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Synthesis of chiral 2,2′-dimethyl-1,1′-binaphthyl-8,8′-diamine and barriers of atropisomerization of the related binaphthyls

Kazunori Tsubaki,[a,*] Dinh T. T. Hai,[a] Valluru K. Reddy,[a] Hiroshi Ohnishi,[a] Kaoru Fuji[b] and Takeo Kawabata[a]

[a]*Institute for Chemical Research, Kyoto University, Gokasho, Uji, Kyoto 611-0011, Japan*
[b]*Faculty of Pharmaceutical Sciences, Hiroshima International University, 5-1-1 Hirokoshingai, Kure, Hiroshima 737-0112, Japan*

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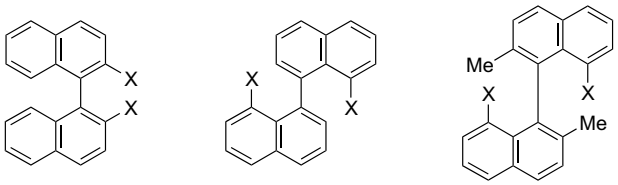
Abstract—Chiral 2,2′-dimethyl-1,1′-binaphthyl-8,8′-diamine **3b** was synthesized via a diastereomeric resolution and determination of the absolute configurations, and the barriers compared for atropisomerization amongst binaphthyl skeletons.

1. Introduction

In asymmetric synthesis, many chiral catalysts and auxiliaries have been generated based upon 1,1′-binaphthyl-2,2′-diol **1a** as the lead compound. These derivatives have been designed so that the target reactions take place in the minor groove of the 1,1′-binaphthalene skeleton. Recently, a few reactions using the major groove as asymmetric environment have been reported. For example, 7,7′-disubstituted derivatives were used for the Michael reaction[1] and allylic alkylation,[2] while 8,8′-disubstituted 1,1′-binaphthalene derivatives **2** have also been investigated not only for use as chiral auxiliaries[3] but also as chiral catalysts.[4] Although these 8,8′-disubstituted-1,1′-binaphthalene derivatives are useful for asymmetric synthesis, the chirality of the 1,1′-binaphthalene axis is easily racemized at elevated temperature.[5] To overcome this troublesome feature, Meyers and Kolotuchin reported 2,2′-dimethyl compound **3a**, which exhibited no atropisomerization at 180 °C for 30 min.[6] Meanwhile, the 2,2′-diamino-1,1′-binaphthalene framework **1b** has also been reported to be a useful chiral ligand.[7] Herein, we report the preparation, resolution and determination of the absolute configurations of 2,2′-dimethyl-1,1′-binaphthyl-8,8′-diamine **3b**, and compare the barriers to atropisomerization amongst binaphthyl skeletons (Fig. 1).



1a: X=OH
1b: X=NH_2

2a: X=OH

3a: X=OH
3b: X=NH_2

Figure 1. 2,2′-Dimethyl-1,1′-binaphthyl-8,8′-diamine **3b** and the related binaphthyls.

2. Results and discussion

2.1. Synthesis of chiral 2,2′-dimethyl-1,1′-binaphthyl-8,8′-diamine 3b

The synthesis of optically active **3b** is outlined in Scheme 1. 1-Bromo-2-methylnaphthalene **4** was added to nitric acid ($d = 1.42$, **4**/HNO_3 = 5 ml/8 ml) at 0 °C and stirred for 30 min to give the desired product **5**[8] and regioisomer **6**[9] in a 1:1 mixture. Other popular nitration conditions, such as HNO_3/H_2SO_4 gave poly-nitrated compounds. After **5** and **6** were separated by column chromatography (SiO_2, hexane/chloroform/ethyl acetate = 5:1:1 as an eluent), a nitro group of **5** was reduced with excess Fe or Zn to give **7** in yields of 78% and 74%, respectively. Reductive homo coupling of bromonaphthylamine **7** was conducted with $NiBr_2$ $(PPh_3)_2$ in THF to give (±)-**3b** in 86% yield.[10] (±)-**3b** was treated with (−)-menthylchloroformate (1.5 equiv)

