PREPARATION OF OPTICALLY ACTIVE 8,8'-DISUBSTITUTED 1,1'-BIISOQUINOLINE†

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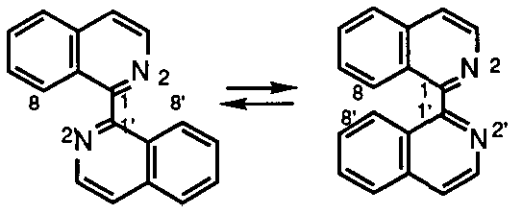
Abstract------Synthesis of 1,1'-biisoquinolines having substituents in the 8,8'-positions and their resolution by hplc on a chiral column on a preparative scale are described.

Studies of stereoisomers which share an enantiomeric relationship constitute a large and fundamentally significant part of stereochemistry. Though the presence of a center of chirality is a necessary condition for the majority of such molecules, chiral molecules without a center of chirality exist. Enantiomers resulting from restricted rotation about a single bond (axes of chirality) are a member of those isomers, and are labeled atropisomers. Biphenyls offer a typical case of particular interest, which has been the subject of many studies and discussions.[1] Further, there have been many studies in calling attention to the importance of 2,2'-bipyridine (bpy), heterocyclic analog of biphenyl, as organic ligand in the fields of organic, inorganic and



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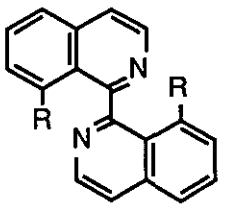
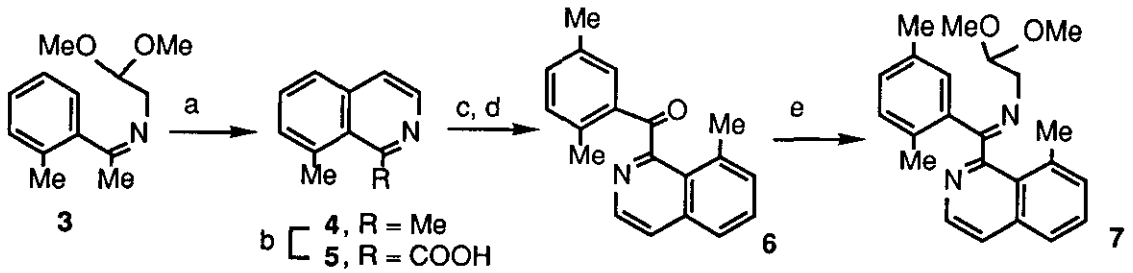


2a, R = *Me*
2b, R = OMe

†This paper is dedicated to the memory of Professor Yoshio Ban.

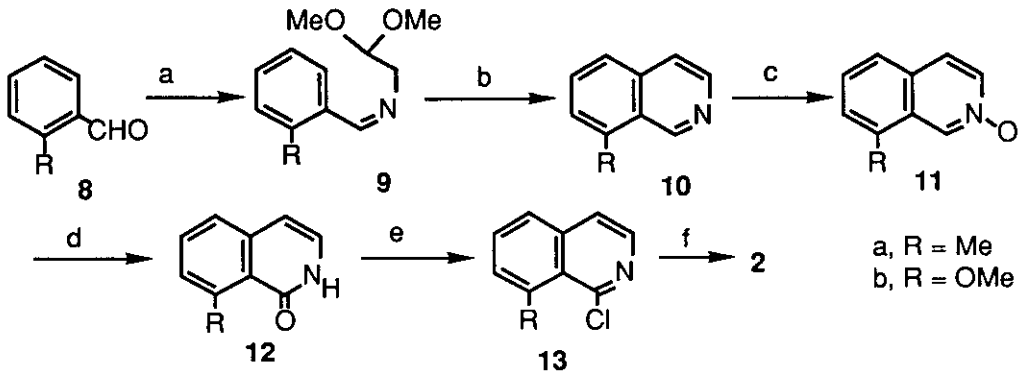
physical chemistry, and also of biochemistry.[2] The present study involves the synthesis of 1,1'-biisoquinoline derivatives, which have additional phenyl groups adjacent to the parent pyridine rings, and it is expected to exhibit more resistance toward atropisomerization than bipyridine skeletons because of transannular steric interaction between H8 and H8', 2-N and H8', and also 2'-N and H8. However, as the parent 1,1'-biisoquinoline (**1**) has no substituents in the 2 and 2' positions, it is presumed to exhibit little resistance to rotation about the s-bond *via* a transition state which brings 2-N and H8' in close proximity to one another. Actually, racemization of the parent 1,1'-biisoquinoline (**1**) is kinetically facile at room temperature.[3] In this paper we present synthesis of 1,1'-biisoquinoline derivatives (**2**), which bear substituents at 8 and 8' positions, with the intention of studying whether steric interaction between such groups and two nitrogen atoms is responsible for the resistance to rotation about the C_1 - $C_{1'}$ bond.



