A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

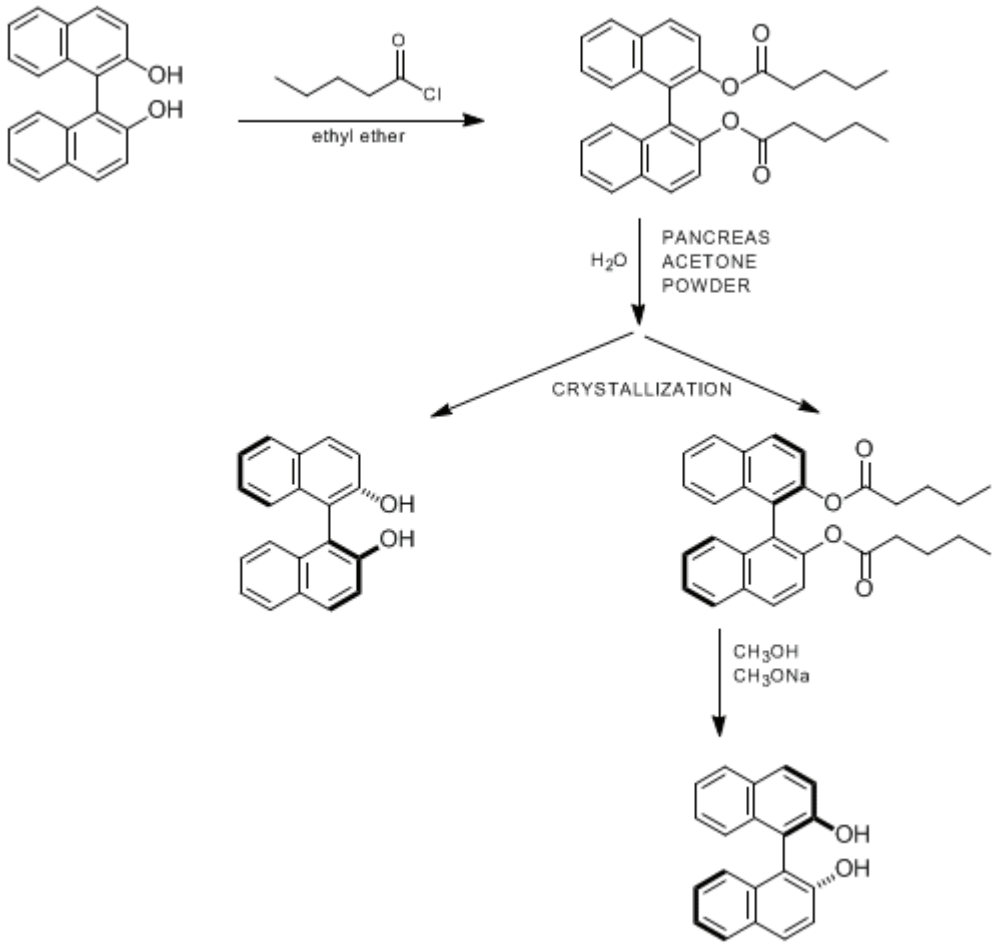
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.070.0060

Organic Syntheses, Coll. Vol. 9, p.77 (1998); Vol. 70, p.60 (1992).

(S)-(−)- AND (R)-(+)-1,1'-BI-2-NAPHTHOL

[[1,1'-Binaphthalene]-2,2'-diol, (S)- and [1,1'-Binaphthalene]-2,2'-diol, (R)-]



Submitted by Romas J. Kazlauskas[1]
Checked by Mark R. Sivik and Leo A. Paquette.

1. Procedure

A. *Racemic 1,1'-bi-2-naphthyl pentanoate*. A suspension of 203 g (0.71 mol) of racemic 1,1'-bi-2-naphthol (Note 1) and 215 mL (1.54 mol) of triethylamine in 2 L of ethyl ether is stirred magnetically in a 4-L Erlenmeyer flask. Over a period of 20 min 185 mL (1.56 mol) of pentanoyl chloride is added (Note 2) and the suspension is stirred for an additional hour to ensure complete reaction (Note 3). The mixture is poured into a 6-L separatory funnel and washed twice with 2-L portions of aqueous 1 M sodium bicarbonate and once with a 2-L portion of water resulting in a clear yellow-orange ether solution.