* Corresponding author. E-mail: tsubaki@fos.kuicr.kyoto-u.ac.jp

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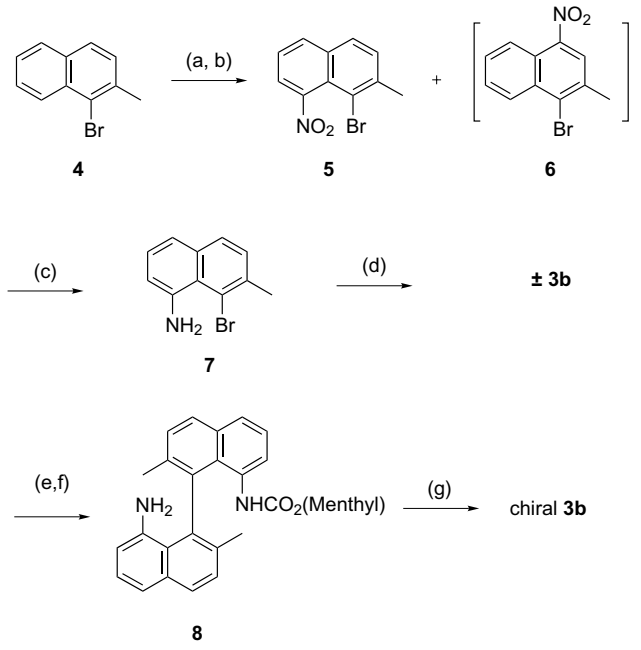

Scheme 1. Reagents and conditions: (a) HNO_3 ($d = 1.42$), **5** (45%), **6** (44%); (b) separation with SiO_2 column chromatography; (c) Fe (78%) or Zn (74%); (d) $NiBr_2$ $(PPh_3)_2$, Zn, KI, (86%); (e) (−)-menthylchloroformate, Et_3N; (f) separation with SiO_2 column chromatography. (a*S*)-**8** (19%), (a*R*)-**8** (15%); (g) HBr/AcOH (98%).

and the diastereomeric monomenthylcarbamates **8** were resolved by column chromatography (SiO_2, hexane/chloroform/ethyl acetate = 20:5:1 as an eluent) in 15–19% yields as well as recovered (±)-**3b** and diastereomeric bisadducts. Removal of the menthyl group of **8** with HBr/acetic acid gave optically active **3b** in 98% yield. A higher R_f value on TLC or the first fraction on the column chromatography of **8** leads to (−)-**3b**.

2.2. Determination of the absolute configuration

The absolute configuration of chiral **3b** was determined by a combination of the exciton chirality method and theoretical calculation. In the CD spectra of 1,1′-binaphthalene derivatives, the sense of the exciton-split at around 220 nm, which is attributed to the ^1L_a transition moment (along with the long axis of the naphthalene ring) reflects the twisting of two naphthalene rings.[11] Thus, two naphthalenes twisting in a clockwise direction lead to a positive split Cotton effect. Although no exceptions have been reported for this empirical rule, calculations reveal that the sense of the CD is inverted at a dihedral angle of 110°.[12] Therefore, to determine the absolute configuration of **3b**, we calculated the most stable conformation of **3b**. After the initial structure was selected through molecular mechanics calculations (COFLEX-MM2), the structure was successively refined by semiempirical molecular orbital calculation (MOPAC-PM5)[13] and DFT calculation (GAUSSIAN 03w/B3LYP/6-31G(d))[14] to identify the most stable conformation of **3b** (Fig. 2).

The dihedral angle of C(2)–C(1)–C(1′)–C(2′) was predicted to be 91.45°. In addition, the structure of **3b** in which the dihedral angle of C(2)–C(1)–C(1′)–C(2′) was fixed at 110°, was also calculated by the same procedure. The energy difference between the two conformers is estimated to be about 2.05 kcal/mol. These data indicate that with regards to the sense of the CD spectrum of **3b**, conformers with a dihedral angle >110° should have a slightly smaller effect.

