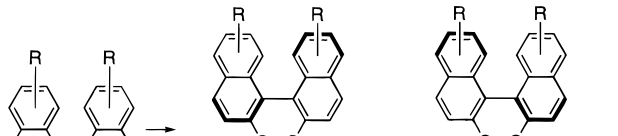
A Versatile Method for the Resolution and Absolute Configuration Assignment of Substituted 1,1′-Bi-2-naphthols

Hak-Fun Chow,* Chi-Wai Wan, and Man-Kit Ng

Department of Chemistry, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong

Received June 10, 1996

Optically active 1,1′-bi-2-naphthols are extremely useful C_2-symmetrical compounds employed as chiral auxiliaries or chiral catalysts in asymmetric synthesis.[1] A number of methodologies have been developed to prepare optically pure 1,1′-bi-2-naphthols ranging from classical resolution to enzymatic hydrolysis of their derivatives.[2] Recently attempts have also been made to synthesize them *via* asymmetric oxidative coupling of 2-naphthols in the presence of chiral amines.[2,3] While these methods produce enantiomerically pure 1,1′-bi-2-naphthols in good to excellent purities, they are usually not applicable to a wider range of substituted 1,1′-bi-2-naphthol derivatives. For example, we were unable to resolve 4,4′-dibromo-1,1′-bi-2-naphthol by Toda's procedure,[4] although this method was employed to resolve the parent 1,1′-bi-2-naphthol in good optical purity. The unsubstituted 1,1′-bi-2-naphthol could also be resolved in 100 g quantities by an enzymatic method, but this procedure was again unsuccessful in our hands because of the poor solubility of the 4,4′-dibromo derivative in the reaction medium.[5] Our interest in the preparation of conjugated polymers with main chain chirality called for a preparative route to optically active 4,4′-dibromo-1,1′-bi-2-naphthol to use as the monomeric unit. In the end, we discovered that racemic 4,4′-dibromo-1,1′-bi-2-naphthol, **1c**, could be chromatographically resolved *via* its diastereomeric bis((*S*)-camphorsulfonates) **2c** and **3c**.[6] Here we disclose that this resolution procedure could be applied to a wider range of substituted 1,1′-bi-2-naphthol derivatives. Moreover, on the basis of the spectral evidence, the absolute configurations of the chiral axis of the diastereomeric pairs **2** and **3** can be inferred from their relative chromatographic mobilities.



1 **2** **3**

Entry	$[\alpha]_D^{25}$ [a]	R_f [b]	% yield	$[\alpha]_D^{25}$ [a]	R_f [b]	% yield
a: R = H	+49.9 (*c* = 1.4)	0.31	47	-45.4 (*c* = 1.0)	0.27	47
b: R = 3-Br	+97.3 (*c* = 1.1)	0.40	29	-101.5 (*c* = 1.2)	0.37	29
c: R = 4-Br[c]	+15.2 (*c* = 1.8)[c]	0.47[c]	35[c]	-9.3 (*c* = 1.4)[c]	0.43[c]	34[c]
d: R = 6-OMe	+46.6 (*c* = 1.0)	0.29	47	-41.5 (*c* = 1.1)	0.25	47
e: R= 7-OMe	+70.7 (*c* = 1.1)	0.21	44	-58.1 (*c* = 1.1)	0.17	44

[a] Solvent: Chloroform. [b] Performed on silica gel 60 F_{254} TLC plates coated on aluminium sheets eluting with toluene:ethyl acetate = 10 : 1. [c] Ref. 6.

Results and Discussion

Racemic 1,1′-bi-2-naphthols **1a**,**d**−**e** were prepared by the oxidative coupling of the appropriate substituted 2-naphthols according to the procedure reported by Koga.[7] The 3,3′-dibromo derivative **1b** was prepared by the method described by Yamamoto.[8] The preparation of **1c** had been disclosed before.[6] These binaphthols **1a**−**e** could be converted to the corresponding diastereomeric sulfonates **2** and **3** in good to excellent yields on treatment with (1*S*)-camphor-10-sulfonyl chloride in the presence of triethylamine.