B. *(S)-(−)-1,1'-Bi-2-naphthol*. In a 12-L, round-bottomed flask the above ether solution is diluted to 4 L with additional ethyl ether. A 5.0-mL aliquot of this solution is used to assay the enzyme (Note 4). The remaining ether solution is stirred using an overhead stirrer with 4 L of aqueous 0.1 M phosphate buffer (pH 7.5) containing 60 g of crude sodium taurocholate (Note 5). An opaque emulsion forms. The reaction is started by adding 2000 units of cholesterol esterase activity (100–150 g of bovine pancreas acetone powder, (Note 4)). Stirring is continued at ~25°C and the flask is stoppered to minimize evaporation of ether. The pH of the emulsion is measured occasionally and readjusted to 7.2 ± 0.3 by

adding aqueous 1 M sodium hydroxide. Approximately 250 mL of base is consumed during the first 3 hr; an additional 400 mL is consumed over the next 20 hr. Although the consumption of base virtually ceases after 24 hr, stirring is continued for a total of 3 days (Note 6).

To break the emulsion 400 mL of ethanol is added and the mixture is transferred to separatory funnels and allowed to settle for 4 hr. Three layers form: at the top—a clear yellow ether phase, at the bottom—a brown aqueous phase and in between—an opaque emulsion layer. The brown aqueous layer is discarded. The emulsion layer (~1 L) is transferred to a flask and broken up by addition of 200 g of magnesium sulfate in portions. Heat is evolved, the ether boils and two layers form. This ether layer is combined with the first ether layer, dried over ~50 g of magnesium sulfate, filtered and concentrated by rotary evaporation to ~300 mL of an orange oil. Toluene (500 mL) is added and the solution cooled to 4°C overnight. Fine white crystals (70–71 g) are collected by filtration and washed twice with 20-mL portions of cold toluene (Note 7). The filtrate is concentrated to ~600 mL by rotary evaporation and cooled once again to 4°C. The additional 10 g of crystals which form are collected by filtration and washed twice with 20-mL portions of toluene. Recrystallization of the combined crystals from 375–400 mL of toluene yields 65–68 g (64–67%) of white crystals, mp 211–213.5°C; $[\alpha]_D^{19}$ −33.2 ± 0.8° (THF, *c* 0.2); >99% diol (see (Note 3)), >99.9% enantiomeric purity (Note 8).

C. *(R)-(+)-1,1'-Bi-2-naphthol*. Toluene in the above filtrate is removed by rotary evaporation, and the residue is recrystallized from methanol (500 mL) overnight at 4°C. Yellow crystals (125–141 g) form and are collected by filtration and washed twice with 20 mL of hexane. Recrystallization from 500 mL of methanol yields pure (R)-binaphthol dipentanoate [mp 63–65°C, 89–102 g, >99% ee (R), $[\alpha]_D^{19}$ +15.0 ± 0.3° ($CHCl_3$, *c* 0.4), (Note 9)]. If desired, an additional 25 g of dipentanoate can be isolated from the filtrate by column chromatography on 1 kg of silica gel eluted with methylene chloride followed by crystallization (Note 9).

The crystalline dipentanoate (89–102 g, 0.20 mol) is dissolved in 1 L of methanol containing 6.6 g (0.12 mol) of sodium methoxide. After 4 hr at room temperature, analysis of the solution by thin layer chromatography (Note 3) shows only traces of the mono- and diester. The solution is neutralized to pH <7 (test paper) with ~10 mL of concd hydrochloric acid. The solution is diluted with 1 L of 0.1 M phosphate buffer (pH 7), transferred to a 4-L separatory funnel and extracted with a mixture of 1 L of ethyl ether and 500 mL of toluene. The organic layer is washed with a 1-L portion of water, dried over magnesium sulfate, concentrated to 300 mL and cooled to 4°C. White crystals (48–64 g) separate and are collected by filtration and washed twice with 20-mL portions of cold toluene, mp 211–213.5°C; $[\alpha]_D^{19}$ +33.9 ± 0.2° (THF, *c* 0.2); 99% chemical purity (Note 3), >99% enantiomeric purity (Note 8).