a, PPA,120 °C, 15 h b, SeO_2, dioxane, reflux, 6 h / Ag_2O, NaOH, 60 °C c, $SOCl_2$, 60 °C, 3 h
d, *p*-Xylene, $AlCl_3$, room temperature, 18 h e, $NH_2CH_2CH(OMe)_2$, *p*-TsOH, CF_3CO_2H, H_2SO_4 etc.

In order to develop a method which is applicable to the synthesis of various types of 1,1'-biisoquinolines, our initial effort was directed toward the preparation of the two isoquinoline nuclei severally. The imine (**3**) prepared from *o*-methylacetophenone and aminoacetaldehyde dimethyl acetal in boiling toluene reacted with PPA to yield the first isoquinoline nucleus (**4**) in 43% overall yield.[4] This dimethylisoquinoline (**4**) was oxidized with SeO_2[5] and then with Ag_2O in alkaline solution to give acid (**5**). After treatment of **5** with $SOCl_2$, the resultant acid chloride was reacted with *p*-xylene in the presence of $AlCl_3$ affording the ketone (**6**) in 51% overall yield. For the synthesis of the second isoquinoline ring the ketone (**6**) was allowed to react again with aminoacetaldehyde dimethyl acetal under various conditions. But under any conditions examined, the intended imine (**7**) was not obtained because of the decrease in reactivity of carbonyl group. We then investigated an alternative route for the synthesis of 1,1'-biisoquinoline by using the Tiecco's Ni(0)-

mediated coupling[6] of 1-haloisoquinolines. After the reaction of *o*-tolualdehyde (**8a**) with aminoacetaldehyde dimethyl acetal, the resultant imine (**9a**) was converted to 8-methylisoquinoline (**10a**) in 68 % overall yield by the application of Hendrickson's procedure,[7] *i.e.*, reaction with ethyl chloroformate followed by trimethylphosphite, and finally with titanium tetrachloride in boiling methylene chloride for 36 h. Oxidation of nitrogen of **10a** was carried out by a usual method using hydrogen peroxide in acetic acid (67 %).



a, $(MeO)_2CHCH_2NH_2$, benzene, reflux, 24 h b, 1) $ClCO_2Et$, -10 °C, THF 2) $P(OMe)_3$ 3) $TiCl_4$, CH_2Cl_2, reflux, 36 h c, H_2O_2, AcOH, 60 °C, 20 hd, 1) Ac_2O 2) NaOH e, $POCl_3$, reflux, 3 h f, $NiCl_2$, PPh_3, Zn, 50 °C, 5 h

Conversion to isoquinolone (**12a**) was carried out by the reaction of **11a** with acetic anhydride and then with NaOH[8] in 56% yield. Treatment of **12a** with phosphoryl oxychloride afforded **13a** in 74% yield. Methoxy derivative (**13b**)[9] was also prepared in the same way from anisaldehyde (**8b**). Homocoupling of 1-chloroisoquinoline (**13**) using the nickel(0) complex generated *in situ* by reduction of $NiCl_2$ with Zn gave the aimed 8,8'-disubstituted 1,1'-biisoquinoline (**2**) in moderate yield. The enantiomers of **2a** were actually separated by hplc on a chiral column [Ceramospher Chiral RU-1 (Shiseido)] at room temperature using methanol as eluent.[10] The isomer that eluted first from the RU-1 shows a specific rotation of -69.2 °. Thus, it is revealed that steric hindrance of the methyl groups in 8, 8'-positions of 1,1'-biisoquinoline having no substituents in the 2, 2'-positions, is responsible, in fact, for the atropisomerism.[11] Experimental estimation of the barriers to rotation about C1-C1' bond of 8,8'-disubstituted 1,1'-biisoquinolines (**2**) is now underway in our laboratories.

