidol method using potassium carbonate as a base[3a] to other phenol substrates led to effective syntheses of the corresponding chiral aryloxyaminoalcohols.[3f–3h] In addition, Otera et al.[3i] recently reported an improved glycidol method using caesium fluoride (CsF) as a base, in which excellent enantioselectivity (>98% e.e.) was observed. Thus, we applied the CsF-mediated glycidol method[3i] to the enantioselective preparation of **2**. In this paper we present an eight step synthesis of both enantiomers of **2** from 1,4-dihydroxynaphthalene **3** (Fig. 1).

2. Results and discussion

We selected 4-benzyloxy-1-naphthol **7** as a phenol substrate for the glycidol method leading to **2**. The protected naphthol **7** was prepared from 1,4-dihydroxynaphthalene **3** by four successive reactions (diacetylation, partial hydrolysis, benzylation and hydrolysis).[4] Treatment of **3** with acetic anhydride and pyridine afforded the diacetate **4** in 93% yield. Its partial hydrolysis was carried out with sodium borohydride (0.5 molar equiv.) in ethanol to afford 4-acetoxy-1-naphthol[5] **5**, which was converted into the corresponding benzyl ether **6** by a conventional method. The yield over the two steps was 81%. Alkaline hydrolysis of **6** effectively gave a desired 4-benzyloxy-1-naphthol **7**. Thus, **7** was obtained in 70% overall yield from **3** (Scheme 1).



1: R=H (PL)
2: R=OH (4-OHPL)

Figure 1.

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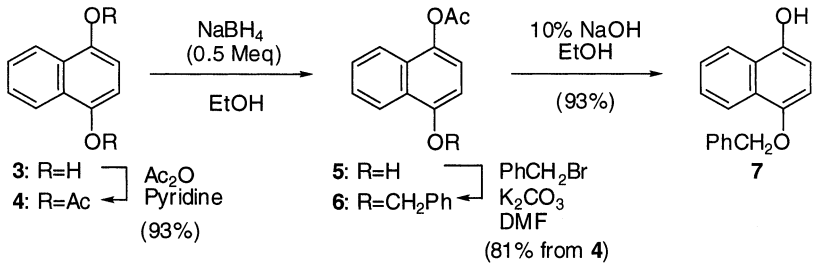


Scheme 1.

Racemic glycidyl 3-nitrobenzenesulfonate (±)-**8** was prepared from glycidyl alcohol and 3-nitrobenzenesulfonyl chloride according to the reported method.[6] We initially examined the CsF-mediated synthesis[3i] of (±)-**2** using (±)-**8**. Treatment of 4-benzyloxy-1-naphthol **7** with (±)-**8** in DMF in the presence of CsF at room temperature for 20 h afforded (±)-glycidyl ether (±)-**9** in 49% yield. Clean separation of each enantiomer by chiral HPLC [retention time: 11.1 min for (*S*)- and 14.1 min for (*R*)-derivatives] was observed under the following conditions; column: CHIRALPAK AS, solvent: hexane-propan-2-ol = 9:1, flow rate: 1.0 mL/min, detection: 254 nm. Reaction of (±)-**9** with *iso*-propylamine gave protected aminoalcohol (±)-**10** in 93% yield, the hydrogenation of which with palladium hydroxide on carbon after salt formation with hydrogen chloride yielded a desired crystalline (±)-**2** as hydrochloride, mp 165–167°C in 61% yield. Each enantiomer of **2**·HCl was also separable by chiral HPLC using an Ultron ES-PhCD and a mixed solvent of 20 mM aq. KH_2PO_4–acetonitrile (77:23) at a flow rate of 1.0 mL/min [retention time: 8.6 min for (*S*)- and 10.1 min for (*R*)-derivatives], detection at 310 nm (Scheme 2).

