

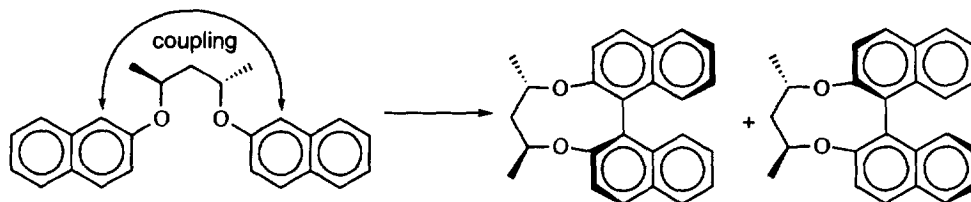
## Axial chirality control by 2,4-pentanediol or its analogue as a simple chiral linking bridge. Highly diastereodifferentiating homocoupling of a 1-lithio-2-naphthyl ether

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**Abstract:** Diastereodifferentiating oxidative homocoupling of 1-lithio-2-naphthyl ether linked by optically active 2,4-pentanediol or 1,3-diphenyl-1,3-propanediol gave 2,2'-binaphthyl ether of over 99% diastereomeric excess. By elimination of the chiral auxiliary from the product, enantiomerically pure binaphthol was obtained in good yield. © 1997 Elsevier Science Ltd. All rights reserved.

As a highly efficient and widely applicable stereocontroller to produce enantiomerically pure materials, we have been developing a simple system by using optically active 2,4-pentanediol (PD) as a chiral linking bridge between a reagent and a prochiral substrate. This intramolecular reaction system worked on various types of diastereofacially differentiating reactions. For example, the cycloaddition to the 1-cyclohexene mono-ether of PD gave 96% de (de=diastereomeric excess) of cyclopropyl ether with zinc carbenoid<sup>1</sup> and over 99% de of the 2-hydroxyacetal with *m*-chloroperbenzoic acid<sup>2</sup>, where the reagents coordinated or reacted with the hydroxyl group of the PD moiety prior to the addition. Highly diastereofacially differentiating photo *meta*-arene-olefin addition between a vinyl group and a phenyl group connected by PD as an ether also resulted in over 99% de of the cycloadduct in good yield<sup>3</sup>. Thus, this stereocontroller has high potential to differentiate diastereofaces even by a small and flexible chiral auxiliary. The present report deals with the reaction leading to an axial chiral compound, which was carried out as a series of studies to prove the versatility of our system as well as to get insight into the origin of the stereocontrol. The reaction employed was the homocoupling of a 2-naphthyl ether to construct a binaphthyl skeleton as shown in Scheme 1<sup>4</sup>. If one of the diastereomers is formed predominantly under the stereocontrol of the PD moiety, optically active binaphthol can be obtained after removal of the PD of the chiral auxiliary<sup>5</sup>.

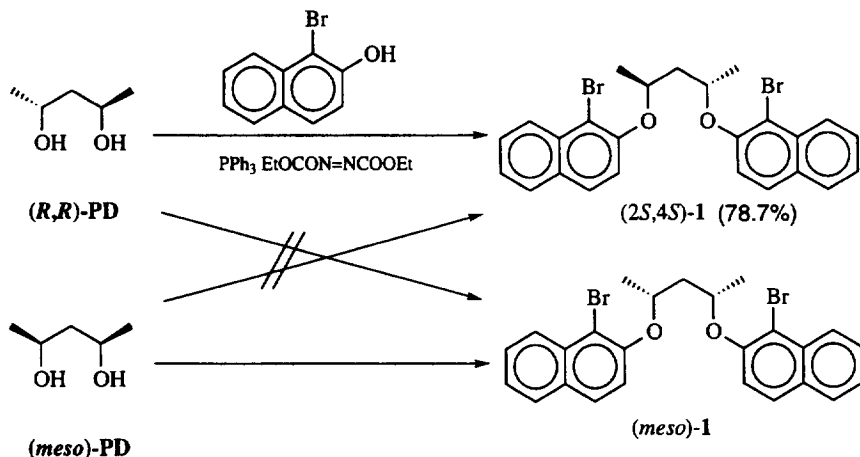


Scheme 1.