2. Notes

1. (±)-1,1'-Bi-2-naphthol was purchased from Aldrich Chemical Company, Inc. or prepared by oxidative coupling of 2-naphthol.[2]

2. The initial suspension is thick and can sometimes be difficult to stir magnetically. In this case, occasional swirling by hand is sufficient. The mixture thins as the reaction proceeds. *Caution: This exothermic reaction causes the ether to boil; pentanoyl chloride should be added slowly, allowing the heat of reaction to dissipate.* The checkers cooled the reaction mixture in an ice bath during addition of the acid chloride. Pentanoyl chloride was obtained from Aldrich Chemical Company, Inc.

3. To ensure high enantiomeric purity of the product there should be <0.5% 1,1'-bi-2-naphthol or its monoester in this solution. The relative amounts of binaphthol species can be accurately determined by HPLC on a reverse-phase column eluted with a water-acetonitrile gradient (50–100% over 10 min). Both 1,1'-bi-2-naphthol and its dipentanoate have equal (within 2%) extinction coefficients at 254 nm. The monopentanoate absorbs more strongly: the relative extinction coefficient at 254 nm is 1.13. Alternatively, the solution composition can be estimated using thin layer chromatography: silica gel eluted with 1:4 ethyl acetate/cyclohexane: 1,1'-bi-2-naphthol, R_f 0.39; monopentanoate, R_f 0.56; dipentanoate, R_f 0.71.

4. The catalyst for this reaction is the enzyme cholesterol esterase (EC 3.1.1.13). Bovine pancreas acetone powder (Sigma Chemical Company), a crude extract from pancreas, is an inexpensive source of cholesterol esterase activity. This extract contains ~15 units of cholesterol esterase activity/gram; unit = µmol of ester hydrolyzed/min. To measure the activity, the ethereal aliquot of binaphthol dipentanoate is

stirred rapidly using a magnetic stirrer with 5.0 mL of 10 mM phosphate buffer (pH 7.0) containing 75 mg of crude sodium taurocholate (Sigma Chemical Company). Approximately 200 mg of acetone powder is added and the pH of the emulsion is monitored with a pH meter and maintained at 7.0 by addition of aqueous 0.1 M sodium hydroxide in portions of 50 µL until ~200 µL has been added, ~70 min. The slope of a plot of µmoles of base consumed vs. time gives the activity of the acetone powder. (The amount of base needed to readjust the pH to 7.0 after the addition of the slightly acidic acetone powder is ignored in the activity calculation.)
5. Directions for the preparation of this buffer solution are given in reference [3].
6. After 24 hr, analysis by HPLC shows 37% binaphthol, 10% monopentanoate and 53% dipentanoate, after an additional 2 days of stirring, analysis shows 45%, 3%, and 52%. Isolation of binaphthol and diester by crystallization is substantially more difficult and less efficient from reaction mixtures containing <40 mol % binaphthol.
7. Binaphthol may not crystallize if the solution is wet. If no crystals form, water can be removed by rotary evaporation of the water-toluene azeotrope.
8. Enantiomeric purity of binaphthol is determined using chiral stationary phase HPLC: Pirkle Type 1-A column (Regis Chemical Company) eluted with 20:1 hexane/2-propanol[4] or poly(triphenylmethyl) methacrylate on silica gel (Chiralpak OT, Daicel Chemical Industries, LTD) eluted with methanol.[5] To determine enantiomeric purities >99% ee an HPLC trace of the unknown is compared to the HPLC trace of unknown containing 0.2% deliberately-added racemic material.
9. Crystallization of (R)-binaphthyl dipentanoate increases its enantiomeric purity from ~92% ee in the reaction mixture to >99% ee. The enantiomeric purity of the final product, binaphthol, is not increased by crystallization. The recrystallization step for the dipentanoate ensures high enantiomeric purity. Usually crystallization from methanol must be induced by scratching the side of the flask with a glass rod. The enantiomeric purity of the dipentanoate is determined after cleavage to binaphthol. A sample of dipentanoate is treated with an equivalent of sodium methoxide in methanol. After 30 min the solution is neutralized with excess acetic acid and analyzed by HPLC as in (Note 8).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Enantiomerically pure binaphthol is used as a chiral auxiliary.[6] For example, it has been used to prepare chiral aluminum hydride reducing agents,[7] chiral Lewis acids catalysts,[8] and chiral crown ethers.[9]