The use of commercially available (*R*)-(+)- and (*S*)-(−)-**8** in place of (±)-**8** in the formation of benzyloxynaphthol **9** smoothly afforded the corresponding glycidyl ethers with high enantioselectivity [99% e.e. for (*R*)-(−)-**9** and 97% e.e. for (*S*)-(+)-**9**]. Ring opening of the enantiomeric **9** followed by deprotection as mentioned above gave the corresponding enantiopure 4-OHPL hydrochlorides in satisfactory yields and 99% e.e. for each enantiomer.

3. Conclusion

In conclusion, we established a preparation method of 4-OHPL **2** from 1,4-dihydroxynaphthalene **3** in eight steps applicable to enantiomeric synthesis. Thus, (*R*)-**2** and (*S*)-**2** were obtained as crystalline hydrochlorides in 30 and 33% overall yields, respectively. Enzymatic approaches to the metabolism of PL **1** using (±)-**2** prepared here are presently under investigation.

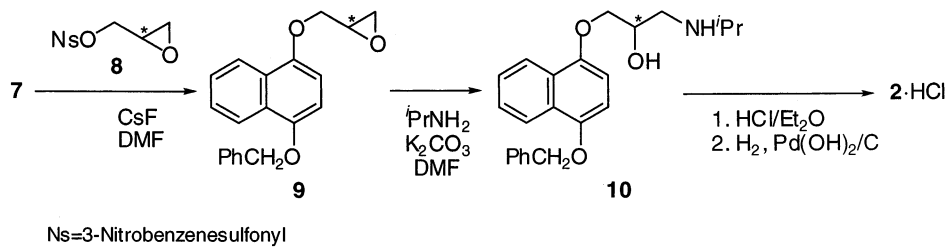
4. Experimental

4.1. General

All melting points were measured on a micro melting-point hot stage (Yanagimoto) and uncorrected. Infrared (IR) spectra were recorded with Nujol on JASCO FT/IR 300E spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on JEOL JNM-GSX400A (400 MHz), -GSX500A (500 MHz), using TMS as an internal standard unless stated otherwise. Electron-impact mass spectra (EIMS) were recorded on JEOL JMS-AUTOMASS 20 with direct inlet. FABMS were recorded on JEOL JMS-HX110 with *m*-nitrobenzyl alcohol as a matrix. ORD ($[\alpha]_{589}$) were measured with a JASCO J-820 polarimeter attached with ORDM-401. HPLC was performed on a Shimazu Class LC-104 system with photodiode array detector SPD-M10AVP. Silica gel (Fuji Silysia FL100D) was used for column chromatography. CH_2Cl_2 was distilled from P_2O_5 before use. *N*,*N*-Dimethylformamide (DMF) was distilled from CaH_2. Organic extracts were dried over $MgSO_4$ before evaporation. (*R*)- and (*S*)-2,3-epoxypropyl 3-nitrobenzenesulfonate (*R*)-**8** and (*S*)-**8** were purchased from Aldrich Chemical Co. Inc.

4.2. 1,4-Diacetoxynaphthalene 4

A mixture of 1,4-dihydroxynaphthalene **3** (5.12 g, 32.0 mmol), pyridine (51.5 mL, 638 mmol) and acetic anhydride (46.0 mL, 487 mmol) was stirred at room temperature (rt) for 1 h. After addition of H_2O (150 mL), the



Scheme 2.

mixture was extracted with AcOEt (3×200 mL). The combined organic layer was washed with H_2O (1×120 mL), saturated aq. $CuSO_4$ (4×120 mL), H_2O (1×120 mL) and brine (1×150 mL) and evaporated. Recrystallization of the residue from benzene gave **4** as pale brown prisms (7.31 g, 94%), mp 128–129°C (lit.[7] mp 128–129°C). IR ν_{max}: 1751 cm^{-1}.