The sulfonates **2** and **3** were not separable by silica gel chromatography using a hexane−ethyl acetate or hexane−CH_2Cl_2 mixture as the eluent. However, they were readily separated using an ethyl acetate−toluene mixture. It was discovered that isomer **2** had a larger R_f value than its corresponding diastereomer **3**. After chromatographic separation, the camphorsulfonyl moieties in **2** or **3** were readily removed in an aqueous sodium hydroxide solution at 60 °C to generate the optically pure (*S*)- and (*R*)-enantiomers **1**, respectively. The hydrolyzed binaphthols could be converted back to the original bis((1*S*)-camphor-10-sulfonates) without racemization, as confirmed by ^{1}H-NMR spectroscopic analysis.

The absolute configurations of the bis(camphorsulfonates) **2** and **3** were determined by a combination of spectroscopic methods. Thus, the absolute configurations of **2a** (R = H) and **3a** (R = H) were ascertained by converting them to the known **(*S*)-1a** and **(*R*)-1a** binaphthols, respectively, followed by polarimetric analysis.[5] On the other hand, the absolute configuration of the chiral axis of the slower running isomer **3c** (R = 4-Br) was determined by X-ray diffraction analysis to have an (*R*) configuration.[6] Examination of the ^{1}H-NMR spectra of all of the diastereomeric **2** and **3** compounds revealed one interesting finding. In all of the faster running bis(camphorsulfonates) **2a**−**e**, the diastereotopic methylene groups adjacent to the sulfonyl moiety appeared as an AX system ($J \approx 15$ Hz) with a chemical shift difference of less than 0.5 ppm, while those of the slower running diastereomeric **3a**−**e** compounds had a significantly larger chemical shift difference of 1.0 ppm. Moreover, circular dichorism (CD) spectra of the hydrolyzed products derived from the slower running diastereoisomers **3a**−**d** all gave a negative first Cotton effect at around 236−240 nm and a positive second Cotton effect at 224−228 nm. On the other hand, the optically active 7,7′-dimethoxy-1,1′-bi-2-naphthol, derived from the faster running diastereoisomeric bis(camphorsulfonate) **2e** (R = 7-OMe), showed a positive first Cotton effect at 244 nm and a negative second Cotton effect at 234 nm. Because of the consistent pattern in both the ^{1}H-NMR and CD spectra, we concluded that the chiral axis of all

(1) For reviews, see: (a) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503. (b) Singh, V. K. *Synthesis* **1992**, 605. (c) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.

(2) For an excellent summary, see: Smrcina, M.; Poláková, J.; Vyskocil, S.; Kocovsky, P. *J. Org. Chem.* **1993**, *58*, 4534.

(3) (a) Yamamoto, K.; Fukushima, H.; Nakazaki, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1490. (b) Brussee, J.; Groenendijk, J. L. G.; te Koppele, J. M.; Jansen, A. C. A. *Tetrahedron* **1985**, *41*, 3313. (c) Osa, T.; Kashiwagi, Y.; Yanagisawa, Y.; Bobbitt, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2535. (d) Nakajima, M.; Kanayama, K.; Miyoshi, I.; Hashimoto, S.-i. *Tetrahedron Lett.* **1995**, *36*, 9519.

(4) Toda, F; Tanaka, K. *J. Org. Chem.* **1988**, *53*, 3607.

(5) Kazlauska, R. J. *J. Am. Chem. Soc.* **1989**, *111*, 4953.

(6) (a) Ng, M.-K.; Chow, H.-F.; Chan, T.-L.; Mak, T. C. W. *Tetrahedron Lett.* **1996**, *37*, 2979. (b) Chow, H.-F.; Ng, M.-K. *Tetrahedron: Asymmetry* **1996**, *7*, 2251.

(7) Noji, M.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1994**, *43*, 7983.

(8) Maruoka, K.; Itoh, T.; Araki, Y.; Shirasaka, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2975.