For the preparation of the substrate, where two naphthyl groups are connected to PD as ether bonds, we planned SN-2 reaction with naphthol to enantiomerically pure PD. From (2*R*,4*R*)-PD, the enantio- and diastereomerically pure (2*S*,4*S*)-product is obtained if the introduction of the two naphthyl groups proceeds through complete inversion in both steps. The substrate **1** was prepared by the Mitsunobu reaction from (2*R*,4*R*)-PD and 1-bromo-2-naphthol. The double Mitsunobu reaction

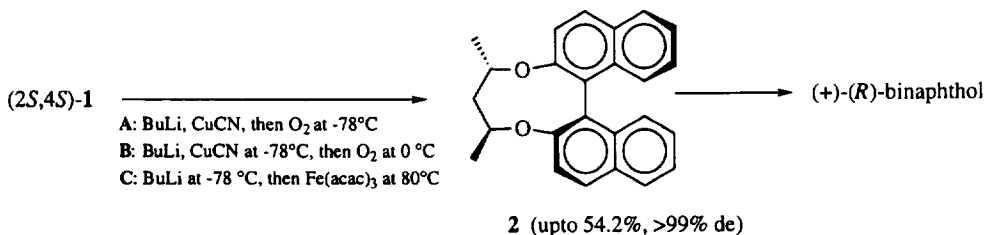
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proceeded smoothly and afforded **1** in 78.7% yield. To determine enantio- and diastereomeric purities of the obtained **1**, *meso*-**1** was prepared from *meso*-PD under the same reaction conditions. The HPLC analysis of the reaction mixture clarified that both reactions yielded diastereomerically pure products. The results indicated that the Mitsunobu reaction underwent stereospecifically in both diastereomers, and thus, the obtained **1** from (*R,R*)-PD was enantiomerically pure (Scheme 2). By the conventional method the readily available ditosylate of (*R,R*)-PD was also investigated. The reaction of the ditosylate with 1-bromo-2-naphthol and potassium carbonate in DMF at 80°C afforded (*2S,4S*)-**1** (60.5%) and *meso*-**1** (6.3%). The specific rotation of the obtained (*2S,4S*)-**1** was the same, within an error range, as that of (*2S,4S*)-**1** obtained by the Mitsunobu reaction.



Scheme 2.

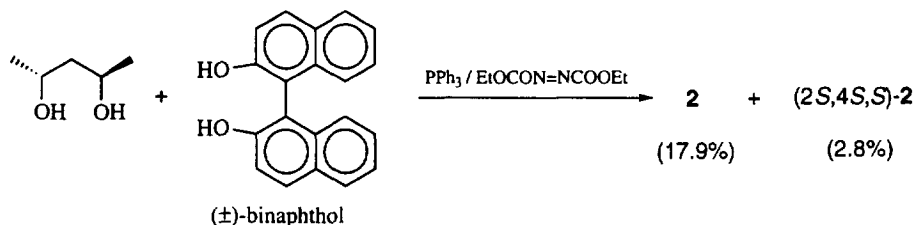
Treatment of (*2S,4S*)-**1** with butyl lithium (2.2 eq.) and copper(I) cyanide (3.0 eq.) afforded higher order cyanocuprate, which was oxidized *in situ* by the bubbling of oxygen at  $-78^\circ\text{C}$  (Scheme 3, Method A)<sup>6</sup>. The reaction mixture after extraction included the intramolecular coupled product **2** as the major compound, but no intermolecular coupled products were detected.



Scheme 3.

The yield of **2** after MPLC purification was 54.2%. Diastereomeric excess of **2** to its axial diastereomer was determined to be over 99% by the following way. The Mitsunobu reaction of (*2R,4R*)-PD and racemic binaphthol afforded a mixture of two diastereomers (Scheme 4). After MPLC purification, **2** and its diastereomer were isolated in 17.9% and 2.8% yields, respectively. Since both diastereomers had a C<sub>2</sub> symmetric structure as determined by <sup>1</sup>H-NMR, stereochemistries of the PD moieties in both diastereomers were *2S,4S*. Thus, they are epimers with respect to the axial chirality. A mixture of them showed two completely separated peaks by HPLC analysis, and the reaction mixture from **1** included no detectable amounts of the axial diastereomer (less than 0.5%). The oxidation of the cyanocuprate at  $0^\circ\text{C}$  (Method B) also afforded **2** of over 99% de in 49.7% yield. When the dilithio intermediate was oxidized with ferric acetylacetonate in benzene/THF under reflux (Method

C)<sup>7</sup>, again over 99% de of **2** was obtained in 36.0% yield. Thus, the diastereo differentiation was highly controlled even at 80°C.



