# Synthesis of 3,3′-(4*H*,4′*H*)-spirobi(2*H*-naphtho[1,2-*b*]pyran)-6,6′-dicarboxylic Acid and Its Optical Resolution

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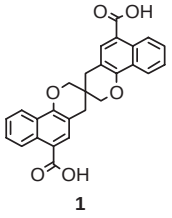
The synthesis and optical resolution of 3,3′-(4*H*,4′*H*)-spirobi(2*H*-naphtho[1,2-*b*]pyran)-6,6′-dicarboxylic acid were successfully accomplished. The formation of the spiro skeleton and the bromination of the aromatic ring were easily achieved in the presence of bromine. Optical resolution was achieved by amidation with L-valinol (2-amino-3-methyl-1-butanol).

Optically active compounds are used industrially as pharmaceutical products, perfume ingredients, and liquid crystalline materials. The majority of these chiral compounds contain asymmetric carbons, however, some axial asymmetric chiral compounds have been reported to be effective chiral ligands for asymmetric synthesis[1] and as chiral dopants with large helical twisting power for nematic liquid crystals.[2,3] Many axial asymmetric chiral compounds have a biaryl structure. Optically active spiro compounds having a rigid asymmetric structure can potentially be used as new chiral materials, but few have been reported.[4–7] For example, spiro phosphoramide ligands derived from optically active 1,1′-spirobiindane-7,7′-diol performed as chiral ligands in the asymmetric rhodium-catalyzed hydrogenation of functionalized olefins[4a] and the rhodium-catalyzed asymmetric addition of arylboronic acids to aldehydes or α-ketoesters.[4b,4c] Also, 2,2′-spirobiindane-5,5′-diheptyloxy-1,1′-dione was reported as a chiral dopant for smectic liquid crystalline mixtures.[7]

Here, we report the synthesis and optical resolution of the novel spiro compound, 3,3′-(4*H*,4′*H*)-spirobi(2*H*-naphtho[1,2-*b*]pyran)-6,6′-dicarboxylic acid (**1**, Figure 1). The two naphthalene rings of **1** are fixed by the spiro structure. In order to facilitate the optical resolution and synthesis of **1** derivatives, two carboxyl groups are introduced. The new optically active carboxylic acid **1** and its derivatives may have the ability to resolve racemic amines, chiral ligands for asymmetric synthesis, and chiral liquid crystalline materials.

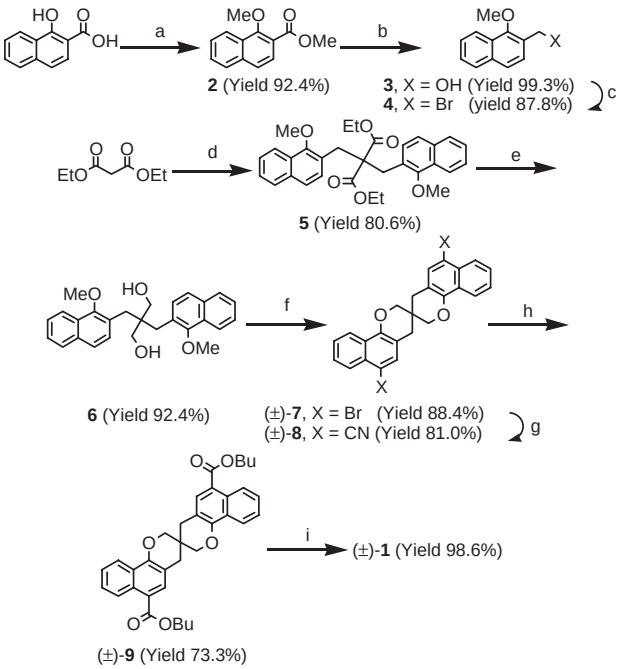
The synthetic route for (±)-**1** is shown in Scheme 1.[8] The starting material, 1-hydroxy-2-naphthoic acid was methylated using iodomethane and sodium hydride. After the methylation, **2** was reduced with lithium aluminum hydride (LAH) to give **3**, which was then successfully brominated using phosphorus tribromide to give **4**. Diethyl malonate was alkylated by using **4** and potassium *t*-butoxide to afford **5**, which was reduced with LAH to give **6**. The diol **6** was treated with bromine to facilitate intramolecular cyclization and concurrent bromination of the aromatic ring, giving **7**. This reaction proceeded under mild conditions, and was quickly completed after addition of the bromine solution. The mechanism of this reaction probably proceeded as follows (Figure 2). First, a bromination of the naphthalene ring occurred, and hydrogen bromide was generated. Second, the oxygen atom of the hydroxy group was protonated by the hydrogen bromide. Third, intramolecular cyclization occurred with elimination of water. Fourth, the bromide ion attacked the methyl carbon. As a result, (±)-**7** and bromomethane were generated. This reaction is useful for obtaining 6-bromo-2*H*-benzo[1,2-*b*]pyran derivatives from 3-(2-methoxy-1-phenyl)propan-1-ol derivatives. The bromide (±)-**7** was converted into the cyanide (±)-**8** using copper cyanide. Owing to the difficulty of hydrolyzing (±)-**8** with sodium hydroxide, (±)-**8** was converted into (±)-**9** using *n*-butanol and *p*-toluenesulphonic acid. Finally, (±)-**9** was easily hydrolyzed to (±)-**1** using sodium hydroxide.