4.3. 1-Acetoxy-4-hydroxynaphthalene 5

$NaBH_4$ (390 mg, 10.3 mmol) was added to a solution of **4** (5.02 g, 20.6 mmol) in EtOH (200 mL) at rt. After stirring at rt for 1.5 h under Ar, H_2O (100 mL) was added and the mixture was acidified with 10% HCl to pH 3–4 under cooling with an ice-water bath and extracted with AcOEt (3×200 mL). The combined organic layer was washed with saturated aq. $NaHCO_3$ (1×200 mL), H_2O (1×200 mL) and brine (1×200 mL) and evaporated to give **5** as a brown oil (4.52 g), which was used in the next reaction without further purification. IR ν_{max}: 3441, 1736 cm^{-1}. ^1H NMR (500 MHz) δ 2.45 (3H, s, COMe), 5.57 (1H, s, OH), 6.72 (1H, d, J=8.1 Hz, 3-H), 7.04 (1H, d, J=8.1 Hz, 2-H), 7.49–7.55 (2H, m, 6-, 7-H), 7.78 (1H, d, J=8.2 Hz, 5-H), 8.16 (1H, d, J=8.2 Hz, 8-H).

4.4. 1-Acetoxy-4-benzyloxynaphthalene 6

Benzyl bromide (6.05 g, 35.4 mmol) was added to a suspension of **5** (8.28 g, 35.6 mmol) and K_2CO_3 (7.38 g, 53.4 mmol) in DMF (100 mL) at rt. After stirring at rt for 5.5 h, H_2O (400 mL) was added and the mixture was extracted with AcOEt (3×300 mL). The combined organic layer was washed with H_2O (5×200 mL) and brine (2×200 mL) and evaporated. Purification of the residue by column chromatography (*n*-hexane: AcOEt=10: 1) gave **6** (9.75 g, 88% from **5**) as colorless prisms, mp 84–85°C. IR ν_{max}: 1758 cm^{-1}. ^1H NMR (400 MHz) δ 2.44 (3H, s, COMe), 5.24 (2H, s, $PhCH_2O$), 6.84 (1H, d, J=8.3 Hz, 3-H), 7.13 (1H, d, J=8.3 Hz, 2-H), 7.36 (1H, dd, J=7.3, 7.3 Hz, 4′-H), 7.42 (2H, dd, J=7.3, 7.3 Hz, 3′-, 5′-H), 7.48–7.56 (4H, m, 6-, 7-, 2′-, 6′-H), 7.79 (1H, dd, J=8.0, 1.5 Hz, 5-H), 8.36 (1H, dd, J=8.0, 1.5 Hz, 8-H). Anal. calcd for $C_{19}H_{16}O_3$: C, 78.07; H, 5.52. Found: C, 77.91; H, 5.46%. EIMS m/z: 292 (M^+, 25.5%), 91 (100%).

4.5. 4-Benzyloxy-1-hydroxynaphthalene 7

To a solution of **6** (102 mg, 0.35 mmol) in EtOH (2.0 mL) was added 10% aq. NaOH (1.8 mL) at rt. After stirring at rt for 1 h, H_2O (5 mL) was added and the mixture acidified with 10% HCl to pH 3–4 and extracted with AcOEt (3×30 mL). The combined organic extract was washed with H_2O (1×30 mL) and brine (1×30 mL) and evaporated. Purification of the residue by column chromatography (*n*-hexane: AcOEt=10: 1) gave **7** as colorless prisms (56.2 mg, 64%), mp 122–123°C. IR ν_{max}: 3200 cm^{-1}. ^1H NMR (500 MHz) δ 5.00 (1H, s, OH), 5.20 (2H, s, $PhCH_2O$), 6.72 (2H, s, 2-, 3-H), 7.35 (1H, dd, J=7.4, 7.4 Hz, 4′-H), 7.42 (2H, dd, J=7.4, 7.4 Hz, 3′-H, 5′-H), 7.50–7.53 (4H, m, 6-, 7-, 2′-, 6′-H), 8.13 (1H, d, J=7.2 Hz, 5- or 8-H), 8.36 (1H, d, J=7.2 Hz, 5- or 8-H).