S0022-3263(96)01092-4 CCC: $12.00

of the faster running isomers **3a**−**e** had an (*S*)-configuration while those of the slower running isomers **2a**−**e** had an (*R*)-configuration. The observed Cotton effect pattern is closely parallel to the previous findings by Mason[9] and Harada,[10] in which case the (*S*)-enantiomer of C_2-symmetrically substituted binaphthyls was shown to consistently exhibit positive first and negative second Cotton effects.

With the rapid development in asymmetric synthesis and the design of chiral catalysts, our method therefore offers a rapid and reliable procedure to resolve a variety of racemic binaphthols using the inexpensive compound camphorsulfonyl chloride. Although this resolution method relies on the chromatographic separation and scaling up could be a problem, we believe this is the only method available for the resolution of substituted binaphthols without the trouble of finding the appropriate resolving agent or recrystallization solvent associated with the other methods. More importantly, this method allows us to assign the absolute configuration of the binaphthol chiral axis from the relative chromatographic mobility data.

Experimental Section

General. All reactions were conducted under a nitrogen atmosphere. Melting points were taken on a hot-plate microscope apparatus and were uncorrected. ^{1}H-NMR spectra were acquired on a 500 MHz NMR spectrometer. (1*S*)-Camphor-10-sulfonyl chloride was purchased from Aldrich Chemical Co. and used without further purification. Mass spectra were obtained by liquid secondary ion mass spectrometry (L-SIMS) technique using 3-nitrobenzyl alcohol as matrix.

Preparation of Bis((1*S*)-camphor-10-sulfonates) 2 and 3. To a solution of the 1,1′-bi-2-naphthol (2 mmol) in dry dichloromethane (15 mL) was added dry triethylamine (5 mmol) at 0 °C followed by (1*S*)-camphor-10-sulfonyl chloride (4.5 mmol). The mixture was stirred at 0 °C until thin layer chromatography indicated completion of the reaction (≈3 h). Water was added, and the reaction mixture was extracted with dichloromethane. The combined extracts were washed with saturated NaCl solution, dried (Na_2SO_4), filtered, evaporated *in vacuo*, and chromatographed on silica gel with an ethyl acetate−toluene mixture as the eluent to give the diastereomeric bis(sulfonates **2** and **3**.

2a (R = H): white solid; mp 148−149 °C; ^{1}H-NMR ($CDCl_3$) δ 0.53 (s, 6 H), 0.77 (s, 6 H), 1.25−1.37 (m, 4 H), 1.78 (d, J = 18.5 Hz, 2 H), 1.81−1.87 (m, 2 H), 1.93−2.05 (m, 4 H), 2.17−2.24 (m, 2 H), 2.43 (d, J = 14.5 Hz, 2 H), 2.87 (d, J = 14.5 Hz, 2 H), 7.29 (d, J = 8.5 Hz, 2 H), 7.37 (t, J = 8 Hz, 2 H), 7.51 (t, J = 7.5 Hz, 2 H), 7.77 (d, J = 9 Hz), 7.95 (d, J = 8.5 Hz, 2 H), 8.05 (d, J = 9 Hz, 2 H); MS (L-SIMS, m/z) 715 (M + H$^+$, 35, $C_{40}H_{43}O_8S_2$ requires 715). Anal. Calcd for $C_{40}H_{42}O_8S_2$: C, 67.21; H, 5.92. Found: C, 67.41; H, 6.27.

3a (R = H): white solid; mp 195−196 °C; ^{1}H-NMR ($CDCl_3$) δ 0.46 (s, 6 H), 0.60 (s, 6 H), 1.20−1.35 (m, 4 H), 1.69−1.84 (m, 4 H), 1.76 (d, J = 18.5 Hz, 2 H), 1.86−1.92 (m, 2 H), 2.17−2.24 (m, 2 H), 2.29 (d, J = 15 Hz, 2 H), 3.25 (d, J = 15 Hz, 2 H), 7.24 (d, J = 8 Hz, 2 H), 7.34 (t, J = 8 Hz, 2 H), 7.49 (t, J = 8 Hz, 2 H), 7.80 (d, J = 9.5 Hz), 7.95 (d, J = 8.5 Hz, 2 H), 8.05 (d, J = 9 Hz, 2 H); MS (L-SIMS, m/z) 715 (M + H$^+$, 70, $C_{40}H_{43}O_8S_2$ requires 715). Anal. Calcd for $C_{40}H_{42}O_8S_2$: C, 67.21; H, 5.92. Found: C, 67.43; H, 6.16.