Next, we attempted the optical resolution of (±)-**1** via its diastereomeric salts and diastereomeric esters. The solubility of the diastereomeric salts prepared from (±)-**1** and (*S*)-(−)-1-



**1**

**Figure 1.** Structure of **1**.




**Scheme 1.** Synthetic route of (±)-**1**: (a) $CH_3I$, NaH, dry DMF. (b) $LiAlH_4$, dry THF, 50 °C. (c) $PBr_3$, dry toluene. (d) 1: *t*-BuOK, THF, 2: **4**. (e) $LiAlH_4$, dry THF. (f) $Br_2$, $CH_2Cl_2$. (g) CuCN, *N*-methylpyrroridone, 200 °C. (h) *n*-BuOH, PTSA. $H_2O$, reflux. (i) NaOHaq., EtOH, THF, reflux.

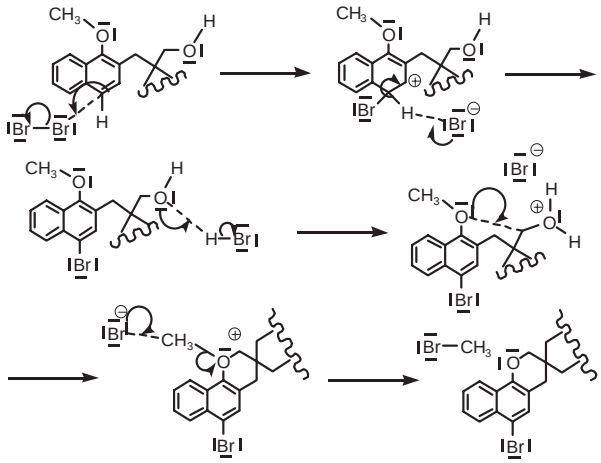
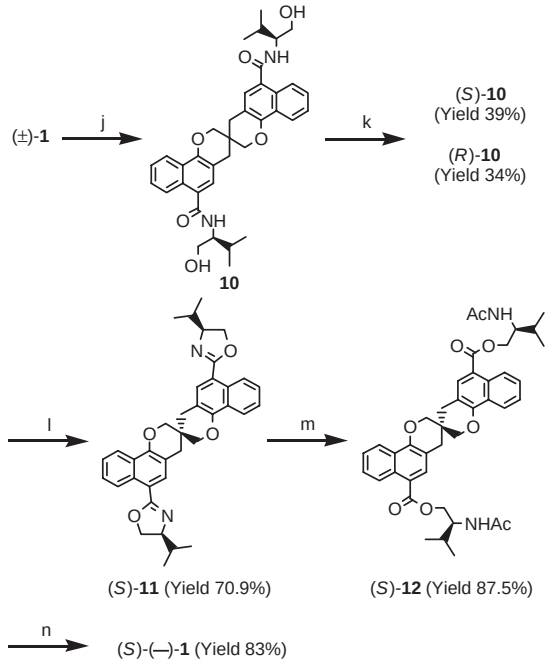


**Figure 2.** A plausible mechanism of the spiro structure formation.




**Scheme 2.** Synthetic route of (*S*)-(−)-**1**: (j): 1) $SOCl_2$, dry toluene, reflux, 2) L-valinol, $Et_3N$, dry $CH_2Cl_2$. (k) Column chromatography (Silicagel 60 N, spherical neutral; eluent: 2-propanol:$CH_2Cl_2$ = 1:9), (l) $SOCl_2$, dry $CH_2Cl_2$. (m): 1) TFA, THF, $H_2O$, 2) AcCl, pyridine, dry $CH_2Cl_2$. (n) *t*-BuOK, $H_2O$, THF.

phenylethylamine or (1*S*,2*R*)-(−)-2-(benzylaminocyclohexyl)-methanol were very low in most solvents, causing separation of the salts to fail. The diastereomeric esters derived from (±)-**1** and (*R*)-(−)-2-butanol, (−)-borneol, or L-menthol could not be separated by silica gel chromatography. Finally, it was found that the optical resolution of (±)-**1** was successfully achieved via the diastereomeric amide **10** derived from (±)-**1** and L-valinol (2-amino-3-methyl-1-butanol) (Scheme 2). The diastereomeric amide was separated by silica gel chromatography (Silica gel 60 N, Spherical, neutral, Kanto, $R_f = 0.6$ and 0.7) using 2-propanol and dichloromethane (1:9) as the eluent. Here, the diastereomeric amide of $R_f = 0.6$ is (*S*)-**10**, and the diastereomeric amide of $R_f = 0.7$ is (*R*)-**10**.