4.6. (±)-2,3-Epoxypropyl 3-nitrobenzenesulfonate (±)-8

A solution of 3-nitrobenzenesulfonyl chloride (8.99 g, 40.6 mmol) in CH_2Cl_2 (10 mL) was added to a solution of (±)-glycidol (3.02 g, 40.8 mmol) and Et_3N (6.2 mL, 44.5 mmol) in CH_2Cl_2 (120 mL) at 0°C. After stirring at 4°C for 5.5 h, 5% H_2SO_4 (100 mL) was added and the mixture was extracted with AcOEt (3×150 mL). The combined organic layer was washed with saturated $NaHCO_3$ (200 mL), H_2O (200 mL) and brine (200 mL) then evaporated. Purification of the residue by column chromatography (*n*-hexane: AcOEt=3:1) gave yellow prisms (5.34 g, 51%), mp 41–44°C (lit. mp 42–50°C). IR ν_{max}: 1533 cm^{-1}. ^1H NMR (400 MHz) δ 2.63 (1H, dd, J=4.6, 2.4 Hz, 3-H), 2.85 (1H, dd, J=4.6, 4.0 Hz, 3-H), 3.21–3.27 (1H, m, 2-H), 4.05 (1H, dd, J=11.6, 6.4 Hz, 1-H), 4.49 (1H, dd, J=11.6, 3.1 Hz, 1-H), 7.82 (1H, dd, J=7.9, 7.9 Hz, 5′-H), 8.27 (1H, dd, J=7.9, 1.5 Hz, 4′-, or 6′-H), 8.53 (1H, dd, J=7.9, 1.5 Hz, 4′-, or 6′-H), 8.78 (1H, dd, J=1.5, 1.5 Hz, 2′-H). EIMS m/z: 259 (M^+, 0.1%), 186 (100%).

4.7. Preparation of (±)-1-benzyloxy-4-oxiranylmethoxynaphthalene (±)-9

A mixture of crude **7** (213 mg, 0.85 mmol) and CsF (380 mg, 2.50 mmol) in DMF (2 mL) was stirred at rt for 20 min under Ar. A solution of (±)-**8** (192 mg, 0.74 mmol) in DMF (1.5 mL) was added. After stirring at rt for 20 h, saturated aq. $NaHCO_3$ (40 mL) was added and the mixture extracted with AcOEt (3×40 mL). The combined organic layer was washed with H_2O (5×40 mL) and brine (1×60 mL) and evaporated. Purification of the residue by column chromatography (*n*-hexane: AcOEt=10: 1) gave (±)-**9** as yellow prisms (103 mg, 40%), mp 103–104°C (lit. mp 107–109°C). ^1H NMR (500 MHz) δ 2.84 (1H, dd, J=4.6, 2.8 Hz, 3′-H), 2.96 (1H, dd, J=4.6, 4.6 Hz, 3′-H), 3.47 (1H, m, 2′-H), 4.11 (1H, dd, J=11.0, 5.5 Hz, 1′-H), 4.35 (1H, dd, J=11.0, 3.1 Hz, 1′-H), 5.21 (2H, s, $PhCH_2O$), 6.71 (1H, d, J=8.2 Hz, 2- or 3-H), 6.76 (1H, d, J=8.2 Hz, 2- or 3-H), 7.35 (1H, dd, J=7.3, 7.3 Hz, 4″-H), 7.41 (2H, dd, J=7.3, 7.3 Hz, 3″-, 5″-H), 7.51–7.53 (4H, m, 6-, 7-, 2″-, 6″-H), 8.24–8.26 (1H, m, 5- or 8-H), 8.36 (1H, m, 5- or 8-H). Anal. calcd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.20; H, 6.06%.