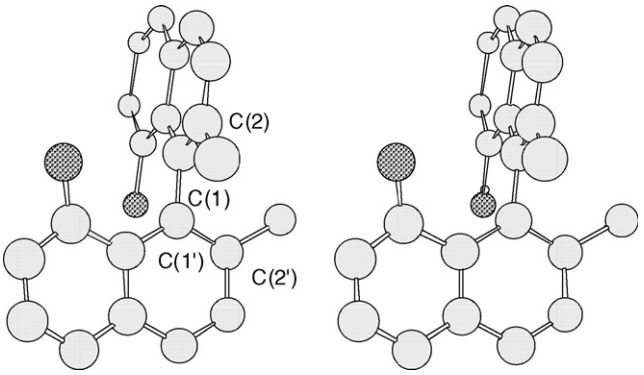

Figure 2. The most stable conformation of **3b** (GAUSSIAN 03w/B3LYP/6-31G(d)). Stereoview. Hydrogens are omitted for clarity.

The CD and UV spectra of chiral **3b** are shown in Figure 3. In the CD spectra, (−)-**3b**, which was obtained from the first fraction in the column separation of **8**, shows a large positive split CD at around 220 nm. Thus, the axial chirality should be (*S*). Similarly, (+)-**3b**, from the second fraction, shows a negative split CD and can be assigned an (*R*)-configuration.

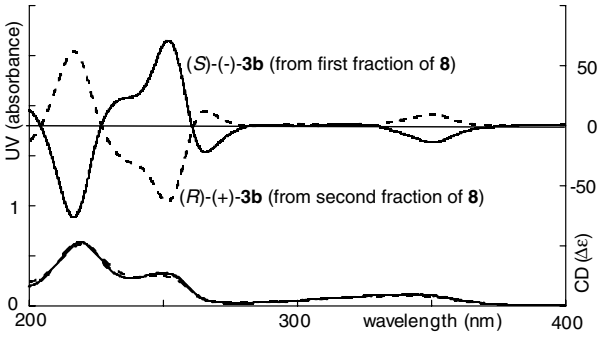

Figure 3. UV and CD spectra of chiral **3b**. conditions, acetonitrile, 1.0×10^{-4} M, 25 °C, light path length 1 mm.

2.3. Determination of the atropisomerization barriers of 3b and the related binaphthyls

With regards to the atropisomerization of binaphthalenes, binaphthol **1a** was examined as follows: (i) under acidic conditions, protonation should take place at C(1) to generate an sp^3 carbon and to decrease the rotation barrier of isomerization, and (ii) under basic conditions, deprotonation of the hydroxy groups may be conducive to decrease the rotation barrier.[15] With 8,8′-disubstituted-1,1′-naphthalenes, relatively small barriers are caused by the destabilization of the ground states through the introduction of substituent groups at the 8,8′ positions.[5] Therefore, it is

Table 1. Atropisomerization barriers of **3b** and the related binaphthyls

	1b (kcal/mol)	**2a** (kcal/mol)	**3b** (kcal/mol)
Acidic condition[a]	32.1[d]	28.7	32.0[d]
Neutral condition[b]	—[d,e]	28.7	—[d,e]
Basic condition[c]	—[d,e]	28.4	—[d,e]

[a] Substrate (0.05 mmol), methansulfonic acid (0.5 mmol), DMSO (10 ml), 110 °C.
[b] Substrate (0.05 mmol), DMSO (10 ml), 110 °C.
[c] Substrate (0.05 mmol), 4 M NaOH aq (0.5 mmol), DMSO (10 ml), 110 °C.
[d] Some degree of decomposition, probably oxidation of nitrogen was observed.
[e] No racemization was observed.

interesting to measure the rotation barriers of newly synthesized **3b** as well as **1b** and **2a**. In Table 1, the free energies of rotation in DMSO at 110 °C are summarized.