Scheme 4.

The PD unit could be removed and dextrorotatory (*R*)-binaphthol was obtained in 38.7% yield, when **2** was treated with 45% aqueous HBr in acetic acid at 100°C<sup>8</sup>, but its enantiomeric excess determined by HPLC on Chiralpak OT(+) was only 68%. Enantiomerically pure (*R*)-binaphthol could be obtained by the reaction of **2** with BBr<sub>3</sub> at -78°C in 59.7% yield.

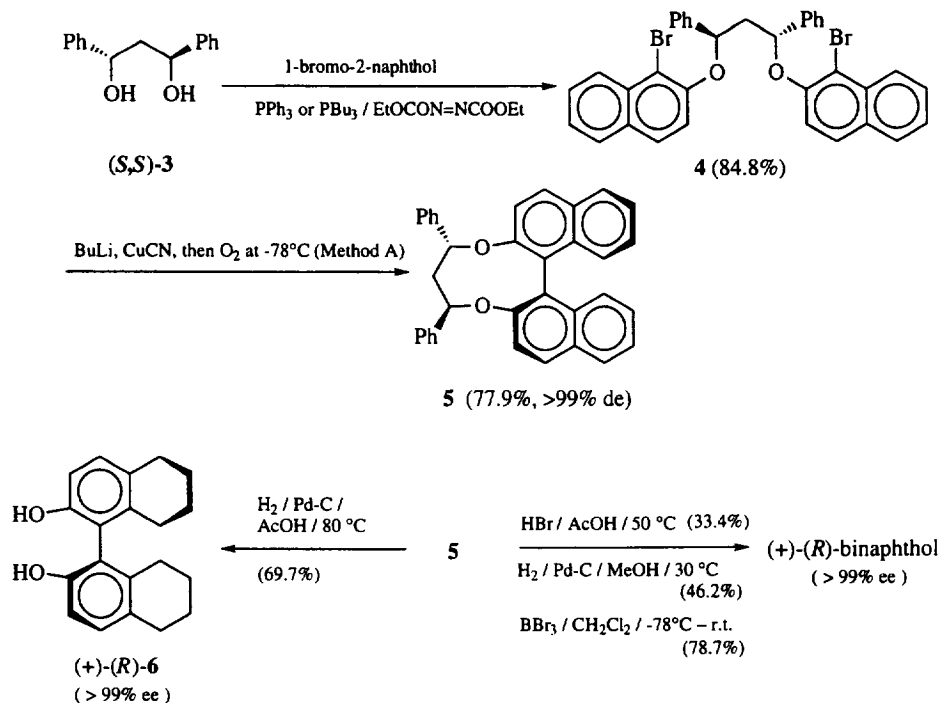
To improve the chemical yields in the coupling step and the removal of the chiral auxiliary, 1,3-diphenyl-1,3-propanediol **3** was employed instead of PD in a hope that benzyl ethers in the product could be easily cleaved (Scheme 5). Enantiomerically pure (1*S*,3*S*)-**3** was obtained by the enantiodifferentiating hydrogenation of dibenzoylmethane over (*R,R*)-tartaric acid modified Raney nickel catalyst followed by three recrystallizations<sup>9</sup>. The Mitsunobu reaction with **3** under the same conditions for **1** afforded (1*R*,3*R*)-**4** in 74.0% yield, and with PBu<sub>3</sub> instead of PPh<sub>3</sub> resulted in better yield of 84.8%. Coupling reaction of **4** by the method A again afforded a single diastereomer **5**, a diphenyl analog of **2**, in 77.9% yield. Removal of the chiral auxiliary from **5** was achieved by three different methods. Hydrogenolysis of **5** over palladium on carbon in methanol at 30°C gave enantiomerically pure (*R*)-binaphthol in 46.2% yield. The yield of the hydrogenolysis could not be improved satisfactorily, since over reduction took place significantly at higher reaction temperature or longer reaction time. When the hydrogenolysis was carried out in acetic acid at 80°C, the product was the octahydro derivative **6** (69.7%)<sup>10</sup>, which was determined to be enantiomerically pure by HPLC analysis. The reaction of **5** with HBr in acetic acid proceeded at 50°C and afforded (+)-(*R*)-binaphthol in 33.4% yield. In contrast to the reaction of **2**, the (*R*)-binaphthol obtained was over 99% ee by the HPLC analysis, because of the lower reaction temperature. Enantiomerically pure (*R*)-binaphthol was also obtained in good yield (78.7%) by the treatment of **5** with BBr<sub>3</sub> in dichloromethane at -78°C. The overall yield of the present process to get optically pure binaphthol was 51.5% yield over three steps.