EXPERIMENTAL

General. Melting points were determined by using a Yazawa Micro Meltingpoint By-1 and uncorrected. Nmr, ms, and ir spectra were obtained on a JEOL EX-400, a JEOL JMS-DX300, and a JASCO A102, respectively. Optical rotations were measured with a JASCO DIP-140 digital polarimeter. Hplc analyses were carried out on a JASCO HPLC system equipped with a 880-PU pump with a JASCO 870-UV and/or JASCO 830-RI detector using a Shiseido Ceramospher Chiral RU-1 column.

2, 5-Dimethylphenyl 8-methylisoquinol-1-yl ketone (6). A mixture of **5** (2.18 g, 11 mmol) and $SOCl_2$ (15 ml, 21 mmol) was stirred for 3 h at 60 °C and evaporated *in vacuo* to give 2.45 g (98%) of the corresponding acid chloride. A solution of the acid chloride and $AlCl_3$ (4.0 g, 0.03 mmol) in *p*-xylene (50 ml) was stirred for 18 h at room temperature and filtered. The filtrate was acidified by an addition of 10% HCl and washed with Et_2O. The aqueous layer was basified by adding 30% NaOH and extracted with $CHCl_3$. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated to dryness. Column chromatography (SiO_2, 10% EtOAc-hexane) and recrystallization from MeOH afforded **6** (1.72 g, 52%) as colorless prisms, mp 177.4-178.2 °C. Ir (Nujol) 1660 cm^{-1}; ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 2.21 (s, 3 H), 2.53 (s, 3 H), 2.66 (s, 3 H), 7.25 (s, 3 H), 7.45 (dd, 1 H, J = 1.0, 7.3 Hz), 7.64 (dd, 1 H, J = 7.3, 7.8 Hz), 7.76 (d, 1 H, J = 5.9 Hz), 7.79 (dd, 1 H, J = 1.0, 7.8 Hz), 8.51 (d, 1 H, J = 5.9 Hz); ms (EI) *m/z* 275 (M^+). Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.69; H, 6.38; N, 5.12.

8-Methylisoquinoline (10a). A solution of *o*-tolualdehyde (10.22 g, 85 mmol) and aminoacetaldehyde dimethyl acetal (8.75 g, 85 mmol) in dry benzene (50 ml) was refluxed overnight; during this period water was removed by using a Dean-Stark trap. After removal of the solvent, the resultant viscous oil was dissolved in dry THF. To the solution was added ethyl chloroformate (8.7 ml, 85 mmol) at -10 °C with vigorous stirring. After stirring for 5 min, 12 ml (100 mmol) of $P(OMe)_3$ was added at room temperature. The mixture was allowed to stir for 15 h at room temperature and then concentrated under reduced pressure. In order to remove trace amount of $P(OMe)_3$, evaporation with toluene was repeated twice. The resulting oil was dissolved in dry CH_2Cl_2, and 6 equimolar amount (56 ml, 0.51 mol) of $TiCl_4$ was added. The mixture was heated under reflux for 36 h. The reaction mixture was neutralized by adding 10 % aqueous NaOH, whereupon TiO_2 precipitated as a white solid. The mixture was filtered, and the filtrate was extracted with 3 M HCl. After washing with CH_2Cl_2, the aqueous layer was basified strongly with 10% aqueous NaOH and

extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated *in vacuo* to afford 8.2 g (68%) of an yellow oil. Ir (neat) 1570, 1580, 1615 cm^{-1}; ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 2.78 (s, 3 H), 7.38 (dd, 1 H, J = 1.0, 6.8 Hz), 7.56 (dd, 1 H, J = 6.8, 7.8 Hz), 7.63 (d, 1 H, J = 5.4 Hz), 7.66 (dd, 1 H, J = 1.0, 7.8 Hz), 8.55 (d, 1 H, J = 5.4 Hz), 9.45 (s, 1 H); ms (EI) *m/z* 143 (M^+, 100), 115 (46). Anal. Calcd for $C_{10}H_9N$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.94; H, 6.48; N, 9.65.