The rotation barriers were calculated as follows: the optically active substrate was stirred in the presence or absence of base or acid in DMSO at 110 °C, and the ee was monitored by chiral HPLC to obtain the rate constant (k) for racemization.[16] The rate constant (k) was then applied to the Eyring equation to determine the free energy of activation. Both **1b** and **3b** were quite stable under all conditions. In particular, under basic and neutral conditions, no racemization was observed (some degree of decomposition, probably oxidation of nitrogen was observed). Under acidic conditions, the rotation barriers of **1b** and **3b** were estimated to be 32.1 and 32.0 kcal/mol at 110 °C, respectively. These values are large compared to that of **2a**.

3. Conclusion

In conclusion, chiral 2,2′-dimethyl-1,1′-binaphthyl-8,8′-diamine **3b** was synthesized through diastereomeric resolution. We believe that chiral **3b** should be useful as either a chiral synthon or for use in synthetic chemistry or supramolecular chemistry. A more effective route for the synthesis of 2,2′-dimethyl-1,1′-binaphthyl-8,8′-diamine derivatives through kinetic resolution using organo catalysts is currently in progress.

4. Experimental

4.1. 1-Bromo-2-methyl-8-nitronaphthalene 5

To nitric acid ($d = 1.42$, 400 ml), 1-bromo-2-methylnaphthalene **4** (250 ml, 1.60 mol) was added dropwise for 1 h under ice-bath cooling, and the mixture was stirred (with a mechanical motor) for 10 min. After ice water (2 l) was slowly added, diethyl ether was added under ice-bath cooling. The organic layer was separated and washed successively with water and brine (twice). After being dried over magnesium sulfate, the solvent was evaporated in vacuo to give a residue (ca. 450 g). The residue was purified by column chromatography (SiO_2, 2 kg, hexane/chloroform/ethyl acetate = 10:1:1) to successively give **6** (87.8 g), a mixture (ca. 280 g) of **5** and **6**, and **5** (66.1 g). The mixture was again purified by column chromatography to give **6** (99.8 g) and **5** (124.0 g). Total yields of **5** and **6** were 190.1 g (45%) and 187.6 g (44%), respectively. Crude **5** (190.1 g) was further purified by recrystallization with ethyl acetate (160 ml) to give pure **5** (158.1 g, 83%) as a yellow powder.

Compound **5**:[8] Mp 92–95 °C (from ethyl acetate); IR (KBr) 1522, 1368, 1313 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.65 (s, 3H), 7.47 (dd, $J = 7.3$, 7.8 Hz, 1H), 7.50 (d, $J = 8.2$ Hz, 1H), 7.74 (d, $J = 7.3$ Hz, 1H); 7.82 (d, $J = 8.2$ Hz, 1H); 7.99 (d, $J = 7.8$ Hz, 1H); HRMS Calcd for $C_{11}H_8{}^{81}BrNO_2$: 266.9718. Found: 266.9724, Calcd for $C_{11}H_8{}^{79}BrNO_2$: 264.9738. Found: 264.9748. Anal. Calcd for $C_{11}H_8BrNO_2$: C, 49.65; H, 3.03; N, 5.26. Found: C, 49.41; H, 3.00; N, 5.32.

Compound **6**:[9] Mp 75–78 °C (from ethyl acetate); IR (KBr) 1519, 1335, 1264 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.69 (s, 3H), 7.65–7.75 (m, 2H), 8.09 (s, 1H), 8.40–8.50 (m, 2H); HRMS Calcd for $C_{11}H_8{}^{81}BrNO_2$: 266.9718. Found: 266.9713, Calcd for $C_{11}H_8{}^{79}BrNO_2$: 264.9738. Found: 264.9731.