The present study proved that our stereocontrol system could apply to the axial chirality control in the homo-coupling reaction with complete diastereodifferentiation without unwanted intermolecular coupling. Among the reported reactions to give axial chirality by using chiral linking bridges<sup>4</sup>, the chiral linking bridge of PD in the present study is the simplest and just flexible enough to bring the two reaction centres close to each other, and hence, enhances intramolecular coupling under rigorous stereocontrol. The steric energies of **2** and its axial diastereomer at the global minimum conformations were calculated to be 4.52 and 11.25 kcal/mol, respectively, by the MM2 method. The compatibility between the calculations and the experimental results suggests that the stereocontrol of the present reaction proceeds through a product-like conformation in the transition state.

## Experimental

### General

All melting points are uncorrected. <sup>1</sup>H-NMR (400 MHz) was recorded on a JEOL GX-400 spectrometer in CDCl<sub>3</sub> as a solvent and as an internal standard (CHCl<sub>3</sub>=7.26 ppm). IR spectra were obtained on a JASCO IR-810 spectrophotometer. Optical rotations were measured on a Perkin-Elmer 243B polarimeter. Analytical GLC was conducted with a Shimadzu GC-17A. MPLC was carried out



Scheme 5.

using a FMI pump (10 ml min<sup>-1</sup>) and a Lobar column (Merck Si-60, type B). HPLC was conducted with Hitachi L-6200 and L-3000. Dry diethyl ether and THF were distilled from sodium-benzophenone ketyl and the other dry solvents were distilled from calcium hydride. All reactions were carried out under dry nitrogen atmosphere.

#### (2*S*,4*S*)-2,4-bis(1-bromo-2-naphthoxy)pentane **1**

To a solution of 1-bromo-2-naphthol (1.61 g, 7.2 mmol) and diethyl azodicarboxylate (0.901 ml, 6.0 mmol) in THF (30 ml) was added a solution of (2*R*,4*R*)-2,4-pentanediol (250 mg, 2.4 mmol) and triphenylphosphine (1.51 g, 5.79 mmol) in THF (5 ml) at 0°C for 10 min, and stirred overnight at the same temperature. The obtained mixture was purified by silica gel short column (10% ethyl acetate in hexane) and MPLC on silica gel (6% ethyl acetate in hexane) to give 968 mg of **1** (78.8%). Pale yellow oil, [α]<sub>D</sub><sup>20</sup> = -21.8 (c 1.0, methanol), <sup>1</sup>H-NMR δ 8.14 (d, J=9.0, 2H), 7.52–7.49 (m, 4H), 7.36 (d, J=9.0 Hz, 2H), 7.29 (m, 2H), 6.99 (d, J=9.0 Hz, 2H), 4.98 (m, 2H), 2.19 (dd, J=7.3, 5.4 Hz, 2H), 1.44 (d, J=6.1 Hz, 6H). MS, *m/z* (M<sup>+</sup>) calcd for C<sub>25</sub>H<sub>22</sub>O<sub>2</sub><sup>81</sup>Br<sub>2</sub>, 515.9947; obsd, 515.9924.