4.8. Preparation of (*R*)-(−)-1-benzyloxy-4-oxiranylmethoxynaphthalene (*R*)-(−)-9

A mixture of a crude **7** (1.33 g, calculated as 897 mg, 3.59 mmol) and CsF (1.73 g,11.4 mmol) in DMF (5 mL) and a solution of (*R*)-**8** (928 mg, 3.58 mmol) in DMF (5 mL) were reacted under the same conditions described for (±)-**9** above. Work-up and purification gave (*R*)-**9** as colorless prisms (855 mg, 78%, 99% e.e.), mp 78–79°C. $[\alpha]_{589}^{24}=-12.4\pm3.1$ (c=0.06, $CHCl_3$). ^1H NMR (500 MHz) δ 2.84 (1H, dd, J=4.8, 2.4 Hz, 3′-H),

2.96 (1H, dd, $J=4.8$, 4.8 Hz, 3′-H), 3.48 (1H, m, 2′-H), 4.11 (1H, dd, $J=11.0$, 5.2 Hz, 1′-H), 4.35 (1H, dd, $J=11.0$, 3.2 Hz, 1′-H), 5.21 (2H, s, $PhCH_2O$), 6.71 (1H, d, $J=8.6$ Hz, 2- or 3-H), 6.76 (1H, d, $J=8.6$ Hz, 2- or 3-H), 7.35 (1H, dd, $J=7.6$, 7.2 Hz, 4″-H), 7.41 (2H, dd, $J=8.4$, 6.4 Hz, 3″-, 5″-H), 7.50–7.55 (4H, m, 6-, 7-, 2″-, 6″-H), 8.24–8.28 (1H, m, 5- or 8-H), 8.28–8.32 (1H, m, 5- or 8-H). HRFABMS m/z: 306.1253 (calcd for $C_{20}H_{18}O_3$: 306.1256).

4.9. Preparation of (*S*)-(+)-1-benzyloxy-4-oxiranylmethoxynaphthalene (*S*)-(+)-9

A mixture of a crude **7** (856 mg, 3.42 mmol) and CsF (1.62 g,10.7 mmol) in DMF (5 mL) and a solution of (*S*)-**8** (870 mg, 3.36 mmol) in DMF (5 mL) were reacted under the same conditions described for (±)-**9** above. Work-up and purification gave (*S*)-**9** as colorless prisms (557 mg, 61%, 97% ee), mp 81–82°C. $[\alpha]_{589}^{24}$ +7.8±2.0 ($c=0.20$, $CHCl_3$). ^{1}H NMR (500 MHz) δ 2.84 (1H, dd, $J=4.9$, 2.4 Hz, 3′-H), 2.96 (1H, dd, $J=4.9$, 4.3 Hz, 3′-H), 3.46–3.50 (1H, m, 2′-H), 4.11 (1H, dd, $J=11.2$, 5.5 Hz, 1′-H), 4.35 (1H, dd, $J=11.2$, 3.4 Hz, 1′-H), 5.20 (2H, s, $PhCH_2O$), 6.71 (1H, d, $J=8.4$ Hz, 2- or 3-H), 6.76 (1H, d, $J=8.4$ Hz, 2- or 3-H), 7.34–7.36 (1H, m, 4″-H), 7.41–7.44 (2H, m, 3″-, 5″-H), 7.50–7.55 (4H, m, 6-, 7-, 2″-, 6″-H), 8.24–8.27 (1H, m, 5- or 8-H), 8.28–8.32 (1H, m, 5- or 8-H). HRFABMS m/z: 306.1253 (calcd for $C_{20}H_{18}O_3$: 306.1256).