2b (R = 3-Br): white solid; mp 177−178 °C; ^{1}H-NMR ($CDCl_3$) δ 0.71 (s, 6 H), 0.92 (s, 6 H), 1.20−1.30 (m, 4 H), 1.80 (d, J = 18 Hz, 2 H), 1.86−1.92 (m, 2 H), 1.95−2.07 (m, 4 H), 2.20−2.29 (m, 2 H), 2.68 (d, J = 15 Hz, 2 H), 2.92 (d, J = 15 Hz, 2 H), 7.23 (d, J = 8.5 Hz, 2 H), 7.38 (t, J = 8 Hz, 2 H), 7.54 (t, J = 7.5 Hz, 2 H), 7.86 (d, J = 8.5 Hz, 2 H), 8.37 (s, 2 H); MS (L-SIMS, m/z) 871 (M + H$^+$, 2, $C_{40}H_{41}{}^{79}Br_2O_8S_2$ requires 871). Anal. Calcd for $C_{40}H_{40}Br_2O_8S_2$: C, 55.05; H, 4.62. Found: 54.93; H, 4.60.

3b (R = 3-Br): white solid; mp 227−229 °C; ^{1}H-NMR ($CDCl_3$) δ 0.41 (s, 6 H), 0.78 (s, 6 H), 1.25−1.48 (m, 4 H), 1.81 (d, J = 18.5 Hz, 2 H), 1.86−1.97 (m, 4 H), 2.02 (d, J = 15.5 Hz, 2 H), 2.20−2.27 (m, 4 H), 3.37 (d, J = 15 Hz, 2 H), 7.21 (d, J = 8.5 Hz, 2 H), 7.34 (t, J = 8.5 Hz, 2 H), 7.50 (t, J = 7.5 Hz, 2 H), 7.84 (d, J = 8 Hz, 2 H), 8.38 (s, 2 H); MS (L-SIMS, m/z) 871 (M + H$^+$, 3, $C_{40}H_{41}{}^{79}Br_2O_8S_2$ requires 871). Anal. Calcd for $C_{40}H_{40}Br_2O_8S_2$: C, 55.05; H, 4.62. Found: 54.79; H, 4.58.

2d (R = 6-OMe): white solid; mp 85−87 °C; ^{1}H-NMR ($CDCl_3$) δ 0.54 (s, 6 H), 0.79 (s, 6 H), 1.25−1.44 (m, 4 H), 1.80 (d, J = 18.5 Hz, 2 H), 1.80−1.90 (m, 2 H), 1.94−1.98 (m, 2 H), 2.02−2.10 (m, 2 H), 2.18−2.26 (m, 2 H), 2.44 (d, J = 14.5 Hz, 2 H), 2.89 (d, J = 14.5 Hz, 2 H), 3.91 (s, 6 H), 7.02 (dd, J = 8.5, 2 Hz, 2 H), 7.19 (d, J = 9 Hz, 2 H), 7.22 (d, J = 2.5 Hz, 2 H), 7.71 (d, J = 9 Hz, 2 H), 7.91 (d, J = 9 Hz, 2 H); MS (L-SIMS, m/z) 775 (M + H$^+$, 30, $C_{42}H_{47}O_{10}S_2$ requires 775).