4.2. 8-Bromo-7-methylnaphthalen-1-amine 7

A mixture of **5** (50.0 g, 0.1 mol), ammonium chloride (25.0 g, 0.47 mol) and Fe powder (100 g, 1.79 mol) in ethanol (2 l) was stirred under reflux conditions for 1 h. After cooling, Fe was filtered off, and the filtrate evaporated in vacuo to give a residue. Since an inseparable emulsion phase was generated when ethyl acetate and aqueous sodium hydrogen carbonate were added to the residue, the emulsion was filtered over Celite. The organic layer was separated and washed successively with water (1 l, three times), and brine. After being dried over sodium sulfate, the solvent was evaporated in vacuo to give a dark grey solid. The solid was collected and triturated with hexane to give **7** as a dark grey solid (34.5 g, 78% yield). Crude **7** was used directly for the next step without further purification. A small portion of the sample was subjected to further purification by PTLC to give an analytical sample. Mp 80–82 °C; IR (KBr) 3443, 3347, 1619, 1558, 1432 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.55 (s, 3H), 5.25 (br s, 2H), 6.74 (dd, $J = 2.7$, 6.4 Hz, 1H), 7.17–7.25 (m, 3H), 7.59 (d, $J = 8.3$ Hz, 1H); HRMS Calcd for $C_{11}H_{10}N^{79}Br$: 234.9996. Found: 234.9986, Calcd for $C_{11}H_{10}N^{81}Br$: 236.9976. Found: 236.9975. Anal. Calcd for $C_{11}H_{10}NBr$: C, 55.96; H, 4.27; N, 5.93. Found: C, 55.91; H, 4.12; N, 5.82.

4.3. 2,2′-Dimethyl-1,1′-binaphthyl-8,8′-diamine 3b

A mixture of activated zinc (7.75 g, 119 mmol), dibromobis(triphenylphosphine)nickel(II) (8.50 g, 11.4 mmol), and tetraethylammonium iodide (30.5 g, 119 mmol) in dry THF (280 ml) was stirred for 1 h under an Ar atmosphere. To the mixture was added **7** (28.0 g, 119 mmol) in dry THF (200 ml) at room temperature, and the mixture was stirred for 1 h at 50 °C. Aqueous ammonium chloride was added to the mixture and the organic layer was separated and

washed with brine. The combined aqueous layers were extracted with ethyl acetate. The organic layers were combined and washed with brine, dried over sodium sulfate and evaporated in vacuo to give a residue. The residue was purified by column chromatography (SiO_2, 0.5 Kg, hexane/chloroform/ethyl acetate = 8:1:1) to give **3b** as a pale purple solid. (13.2 g, 60%) Mp 125–127 °C; IR (KBr) 3448, 1619, 1561 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.92 (s, 6H), 3.6 (br s, 4H), 6.53 (dd, $J = 1.2$, 7.2 Hz, 2H), 7.20 (dd, $J = 7.6$, 7.6 Hz, 2H), 7.27 (dd, $J = 1.2$, 8.1 Hz, 2H), 7.34 (d, $J = 8.6$ Hz, 2H), 7.52 (d, $J = 8.3$ Hz, 2H); HRMS Calcd for $C_{22}H_{20}N_2$: 312.1627. Found: 312.1623. Anal. Calcd for $C_{22}H_{20}N_2 \cdot 1/3H_2O$: C, 82.99; H, 6.54; N, 8.80. Found: C, 82.85; H, 6.35; N, 8.45.

4.4. Monomenthylcarbamate (a*S*)-8 and (a*R*)-8

A solution of (±)-**3b** (1.00 g, 3.2 mmol), (−)- menthylchloroformate (1.44 ml, 6.72 mol), and triethylamine (1.34 ml, 9.60 mmol) in THF (20 ml) was stirred under ice-bath cooling for 7 h. The reaction mixture was poured into a mixed solvent of ethyl acetate and aqueous hydrochloric acid solution. The organic layer was separated and washed successively with water and brine. After being dried over sodium sulfate, the solvent was evaporated in vacuo to give a residue (brown oil, 2.16 g). The residue was purified by column chromatography (SiO_2, 400 g, hexane/chloroform/ethyl acetate = 20:5:1) to successively give (a*S*)-**8** (higher R_f value or first fraction) (292 mg, 19%) and (a*R*)-**8** (lower R_f value or second fraction) (241 mg, 15%), respectively.