8-Methylisoquinoline *N*-oxide (11a). A mixture of **10a** (332 mg, 2.3 mmol) and 30% H_2O_2 (0.3 ml, 3.0 mmol) in AcOH (10 ml) was stirred for 3 h at 60-70 °C. After an additional 30% H_2O_2 (0.3 ml, 0.3 mmol) was added, stirring was continued for 9 h. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2, and washed with saturated aqueous $NaHCO_3$. After the aqueous layer was reextracted with CH_2Cl_2, the organic layers were combined and dried over Na_2SO_4. Removal of the solvent gave crude **11a**, which was subjected to column chromatography on SiO_2 with hexane/EtOAc/MeOH (6:3:1) as an eluent. Recrystallization from MeOH afforded 246 mg (67%) of colorless needles, mp 136.5-138.5 °C. Ir (Nujol) 1620, 1590, 1560, 1250 cm^{-1}; ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 1.86 (s, 3 H), 7.43 (dd, 1 H, J = 1.0, 7.3 Hz), 7.49 (dd, 1 H, J = 7.3, 8.3 Hz), 7.63 (dd, 1 H, J = 1.0, 8.3 Hz), 7.66 (d, 1 H, J = 7.1 Hz), 7.43 (dd, 1 H, J = 1.5, 7.1 Hz), 8.94 (d, 1 H, J = 1.5 Hz); ms (EI) *m/z* : 159 (M^+, 30), 143 (100), 115 (42). Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 74.72; H, 5.78; N, 8.69.

8-Methyl-1-isoquinolone (12a). A mixture of **11a** (246 mg, 1.5 mmol) and Ac_2O (5 ml) was refluxed for 5 h. After removal of Ac_2O i*n vacuo*, the resulting residue was heated with 1 M NaOH (4.1 ml) for about 40 min and allowed to stand at room temperature overnight. The mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by chromatography on SiO_2 with hexane/EtOAc/MeOH (6:3:1). Recrystallization from MeOH gave 137 mg (56%) of colorless plates, mp 138.6-140.7 °C. Ir (Nujol) 3130, 1660, 1640, 1590 cm^{-1}; ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 2.93 (s, 3 H), 6.44 (d, 1 H, J = 6.8 Hz), 7.01 (d, 1 H, J = 6.8 Hz), 7.22 (dd, 1 H, J = 1.0, 7.3 Hz), 7.35 (dd, 1 H, J = 1.0, 7.8 Hz), 7.48 (dd, 1 H, J = 7.3, 7.8 Hz), 9.54 (s, 1 H, exchange with D_2O); ms (EI) *m/z* 159 (M^+, 100), 141 (28), 130 (24), 114 (25). Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.76; H, 5.83; N, 8.56.

8-Methoxy-1-isoquinolone (12b). This compound was prepared in 70% yield starting from **11b**[9] by a similar procedure as that described for **12a**. **12b**: colorless prisms from MeOH, mp 138.0-139.2 °C. Ir

(Nujol) 3200, 1660, 1620, 1460 cm^{-1}; ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 4.03 (s, 3 H), 6.46 (d, 1 H, J = 6.8 Hz), 6.91 (dd, 1 H, J = 1.0, 8.3 Hz), 7.10 (dd, 1 H, J = 1.0, 7.8 Hz), 7.18 (d, 1 H, J = 6.8 Hz), 7.56 (dd, 1 H, J = 7.8, 8.3 Hz), 11.42 (s, 1 H, exchange with D_2O); ms (EI) *m/z* 175 (M^+, 63), 158 (13), 146 (100), 128 (43), 118 (55). Anal. Calcd for $C_{10}H_9NO$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.03; H, 5.21; N, 7.92.

1-Chloro-8-methylisoquinoline (13a). A mixture of **12a** (6.58 g, 43 mmol) and $POCl_3$ (100 ml, 1.07 mol) was refluxed for 3 h. After excess amount of $POCl_3$ was evaporated *in vacuo*, saturated aqueous $NaHCO_3$ and CH_2Cl_2 were added. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Column chromatography (SiO_2, CH_2Cl_2) and recrystallization from MeOH gave 5.68g (74%) of brown prisms, mp 144.2-145.6 °C. Ir (Nujol) 1605, 1580, 1550 cm^{-1}; ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 3.08 (s, 3 H), 7.46 (dd, 1 H, J = 1.0, 6.8 Hz), 7.55 (d, 1 H, J = 5.4 Hz), 7.56 (dd, 1 H, J = 6.8, 8.3 Hz), 7.68 (dd, 1 H, J = 1.0, 8.3 Hz), 8.20 (d, 1 H, J = 5.4 Hz); ms(EI) *m/z* 179 (M^+, ^{37}Cl, 36), 177 (M^+, ^{35}Cl, 100), 142 (54), 114 (40). Anal. Calcd for $C_{10}H_8NCl$: C, 67.62; H, 4.54; N, 7.89. Found: C, 67.72; H, 4.61; N, 8.00.