#### (2*S*,4*R*)-2,4-bis(1-bromo-2-naphthoxy)pentane *meso*-**1**

Under the same conditions for the preparation of (2*S*,4*S*)-**1**, from (2*R*,4*S*)-2,4-pentanediol (108 mg, 1.04 mmol), *meso*-**1** was obtained (42.2 mg, 7.8%). <sup>1</sup>H-NMR δ 8.24 (dd, J=8.5, 0.7, 2H), 7.82–7.78 (m, 4H), 7.57 (m, 12H), 7.40 (d, J=8.5 Hz, 2H), 4.92 (m, 2H), 2.55 (dt, J=14.2, 6.7 Hz, 1H), 2.01 (dt, J=14.2, 5.9 Hz, 1H), 1.46 (d, J=6.8 Hz, 6H), MS, *m/z* (M<sup>+</sup>) calcd for C<sub>25</sub>H<sub>22</sub>O<sub>2</sub><sup>81</sup>Br<sub>2</sub>, 515.9947; obsd, 515.9951. HPLC analysis (ODS, methanol, 1 ml/min), retention time for (2*S*,4*S*)-**1**, 5.53 min; for *meso*-**1**, 10.22 min.

#### Preparation of **1** via the ditosylate of PD

Ditosylate of (2*R*,4*R*)-2,4-pentanediol was prepared by the conventional method. A solution of the ditosylate (501 mg, 1.21 mmol) and 1-bromo-2-naphthol (545 mg, 2.2 equiv.) in dry DMF (30 ml) was heated to 80°C in the presence of potassium carbonate (340 mg, 2.2 equiv.) for 2.5 hours. After

cooling the mixture, water (30 ml) was added and extracted with ether (30 ml $\times$ 4). The mixture was purified on a silica gel column (6% ethyl acetate in hexane) to give 377 mg of (2*S*,4*S*)-**1** (60.5%) and 39.3 mg of *meso*-**1** (6.3%). In a large scale experiment, from 10 g of the ditosylate, 6.73 g of (2*S*,4*S*)-**1** was obtained (53.9% yield).

#### *Oxidative coupling of (2S,4S)-1 (Preparation of 2)*

##### *Method A*

To a solution of (2*S*,4*S*)-**1** (221 mg, 0.41 mmol) in THF (10 ml), butyllithium (1.7*N* in hexane, 0.72 ml, 1.23 mmol) was added dropwise for 10 min at  $-78^{\circ}\text{C}$ , and after 1 hour, a suspension of copper(I) cyanide (55.1 mg, 0.615 mmol) in THF (5 ml) was added at the same temperature. The mixture was stirred for 1.5 hours and was oxidized by bubbling of dry oxygen for 1 hour. After addition of saturate ammonium chloride aqueous solution (120 ml), the product was extracted by ether (50 ml $\times$ 4), washed with brine, dried over  $\text{MgSO}_4$ , and purified by MPLC on silica gel (6% ethyl acetate in hexane) to give **2** (74.1 mg, 54.2%). colorless solid, mp $>230^{\circ}\text{C}$  (sublimed),  $[\alpha]_{\text{D}}^{20} = -308$  (c 0.2,  $\text{CHCl}_3$ ),  $^1\text{H-NMR}$   $\delta$  7.93 (d,  $J=8.8$  Hz, 2H), 7.88 (d, 8.1 Hz, 2H), 7.45 (d,  $J=8.8$  Hz, 2H), 7.35 (ddd,  $J=8.1$ , 6.1, 2.0 Hz, 2H), 7.26–7.20 (m, 4H), 4.68 (tq,  $J=6.6$ , 2.5 Hz, 2H), 1.87 (m, 2H), 1.36 (d,  $J=6.6$  Hz, 6H). Anal. Calcd for  $\text{C}_{25}\text{H}_{22}\text{O}_2$ : C, 84.71; H, 6.26. Found: C, 84.49; H, 6.23.

##### *Method B*

The bubbling of oxygen was carried out at room temperature instead of  $-78^{\circ}\text{C}$ . From 201 mg of **1**, 75 mg of **2** was obtained (54%).

##### *Method C*

A solution of dilithio intermediate prepared from **1** (122 mg, 0.217 mmol) and butyllithium (1.7*N* in hexane, 0.284 ml, 0.477 mmol) in THF (10 ml) at  $-78^{\circ}\text{C}$  was added through a canular to a solution of ferric acetylacetonate (347 mg, 0.477 mmol) in benzene (15 ml) under reflux. After 2 hours, the mixture was extracted with ether ( $\times$ 4), washed with 2*N* hydrochloric acid and water ( $\times$ 2), and dried over  $\text{MgSO}_4$ . After the purification indicated in method A, 27.7 mg of **2** was obtained (35.9%).