3d (R = 6-OMe): white solid; mp 94−95 °C; ^{1}H-NMR ($CDCl_3$) δ 0.47 (s, 6 H), 0.64 (s, 6 H), 1.25−1.44 (m, 4 H), 1.75−1.82 (m, 2 H), 1.78 (d, J = 18.5 Hz, 2 H), 1.85−1.94 (m, 4 H), 2.18−2.26 (m, 2 H), 2.23 (d, J = 15 Hz, 2 H), 3.25 (d, J = 15 Hz, 2 H), 3.91 (s, 6 H), 7.00 (dd, J = 9, 2 Hz, 2 H), 7.14 (d, J = 9 Hz, 2 H), 7.21 (d, J = 2 Hz, 2 H), 7.72 (d, J = 9 Hz, 2 H), 7.91 (d, J = 9 Hz, 2 H); MS (L-SIMS, m/z) 775 (M + H$^+$, 100, $C_{42}H_{47}O_{10}S_2$ requires 775). Anal. Calcd for $C_{42}H_{46}O_{10}S_2$: C, 65.10; H, 5.98. Found: C, 65.15; H, 5.92.

2e (R = 7-OMe): white solid; mp 75−76 °C; ^{1}H-NMR ($CDCl_3$) δ 0.50 (s, 6 H), 0.75 (s, 6 H), 1.22−1.45 (m, 4 H), 1.79 (d, J = 18.5 Hz, 2 H), 1.80−1.90 (m, 2 H), 1.92−1.98 (m, 2 H), 2.00−2.10 (m, 2 H), 2.17−2.26 (m, 2 H), 2.35 (d, J = 15 Hz, 2 H), 2.86 (d, J = 15 Hz, 2 H), 3.56 (s, 6 H), 6.60 (d, J = 1.5 Hz, 2 H), 7.16 (dd, J = 9, 2.5 Hz, 2 H), 7.60 (d, J = 9.5 Hz, 2 H), 7.83 (d, J = 9 Hz, 2 H), 7.95 (d, J = 9 Hz, 2 H); MS (Electrospray, m/z) 797 (M + Na$^+$, 100). Anal. Calcd for $C_{42}H_{46}O_{10}S_2$: C, 65.10; H, 5.98. Found: C, 65.48; H, 6.02.

3e (R = 7-OMe): white solid; mp 81−82 °C; ^{1}H-NMR ($CDCl_3$) δ 0.50 (s, 6 H), 0.68 (s, 6 H), 1.25−1.44 (m, 4 H), 1.73−1.82 (m, 2 H), 1.78 (d, J = 18.5 Hz, 2 H), 1.84−1.97 (m, 4 H), 2.18−2.26 (m, 2 H), 2.26 (d, J = 15 Hz, 2 H), 3.24 (d, J = 15 Hz, 2 H), 3.52 (s, 6 H), 6.55 (d, J = 1.5 Hz, 2 H), 7.14 (dd, J = 9, 1.5 Hz, 2 H), 7.64 (d, J = 9 Hz, 2 H), 7.83 (d, J = 9 Hz, 2 H), 7.96 (d, J = 9 Hz, 2 H); MS (Electrospray, m/z) 797 (M + Na$^+$, 100). Anal. Calcd for $C_{42}H_{46}O_{10}S_2$: C, 65.10; H, 5.98. Found: C, 65.54; H, 6.38.

Hydrolysis of Bis((1*S*)-camphor-10-sulfonates). To a suspension of the sulfonate **2** or **3** (1 mmol) in methanol (20 mL) was added an aqueous solution of sodium hydroxide (1.1 M, 15 mL). The resulting mixture was warmed to 60 °C until tlc indicated completion of hydrolysis (≈20 h). After the solution was cooled to room temperature, it was acidifed with a diluted HCl solution, and excess methanol evaporated *in vacuo*. The residue was taken up in dichloromethane and washed with a saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give the optically pure binaphthol **1** as a solid.

(*S*)-1,1′-Bi-2-naphthol [(*S*)-1a]: 50% yield from **2a**; $\alpha_D{}^{25}$ = −29.6 (c = 0.24, THF) [lit.[11] $\alpha_D{}^{25}$ = −35.2 (c = 1.0, THF)]; mp 205−207 °C (lit.[11] 206−207 °C). **(*R*)-1,1′-Bi-2-naphthol [(*R*)-1a]:** 57% yield from **3a;** $\alpha_D{}^{25}$ = +30.2 (c = 0.12, THF); mp 205−208 °C (lit.[11] 206−207 °C).