4.10. Preparation of (±)-3-(4-benzyloxy-1-naphthoxy)-1-isopropylamino-2-propanol (±)-10

A mixture of (±)-**9** (189 mg, 0.62 mmol), K_2CO_3 (479 mg, 3.47 mmol) and *iso*-propylamine (1.4 mL, 16.4 mmol) in DMF (2 mL) was heated at 50°C for 15 h. After further addition of *iso*-propylamine (1.4 mL, 16.4 mmol), the mixture was heated at 50°C for 6 h. After excess *iso*-propylamine was evaporated, H_2O (100 mL) was added and the mixture extracted with AcOEt (3× 100 mL). The combined organic layer was washed with H_2O (5×100 mL) and brine (120 mL) and evaporated. Recrystallization of the residue from benzene gave (±)-**10** as yellow prisms (209 mg, 93%), mp 107–109°C. IR ν_{max}: 3271 cm^{-1}. ^{1}H NMR (400 MHz) δ 1.17 (6H, d, $J=5.5$ Hz, $CHMe_2$), 2.86–2.91 (1H, m, $NHCHMe_2$), 2.96 (1H, m, 1-H), 3.06 (1H, m, 1-H), 4.08 (1H, dd, $J=9.2$, 5.2 Hz, 3-H), 4.15 (1H, dd, $J=9.2$, 5.2 Hz, 3-H), 4.29 (1H, m, 2-H), 5.19 (2H, s, $PhCH_2O$), 6.68 (1H, d, $J=8.2$ Hz, 2′- or 3′-H), 6.74 (1H, d, $J=8.2$ Hz, 2′- or 3′-H), 7.34 (1H, dd, $J=9.4$, 9.4 Hz, 4″-H), 7.41 (2H, dd, $J=9.4$, 9.4 Hz, 3″-, 5″-H), 7.50–7.52 (4H, m, 6′-, 7′-, 2″-, 6″-H), 8.18–8.21 (1H, m, 5′- or 8′-H), 8.28–8.31 (1H, m, 5′- or 8′-H). Anal. calcd for $C_{23}H_{27}NO_3$: C, 75.58; H, 7.45; N, 3.83. Found: C, 75.51; H, 7.48; N, 3.78%.

4.11. Preparation of (*R*)-3-(4-benzyloxy-1-naphthoxy)-1-isopropylamino-2-propanol (*R*)-10

A mixture of (*R*)-**9** (705 mg, 2.30 mmol), K_2CO_3 (1.59 g, 11.5 mmol) and isopropylamine (4.7 mL, 55.2 mmol) in DMF (5 mL) was heated at 50°C for 14 h. Work-up and purification gave (*R*)-**10** as yellow prisms (656 mg, 76%), mp 103–104°C. IR ν_{max}: 3273 cm^{-1}. ^{1}H NMR (400 MHz) δ 1.13 (6H, d, $J=6.1$ Hz, $CHMe_2$), 2.86 (1H, dd, $J=12.0$, 7.6 Hz, 1-H), 2.90 (1H, m, $NHCHMe_2$), 3.02 (1H, br d, $J=12.0$ Hz, 1-H), 4.09 (1H, dd, $J=9.5$, 5.2 Hz, 3-H), 4.15 (1H, dd, $J=9.2$, 4.9 Hz, 3-H), 4.19 (1H, m, 2-H), 5.20 (2H, s, $PhCH_2O$), 6.71 (1H, d, $J=8.2$ Hz, 2′- or 3′-H), 6.76 (1H, d, $J=8.2$ Hz, 2′- or 3′-H), 7.35 (1H, dd, $J=7.3$, 7.3 Hz, 4″-H), 7.41 (2H, dd, $J=7.3$, 7.3 Hz, 3″-, 5″-H), 7.49-7.53 (4H, m, 6′-, 7′-, 2″-, 6″-H), 8.19–8.22 (1H, m, 5′- or 8′-H), 8.28–8.32 (1H, m, 5′- or 8′-H). Anal. calcd for $C_{23}H_{27}NO_3$: C, 75.58; H, 7.45; N, 3.83. Found: C, 75.49; H, 7.48; N, 3.65%.