#### *Preparation of the (2S,4S,S)-diastereomer of 2*

To a mixture of ( $\pm$ )-binaphthol (200 mg, 0.698 mmol) and diethyl azodicarboxylate (0.26 ml, 2.5 equiv.) in THF (8 ml), a solution of (2*R*,4*R*)-2,4-pentanediol (80 mg, 0.768 mmol) and triphenylphosphine (441 mg, 2.4 equiv.) in THF was added at ambient temperature. After three days, the mixture was purified by MPLC on silica gel (10% ethyl acetate in hexane) to give **2** (43.6 mg, 17.6%) and its diastereomer (7.7 mg, 2.82%).

HPLC analysis (ODS, 10% water in methanol, 1 ml/min), retention time for **2**, 10.02 min; for the (*S*)-enantiomer, 14.18 min. (2*S*,4*S*,*S*)-diastereomer of **2**: mp=88.9–91.0 $^{\circ}\text{C}$ ,  $[\alpha]_{\text{D}}^{20} = 33.9$  (c 0.1,  $\text{CHCl}_3$ ),  $^1\text{H-NMR}$   $\delta$  7.87–7.82 (m, 4H), 7.32 (m, 2H), 7.30 (d,  $J=8.8$  Hz, 2H), 7.14 (ddd,  $J=8.6$ , 6.6, 1.2 Hz, 1H), 1H), 6.87 (d,  $J=8.6$  Hz, 2H), 4.76 (m, 2H), 1.83 (dd,  $J=7.5$ , 5.5 Hz, 2H), 1.12 (d,  $J=6.1$  Hz, 6H), MS,  $m/z$  ( $\text{M}^+$ ) calcd for  $\text{C}_{25}\text{H}_{22}\text{O}_2$ , 354.1621; obsd, 354.1621.

#### *Elimination of the chiral auxiliary from 2*

To a solution of **2** (33.6 mg, 0.095 mmol) in dichloromethane (2 ml), a solution of tribromoborane (0.19 ml of 1*M* dichloromethane solution, 2.0 equiv.) was added at  $-78^{\circ}\text{C}$  and stirred for 1 hour. The reaction mixture was quenched with 2*N* HCl at the same temperature, extracted with ether ( $\times$ 4), dried over magnesium sulfate and purified by MPLC on silica gel (15% ethyl acetate in hexane) to give 16.2 mg of binaphthol (59.7%). Enantiomeric excess of the binaphthol was determined to be over 99% by HPLC analysis (CHIRALPAC OT(+), methanol, 0.5 ml/min,  $5^{\circ}\text{C}$ ). Specific rotation of the obtained (*R*)-binaphthol:  $[\alpha]_{\text{D}}^{25} = 33.6$  (0.4, THF), litt.  $[\alpha]_{\text{D}}^{25} = 33.6$  (1.1, THF). L. K. Truesdale, *Organic Synthesis Coll. Vol. 8*, p. 46.

*(1R,3R)-1,3-bis(1-bromo-2-naphthoxy)-1,3-diphenylpropane 4*

To a solution of 1-bromo-2-naphthol (7.52 g, 67.5 mmol) and diethyl azodicarboxylate (8.46 ml, 56.3 mmol) in THF (100 ml), a mixture of **3** (5.01 g 22.5 mmol) and tributylphosphine (10.9g, 54.0 mmol) in THF (50 ml) was added for 10 min at 0°C. The mixture was gradually warmed up to room temperature. After overnight, diethyl azodicarboxylate (1.70 ml) and tributylphosphine (2.81 ml) were added to this. The reaction was completed in an additional two days monitored by TLC. The concentrated mixture was purified by silica gel short column (15% ethyl acetate in hexane), column chromatography (200 g of silica gel, twice, elution 6% ethyl acetate and 3% ethyl acetate in hexane), and then recrystallization (methanol) to give 12.4 g of **4** in 84.8% yield. Colorless solid, mp=71.0–71.8°C,  $[\alpha]_D^{20} = -26.3$  (c 0.1, methanol),  $^1\text{H-NMR}$   $\delta$  8.14 (d, J=8.5 Hz, 2H), 7.55–7.46 (m, 8H), 7.35 (m, 6H), 7.26 (m, 2H), 6.97 (d, J=9.0 Hz, 2H), 5.99 (dd, J=7.6, 5.4 Hz, 2H), 2.62 (dd, 7.6, 5.4 Hz, 2H). Anal. Calcd for  $\text{C}_{35}\text{H}_{26}\text{O}_2\text{Br}_2$ : C, 65.85; H, 4.11. Found: C, 66.01; H, 4.06.