(*S*)-3,3′-Dibromo-1,1′-bi-2-naphthol [(*S*)-1b]: 63% yield from **2b**; $\alpha_D{}^{25}$ = −40.0 (c = 0.15, $CHCl_3$); mp 242−244 °C; ^{1}H-NMR ($CDCl_3$) δ 5.56 (br s, 2 H), 7.10 (d, J = 8.4 Hz, 2 H), 7.31 (t, J = 8 Hz, 2 H), 7.39 (t, J = 8 Hz, 2 H), 7.82 (d, J = 7.7 Hz, 2 H), 8.26 (s, 2 H); HRMS calcd for $C_{20}H_{12}{}^{79}Br^{81}BrO_2$ 443.9185, found 443.9187. **(*R*)-3,3′-Dibromo-1,1′-bi-2-naphthol [(*R*)-1b]:** 67% from **3b**; $\alpha_D{}^{25}$ = +43.0 (c = 0.22, $CHCl_3$); mp 243−244 °C; MS (L-SIMS, m/z) 443.9 (M$^+$, 10, $C_{20}H_{12}{}^{79}Br^{81}BrO_2$ requires 444).

(*S*)-6,6′-Dimethoxy-1,1′-bi-2-naphthol [(*S*)-1d]: 42% yield from **2d**; $\alpha_D{}^{25}$ = +25.8 (c = 0.10); mp 177−179 °C; ^{1}H-NMR ($CDCl_3$) δ 3.91 (s, 6 H), 5.30 (br s, 2 H), 6.98 (dd, J = 9.2, 2.4 Hz, 2 H), 7.06 (d, J = 9.2 Hz, 2 H), 7.22 (d, J = 2.4 Hz, 2 H), 7.35 (d, J = 8.9 Hz, 2 H), 7.86 (dd, J = 8.9 Hz, 2 H); HRMS

(9) Mason, S. F.; Seal, R. H.; Roberts, D. R. *Tetrahedron* **1974**, *30*, 1671.

(10) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy, Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983: pp 193−201.

(11) Gong, B.-q.; Chen, W.-y.; Hu, B.-f. *J. Org. Chem.* **1991**, *56*, 423.

calcd for $C_{22}H_{18}O_4$ 346.1204, found 346.1193. **(*R*)-6,6′-Dimethoxy-1,1′-bi-2-naphthol [(*R*)-1d]:** 52% yield from **3d**; $\alpha_D^{25} = -23.0$ ($c = 0.21$); mp 176−178 °C; HRMS calcd for $C_{22}H_{18}O_4$ 346.1204, found 346.1198.

(*S*)-7,7′-Dimethoxy-1,1′-bi-2-naphthol [(*S*)-1e]: 67% yield from **2e**; $\alpha_D^{25} = +127.4$ ($c = 0.17$); mp 55−57 °C; ^{1}H-NMR ($CDCl_3$) δ 3.58 (s, 6 H), 5.06 (br s, 2 H), 6.49 (d, $J = 2.4$ Hz, 2 H), 7.04 (dd, $J = 8.8$, 2.4 Hz, 2 H), 7.23 (d, $J = 8.8$ Hz, 2 H), 7.79 (d, $J = 8.8$ Hz, 2 H), 7.89 (dd, $J = 8.8$ Hz, 2 H); HRMS calcd for $C_{22}H_{18}O_4$ 346.1204, found 346.1197. **(*R*)-7,7′-Dimethoxy-1,1′-bi-2-naphthol [(*R*)-1e]:** 54% yield from **3e**; $\alpha_D^{25} = -125.5$ ($c = 0.17$); mp 56−58 °C; HRMS calcd for $C_{22}H_{18}O_4$ 346.1204, found 346.1204.

Acknowledgment. We thank the Research Grants Council, Hong Kong for the financial support.

Supporting Information Available: ^{1}H-NMR spectra for compounds **2a**−**b**, **2d**−**e**, **3a**−**b**, **3d**−**e**, **(R)-1b**, **(R)-1d** and **(R)-1e** and CD spectra for compounds **(*R*)-1a**, **(R)-1b**, **(R)-1d**, and **(S)-1e** (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9610927