4.12. Preparation of (*S*)-3-(4-benzyloxy-1-naphthoxy)-1-isopropylamino-2-propanol (*S*)-10

A mixture of (*S*)-**9** (567 mg, 1.85 mmol), K_2CO_3 (1.27 g, 9.25 mmol) and isopropylamine (3.8 mL, 44.4 mmol) in DMF (4 mL) was heated at 50°C for 18 h. Work-up and purification gave (*S*)-**10** as yellow prisms (516 mg, 76%), mp 103–104°C. IR ν_{max}: 3272 cm^{-1}. ^{1}H NMR (400 MHz) δ 1.14 (6H, d, $J=5.8$ Hz, $CHMe_2$), 2.86 (1H, dd, $J=11.9$, 7.6 Hz, 1-H), 2.91 (1H, m, $NHCHMe_2$), 3.02–3.05 (1H, m, 1-H), 4.08 (1H, dd, $J=9.5$, 4.9 Hz, 3-H), 4.15 (1H, dd, $J=8.9$, 4.9 Hz, 3-H), 4.21 (1H, m, 2-H), 5.20 (2H, s, $PhCH_2O$), 6.70 (1H, d, $J=8.2$ Hz, 2′- or 3′-H), 6.75 (1H, d, $J=8.2$ Hz, 2′- or 3′-H), 7.34 (1H, dd, $J=7.3$, 7.3 Hz, 4″-H), 7.41 (2H, dd, $J=7.3$, 7.3 Hz, 3″-, 5″-H), 7.50-7.53 (4H, m, 6′-, 7′-, 2″-, 6″-H), 8.19–8.21 (1H, m, 5′- or 8′-H), 8.29–8.31 (1H, m, 5′- or 8′-H). Anal. calcd for $C_{23}H_{27}NO_3$: C, 75.58; H, 7.45; N, 3.83. Found: C, 75.75; H, 7.47; N, 3.71%.

4.13. Preparation of (±)-4-OHPL hydrochloride (±)-2·HCl

A 3.3% solution of HCl gas in Et_2O (3 mL) was added to a solution of (±)-**10** (50 mg, 0.14 mmol) in Et_2O (20 mL) under ice-cooling and then the solvent was evaporated to give (±)-**10**·HCl as colorless prisms (106 mg), mp 172–173°C. A suspension of 20% $Pd(OH)_2$ on C (26 mg) in EtOH (1 mL) was stirred at rt and atmospheric pressure for 20 min under H_2. A solution of (±)-**10**·HCl in EtOH (2.5 mL) was added and the mixture was then stirred under the same conditions for 1.5 h and diluted with EtOH (30 mL). The catalyst was filtered off through a Celite pad and the filtrate was evaporated. The residue was washed with AcOEt and Et_2O to give (±)-**2**·HCl as pale brown prisms (168 mg, 61%), mp 165–167°C. IR ν_{max}: 3193 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) δ 1.36 (6H, dd, $J=7.0$, 7.0 Hz, $CHMe_2$), 3.20 (1H, dd, $J=12.5$, 9.8 Hz, 1-H), 3.34 (1H, dd, $J=12.5$, 2.8 Hz, 1-H), 3.45 (1H, dq, $J=6.4$, 6.4 Hz, $NCHMe_2$), 4.08 (1H, dd, $J=10.1$, 6.8 Hz, 3-H), 4.15 (1H, dd, $J=10.1$, 5.0 Hz, 3-H), 4.37 (1H, m, 2-H), 6.73 (1H, d, $J=8.2$ Hz, 2′- or 3′-H), 6.76 (1H, d, $J=8.2$ Hz, 2′- or 3′-H), 7.42–7.47 (2H, m, 6′-, 7′-H), 8.12–8.15 (1H, m, 5′- or 8′-H), 8.18–8.20 (1H, m, 5′- or 8′-H).