1-Chloro-8-methoxyisoquinoline (13b). This compound was synthesized from **12b** in the same manner as **13a**. The yield was 69%. **13b**: brown prisms, whose spectral data were virtually identical to those reported.[9]

8,8'-Dimethyl-1,1'-biisoquinoline (2a). Zinc powder (25 mg, 0.37 mmol) was added to a stirred solution of $NiCl_2$•$6H_2O$ (90 mg, 0.37 mmol) and PPh_3 (390 mg, 1.5 mmol) in DMF (6 ml) under argon at 50 °C. After stirring for 1 h, **13a** (66 mg, 0.37 mmol) was added. After 5 h, the mixture was poured into dilute 28% aqueous NH_3 and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated. Column chromatography on SiO_2 with hexane/EtOAc/MeOH (5:4:1) as an eluent gave crude **2a**, which was recrystallized from MeOH to yield 32 mg (61%) of colorless prisms, mp 175.8-177.0 °C. Ir (Nujol) 1600, 1580, 1550 cm^{-1}; ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 1.86 (s, 6 H), 7.34 (dd, 2 H, J = 6.8, 1.0 Hz), 7.58 (dd, 2 H, J = 6.8, 7.8 Hz), 7.75 (d, 2 H, J = 4.9 Hz), 7.79 (dd, 2 H, J = 1.0, 7.8 Hz), 8.55 (d, 2 H, J = 4.9 Hz); ms (EI) *m/z* 284 (M^+, 5), 269 (100), 83 (44). Anal. Calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.65; H, 5.67; N, 9.76.

Resolution of (±)-2a. Racemic 8, 8' -dimethyl - 1, 1' -biisoquinoline (**2a**, 94.2 mg) was resolved to its enantiomers by hplc on Ceramospher Chiral RU-1 (Shiseido) at room temperature using MeOH as eluent (flow rate 1.0 ml/min). The first eluted enantiomer (19.2 mg: retention time, ~11 min) and the second eluted

one (13.3 mg: retention time, 47 min) show $[\alpha]_D$ of - 69.2 °(c = 0.8, MeOH) and + 61.7 ° (c = 1.6, MeOH) at 20 °C, respectively.

8,8'-Dimethoxy-1,1'-biisoquinoline (2b). Compound (**2b**) was prepared in 70% yield from **13b** *via* the same method as that already mentioned for **2a**. **2b**: colorless prisms from MeOH, mp 177.4-178.2 °C. Ir (Nujol) 1610, 1550, 1450 cm^{-1}; ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 3.20 (s, 6 H), 6.74 (dd, 2 H, J = 1.0, 7.8 Hz), 7.46 (dd, 2 H, J = 1.0, 7.8 Hz), 7.56 (dd, 2 H, J = 7.8, 7.8 Hz), 7.63 (d, 2 H, J = 5.9 Hz), 8.53 (d, 2 H, J = 5.9 Hz); ms (EI) *m/z* 316 (M^+, 0.2), 285 (100), 270 (7), 256 (8), 242 (18). Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.85. Found: C, 75.77; H, 5.17; N, 8.74.

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10. All attempts to resolve dimethoxy-biisoquinoline (**2b**) were unsuccessful, whereas resolution of *N, N'*-dioxide of **2b** was achieved by hplc on the RU-1 column. Studies on reduction of *N*-oxide groups to

aromatic amines without racemization are now in progress.

11. This is the first example of the resolution of chiral 1,1'-biisoquinoline nucleus. Recently, optical resolution of 1,1'-biisoquinoline-*N,N'*-dioxide was reported (M. Fujii and A. Honda, *J. Heterocycl. Chem.*, 1992, **29**, 931), and optically active 7,7' - dimethoxy - 8,8' - biisoquinoline was also prepared (K. Yamamoto, K. Watanabe, H. Chikamatsu, Y. Okamoto, and T. Yoshida, *J. Chem. Soc., Chem. Commun.*, 1987, 807). However, these examples are equivalent to 1,1' - binaphthalene from the standpoint of stereochemistry.

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