Compound (a*S*)-**8**: Mp 65–67 °C; $[\alpha]_D^{20} = -103$ (*c* 0.5, $CHCl_3$); IR (KBr) 3392, 2954, 1719, 1563 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.48 (d, $J = 7.2$ Hz, 3H), 0.6–1.8 (m, 9H), 0.74 (d, $J = 6.9$ Hz, 3H), 0.88 (d, $J = 6.9$ Hz, 3H), 1.84 (s, 3H), 1.94 (s, 3H), 3.6 (br s, 2H), 4.2–4.3 (m, 1H), 6.53 (d, $J = 7.5$ Hz, 1H), 6.95 (br s, 1H), 7.18–7.45 (m, 5H), 7.63 (d, $J = 8.1$ Hz, 1H), 7.76 (d, $J = 8.1$ Hz, 1H), 7.83 (d, $J = 8.1$ Hz, 1H), 7.96 (d, $J = 7.5$ Hz, 1H); HRMS Calcd for $C_{33}H_{38}N_2O_2$: 494.2933. Found: 494.2921. Anal. Calcd for $C_{33}H_{38}N_2O_2 \cdot 1/4H_2O$: C, 79.40; H, 7.77; N, 5.61. Found: C, 79.69; H, 7.89; N, 5.51.

Compound (a*R*)-**8**: Mp 60–62 °C; $[\alpha]_D^{20} = -109$ (*c* 0.9, $CHCl_3$); IR (KBr) 3392, 2954, 1718, 1615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.3–2.1 (m, 9H), 0.65 (d, $J =$ 6.8 Hz, 3H), 0.79 (d, $J = 6.8$ Hz, 3H), 0.88 (d, $J = 7.3$ Hz, 3H), 1.82 (s, 3H), 1.93 (s, 3H), 3.59 (br s, 2H), 4.0–4.2 (m, 1H), 6.51 (d, $J = 7.3$ Hz, 1H), 6.82 (br s, 1H), 7.15–7.45 (m, 6H), 7.63 (d, $J = 8.3$ Hz, 1H), 7.76 (d, $J =$ 8.7 Hz, 1H), 7.83 (d, $J = 8.7$ Hz, 1H); HRMS Calcd for $C_{33}H_{38}N_2O_2$: 494.2933. Found: 494.2917. Anal. Calcd for $C_{33}H_{38}N_2O_2$: C, 80.13; H, 7.74; N, 5.66. Found: C, 79.87; H, 7.85; N, 5.78.

4.5. (*S*)-(−)-2,2′-Dimethyl-1,1′-binaphthyl-8,8′-diamine (*S*)-3b

A solution of (a*S*)-**8** (16 mg, 0.03 mmol) in acetic acid (2 ml) and 48% HBr/acetic acid (0.2 ml) was stirred at 90 °C for 7 h. The reaction mixture was poured into the mixed solvent of water and ethyl acetate. The organic layer was washed successively with 1 M sodium hydroxide solution, water (twice), and brine. After being dried over sodium sulfate, the solvent was evaporated in vacuo to give a residue. The residue was purified by PTLC to give (*S*)-(−)-**3a** as a pink color powder (10 mg, 98%). Mp = 124–125 °C; $[\alpha]_D^{20} = -43$ (*c* 0.5, $CHCl_3$) for >99% ee; HPLC t_R 38.3 min (*S*) (Chiralcel OD, *i*-PrOH/hexane = 5:95, 0.5 ml/min, $\lambda = 254$ nm).

Compound (*R*)-(+)-**3b**. Using the same method as described above, optically active (*R*)-(+)-**3b** was obtained from (a*R*)-**8** 80%, mp = 126–127 °C; $[\alpha]_D^{20} = +43$ (*c* 0.50, $CHCl_3$) for > 99% ee; HPLC t_R 46.9 min (Chiralcel OD, *i*-PrOH/hexane = 5:95, 0.5 ml/min, $\lambda = 254$ nm).

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16. The half life of chiral **3b** is about 23 h under the acidic condition at 110 °C.