4.14. Preparation of (*R*)-4-OHPL hydrochloride (*R*)-(+)-2·HCl

(*R*)-**10**·HCl was obtained as colorless prisms (628 mg), mp 174–176°C, by treatment of (*R*)-**10** (450 mg, 1.23 mmol) in Et_2O (120 mL) with the HCl solution in Et_2O (3 mL). A solution of (*R*)-**10**·HCl (589 mg) in EtOH (40 mL) was treated with a suspension of 20% $Pd(OH)_2$ on C (234 mg) in EtOH (2 mL) for 2 h under the same condition described above and work-up gave (*R*)-(+)-**2**·HCl as pale brown prisms (335 mg, 73%, 99% ee), mp 159–160°C. IR ν_{max}: 3351 cm^{-1}. $[\alpha]_{589}^{24}=+22.9\pm1.4$ ($c=0.30$, MeOH). ^1H NMR (400 MHz, CD_3OD) δ 1.32 (3H, d, $J=6.6$ Hz, $CHMe_2$), 1.34 (3H, d, $J=6.6$ Hz, $CHMe_2$), 3.19 (1H, dd, $J=12.5$, 9.8 Hz, 1-H), 3.33 (1H, dd, $J=12.5$, 2.7 Hz, 1-H), 3.44 (1H, dq, $J=6.7$, 6.7 Hz, $NCHMe_2$), 4.06 (1H, dd, $J=14.0$, 7.0 Hz, 3-H), 4.13 (1H, dd, $J=10.0$, 4.9 Hz, 3-H), 4.29–4.35 (1H, m, 2-H), 6.67 (1H, d, $J=8.5$ Hz, 2′- or 3′-H), 6.73 (1H, d, $J=8.5$ Hz, 2′- or 3′-H), 7.40–7.43 (2H, m, 6′-, 7′-H), 8.08–8.11 (1H, m, 5′- or 8′-H), 8.13–8.15 (1H, m, 5′- or 8′-H). HRFABMS m/z: 276.1608 (calcd for $C_{16}H_{22}NO_3$: 276.1600).

4.15. Preparation of (*S*)-4-OHPL hydrochloride (*S*)-(−)-2·HCl

(*S*)-**10**·HCl was obtained as colorless prisms (130 mg), mp 169–171°C, by treatment of (*S*)-**10** (109 mg, 0.30 mmol) in Et_2O (30 mL) with the HCl solution in Et_2O (1 mL). A solution of (*S*)-**10**·HCl (117 mg) in EtOH (6 mL) was treated with a suspension of 20% $Pd(OH)_2$ on C (58 mg) in EtOH (1 mL) for 2 h under the same condition described above and work-up gave (*S*)-(−)-**2**·HCl as pale brown prisms (81 mg, quant., 99% ee), mp 163–164°C. IR ν_{max}: 3403 cm^{-1}. $[\alpha]_{589}^{24}=-21.2\pm1.4$ ($c=0.29$, MeOH). ^1H NMR (400 MHz, CD_3OD) δ 1.37 (6H, d, $J=6.4$ Hz, $CHMe_2$), 3.23 (1H, dd, $J=12.7$, 9.8 Hz, 1-H), 3.37 (1H, dd, $J=12.7$, 3.1 Hz, 1-H), 3.47 (1H, m, $NCHMe_2$), 4.10 (1H, dd, $J=10.1$, 5.8 Hz, 3-H), 4.17 (1H, dd, $J=10.1$, 5.2 Hz, 3-H), 4.34–4.35 (1H, m, 2-H), 6.71 (1H, d, $J=8.3$ Hz, 2′- or 3′-H), 6.76 (1H, d, $J=8.3$. Hz, 2′- or 3′-H), 7.43–7.47 (2H, m, 6′-, 7′-H), 8.12–8.14 (1H, m, 5′- or 8′-H), 8.17–8.19 (1H, m, 5′- or 8′-H). HRFABMS m/z: 276.1618 (calcd for $C_{16}H_{22}NO_3$: 276.1600).

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