The best previous resolution of binaphthol uses fractional crystallization of the diastereomeric cinchonine salts of binaphthol cyclic phosphate ester.[10] The resolution using cholesterol esterase involves fewer manipulations and thus is simpler and faster than the cinchonine method. Fewer manipulations also enable the resolutions using cholesterol esterase to be carried out on a larger scale. The high enantioselectivity of cholesterol esterase assures high ee for the (S)-enantiomer, while crystallization of (R)-binaphthyl dipentanoate assures high enantiomeric purity for the (R)-enantiomer.

Octahydrobinaphthol and several spirobiindanols can also be resolved using this method, but several bromo-substituted binaphthols could not be resolved because their esters were not hydrolyzed.[11]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 10, 93

References and Notes

1. Department of Chemistry, McGill University, 801 Sherbrooke St., W., Montreal, PQ H3A 2K6 Canada. Initial work was done at General Electric Company, Corporate Research and

Development, Schenectady, NY.
2. Pummerer, R.; Prell, E.; Reiche, A. *Ber.* **1926**, *59B*, 2159; note correction in Note 12 of Reiche, A.; Jungholt, K.; Frühwald, E. *Ber.* **1931**, *64B*, 578.
3. Irochijima, S.; Kojima, N. *Agric. Biol. Chem.* **1980**, *46*, 1593.
4. Pirkle, W. H.; Schreiner, J. L. *J. Org. Chem.* **1981**, *46*, 4988.
5. Okamoto, Y.; Honda, S.; Okamoto, I.; Yuki, H. *J. Am. Chem. Soc.* **1981**, *103*, 6971.
6. Review (in Japanese): Miyano, S.; Hashimoto, H. *Yuki Gosei Kagaku Kyokaishi* **1986**, *44*, 713; *Chem. Abstr.* **106**, 137988e.
7. Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709; Noyori, R.; Tomino, I.; Yamada,. M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717.
8. Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1985**, *26*, 5535; Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310.
9. Sogah, G. D. Y.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3035.
10. Jacques, J.; Fouquey, C. *Org. Synth., Coll. Vol. VIII* **1993**, 50; Truesdale, L. K. *Org. Synth., Coll. Vol. VIII* **1993**, 46; Kyba, E. P.; Gokel, G. W.; de Jong, F.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Kaplan, L.; Sogah, G. D. Y.; Cram, D. J. *J. Org. Chem.* **1977**, *42*, 4173.
11. Kazlauskas, R. J. *J. Am. Chem. Soc.* **1989**, *111*, 4953.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

silica gel

(S)-(−)- AND (R)-(+)-1,1'-BI-2-NAPHTHOL

poly(triphenylmethyl)methacrylate

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether,
ethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

2-naphthol (135-19-3)

cyclohexane (110-82-7)

sodium methoxide (124-41-4)

toluene (108-88-3)

2-propanol (67-63-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

triethylamine (121-44-8)

binaphthol

Octahydrobinaphthol

(R)-(+)-1,1'-Bi-2-naphthol,
1,1'-bi-2-naphthol,
(S)-(-)-1,1'-Bi-2-naphthol,
[1,1'-Binaphthalene]-2,2'-diol, (R)-,
(±)-1,1'-bi-2-naphthol,
[1,1'-Binaphthalene]-2,2'-diol, (S)- (18531-99-2)

1,1'-bi-2-naphthyl pentanoate (110902-38-0)

pentanoyl chloride (638-29-9)

sodium taurocholate

binaphthol dipentanoate,
(R)-binaphthol dipentanoate

(R)-binaphthyl dipentanoate