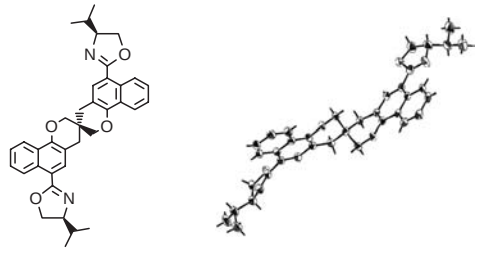


**Figure 3.** X-ray analysis of (*S*)-**11** derived from **10** having higher $R_f$.

Because of the steric hindrance between the carbonyl group and the isopropyl group, it was difficult to hydrolyze (*S*)-**10** using sodium hydroxide. Therefore, (*S*)-**10** was converted into the oxazoline ((*S*)-**11**) using thionyl chloride (Scheme 2).[9,10] The oxazoline ring was opened with trifluoroacetic acid and water, and the liberated amino group was acetylated.[9,10] Finally, the ester (*S*)-**12** was hydrolyzed into (*S*)-(−)-**1** using potassium *t*-butoxide and water.[9,10] The optically active (*S*)-(−)-**1** was converted into (*S*)-**9** using *n*-butanol and phosphoryl chloride for determination of enantiomeric excess (ee). The ee of (*S*)-**9** was determined by chiral HPLC analysis [Daicel Chiralpak AD-H column, *n*-hexane/2-propanol = 9:1 as eluent, flow rate = 0.50 mL/min, $t_R = 25.6$ min for (*S*)-**9** and 31.1 min for (*R*)-**9**]. The absolute configuration of (−)-**1** was determined to be the S configuration by single crystal X-ray diffraction of **11** derived from **10** having higher $R_f$ (Figure 3).[11]

In conclusion, the synthesis and the optical resolution of the new spiro compound **1** were achieved. The absolute configuration of (−)-**1** was determined by single crystal X-ray diffraction of the diastereomeric oxazoline **11**. The applications of **1** and the synthesis of its derivatives as novel chiral materials are in progress.

## References and Notes


1 R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**.
2 R. Holzwarth, R. Bartsch, Z. Cherkaoui, G. Solladié, *Chem.—Eur. J.* **2004**, *10*, 3931.
3 H.-J. Deußen, P. V. Shibaev, R. Vinokur, T. Bjørnholm, K. Schaumburg, K. Bechgaard, V. P. Shibaev, *Liq. Cryst.* **1996**, *21*, 327.
4 a) Y. Fu, J.-H. Xie, A.-G. Hu, H. Zhou, L.-X. Wang, Q.-L. Zhou, *Chem. Commun.* **2002**, 480. b) H.-F. Duan, J.-H. Xie, W.-J. Shi, Q. Zhang, Q.-L. Zhou, *Org. Lett.* **2006**, *8*, 1479. c) H.-F. Duan, J.-H. Xie, X.-C. Qiao, L.-X. Wang, Q.-L. Zhou, *Angew. Chem., Int. Ed.* **2008**, *47*, 4351.
5 H. Zhou, W.-H. Wang, Y. Fu, J.-H. Xie, W.-J. Shi, L.-X. Wang, Q.-L. Zhou, *J. Org. Chem.* **2003**, *68*, 1582.
6 T. Takahashi, H. Tsutsui, M. Tamura, S. Kitagaki, M. Nakajima, S. Hashimoto, *Chem. Commun.* **2001**, 1604; M. A. Arai, M. Kurihashi, T. Arai, H. Sasai, *J. Am. Chem. Soc.* **2001**, *123*, 2907; M. L. Patil, C. V. L. Rao, K. Yonezawa, S. Takizawa, K. Onitsuka, H. Sasai, *Org. Lett.* **2006**, *8*, 227; M. L. Patil, H. Sasai, *Chem. Rec.* **2008**, *8*, 98.
7 C. J. Boulton, J. Sutherland, R. P. Lemieux, *J. Mater. Chem.* **2003**, *13*, 644.
8 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.
9 G. Solladié, P. Hugelé, R. Bartsch, A. Skouious, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1533.
10 G. Solladié, P. Hugelé, R. Bartsch, *J. Org. Chem.* **1998**, *63*, 3895.
11 CCDC 685376 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).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