*Oxidative coupling of 4*

By using the method A employed for preparation of **2**, intramolecular coupling of **4** was carried out. The reaction mixture was purified by chromatography (silica gel, twice, 10% and then 6% ethyl acetate in hexane) to give 295 mg of **5** from 501 mg of **4** (77.9% yield). mp=126.1–128.3°C,  $[\alpha]_D^{20} = -89.3$  (c 0.1,  $\text{CHCl}_3$ ),  $^1\text{H-NMR}$   $\delta$  7.95 (d, J=8.55, 2H), 7.93 (d, J=6.83, 2H), 7.44–7.26 (m, 4H), 7.22 (m, 2H), 7.41 (d, J=6.8 Hz, 2H), 7.30 (m, 2H), 7.23 (d, J=1.7 Hz, 2H), 7.22 (d, J=6.8 Hz, 2H), 7.11 (d, J=1.7 Hz, 2H), 7.10 (d, J=6.6 Hz, 2H), 5.52 (t, J=3.9 Hz, 2H), 2.48 (t, J=3.9 Hz, 2H). Anal. Calcd for  $\text{C}_{35}\text{H}_{26}\text{O}_2 + 0.5\text{H}_2\text{O}$ : C, 86.21; H, 5.58. Found: C, 86.15; H, 5.69.

*Elimination of the chiral auxiliary from 5 by BBr<sub>3</sub>*

**By hydrogenolysis:** A mixture of **5** (18.2 mg, 0.039 mmol) and catalytic amount of Pd–C (5%) in 20 ml of methanol was stirred under the hydrogen atmosphere at room temperature for 3 days. After MPLC purification on silica gel (20% ethyl acetate in hexane), 5.1 mg of (*R*)-binaphthol (46.2% yield) and ca. 1 mg of **6** were obtained. Specific rotation of the obtained (*R*)-binaphthol:  $[\alpha]_D^{25} = 33.2$  (0.1, THF)

**With HBr:** A solution of **5** (19.8 mg, 0.042 mmol) and 48% aqueous HBr in acetic acid (3 ml) was stirred at 50°C over 3 hours (33.4%).

**With BBr<sub>3</sub>:** To a solution of **5** (88.7 mg, 0.188 mmol) in dry dichloromethane (7 ml), BBr<sub>3</sub> (1M solution, 0.31 ml, 2.1 equivalent) was added at –78°C, and the solution was stirred for 1 hour. The mixture was extracted with ether (×4), washed with 2N HCl (×2) and dried over MgSO<sub>4</sub>. After MPLC purification on silica gel (15% ethyl acetate in hexane), 42.5 mg of (*R*)-binaphthol (78.7%) and diastereomerically homogeneous 1,3-dibromo-1,3-diphenylpropane (60.1 mg, 90.4%,  $[\alpha]_D^{20} = 116$  (c 1.0, methanol)) were obtained.

*Preparation of 6 from 5*

A solution of **5** (107.8 mg, 0.228 mmol) in acetic acid (40 ml) was heated to 80°C in the presence of a catalytic amount of Pd–C (5%) under hydrogen atmosphere for 2 days. By filtration and MPLC purification (silica gel, 20% ethyl acetate in hexane), 46.7 mg of **6** was obtained (69.7% yield). Enantiomeric purity of **6** was confirmed to be over 99% ee by HPLC on CHIRALPAC OT(+) eluted with methanol. Racemic **6** prepared from racemic binaphthol under the same reduction conditions showed two completely separated peaks on the HPLC, whereas (*R*)-**6** obtained from **5** showed a single peak. (*R*)-**6**: mp=161.3–162.5°C;  $[\alpha]_D^{20} = 53.3$  (c 0.7, methanol), litt<sup>10</sup>,  $[\alpha]_{589}^{25} = 52.8$  (c 1.1,  $\text{CHCl}_3$ ).

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