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Selective Preparation of Optically Pure (*R*,*R*)-1,1':5',1"-Ternaphthalene-2,2',6',2"-tetraol: A New Higher Homolog of BINOL

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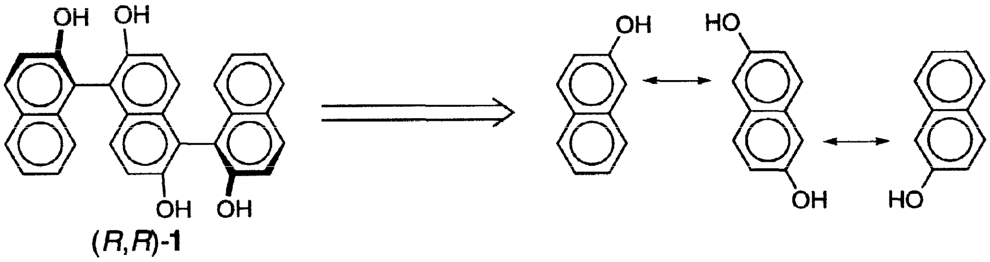
Abstract: As a new chiral auxiliary, the title compound of an enantiomerically pure higher homolog of BINOL was synthesized through stepwise formation of optically pure 2,4-pentanediol tethers connecting three naphthyl groups by Mitsunobu reaction, oxidative intramolecular coupling, and elimination of the tethers. © 1998 Elsevier Science Ltd. All rights reserved.

Optically active 1,1'-bi-2-naphthol (BINOL) has been a key chiral auxiliary in asymmetric reactions.[1] In this communication, we would like to present a new higher homolog of BINOL; optically active 1,1':5',1"-ternaphthalene-2,2',6',2"-tetraol (**1**). The compound **1** has two forms, chiral and *meso*, and the chiral one (TERNOL) has two pairs of bidentate sites on the same side of the central naphthalene ring in a similar chiral environment as that of BINOL. New properties of the metalated TERNOL as a chiral reagent are expected to come from the two-point interaction to a substrate and/or a reagent, which will enhance the effectiveness of BINOL chemistry in asymmetric reactions. Although stereoselective preparation of racemic TERNOL has recently been reported using SNAr reaction of 1,5-dibromo-2,6-naphthodiol and 2-naphthol,[2] optically active TERNOL has not been reported. Formally, the oxidative coupling reaction of two molecules of 2-naphthol and one molecule of 2,6-naphthodiol produced **1**, but practically, strict control of the axial stereochemistry as well as the chemoselectivity is required to get TERNOL of high optical purity in good yield. Our strategy for the synthesis of (*R*,*R*)-**1** was planned through **2** and **3** (Scheme 2). That is, the stepwise preparation of **2** and the intramolecular coupling of **2** to give **3**, of which stereochemical causes have been already established during the synthesis of optically pure BINOL.[3]



Scheme 1.

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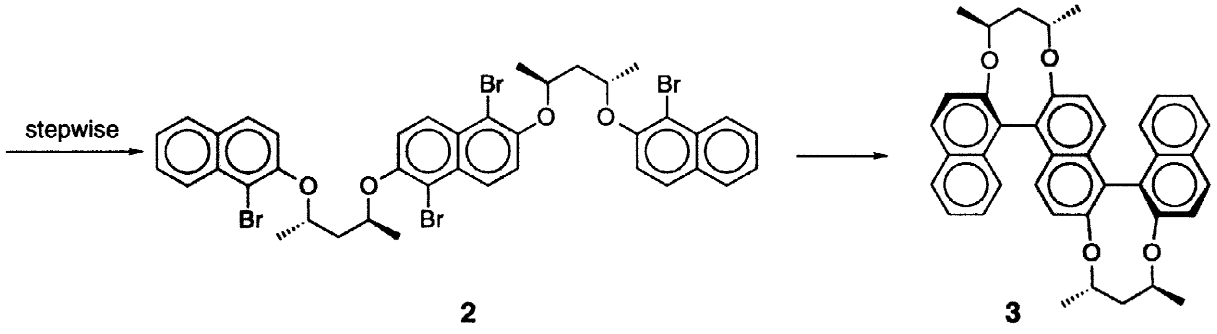
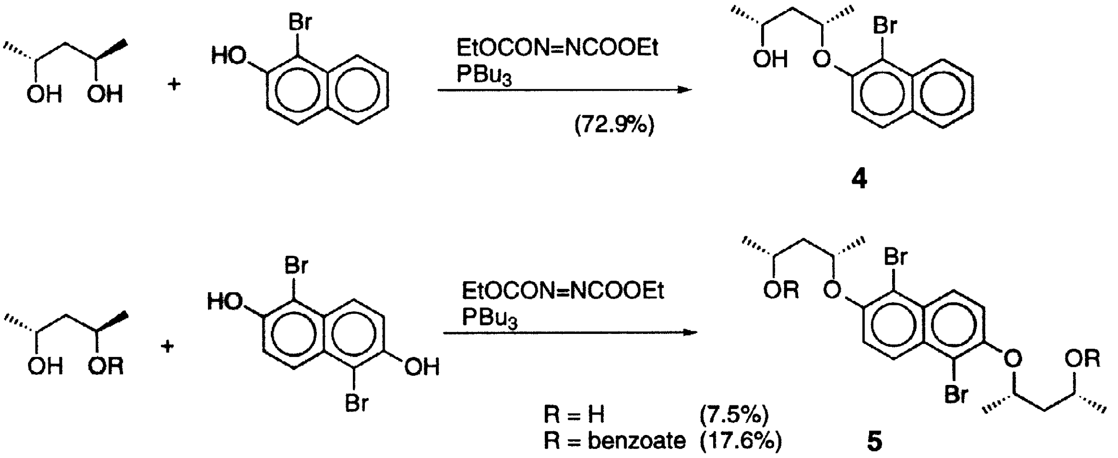


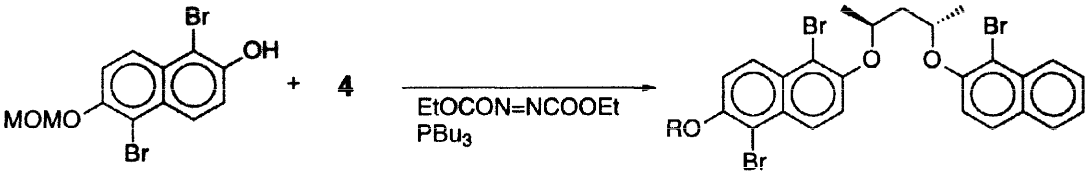
Scheme 2.

The Mitsunobu reaction of (2*R*,4*R*)-2,4-pentanediol (PD, > 99% ee) and 1-bromo-2-naphthol proceeded smoothly with inversion of the chiral center on PD affording diastereomerically pure **4** in 73% yield.[3,4] On the other hand, the introduction of two units of PD to 1,5-dibromo-2,6-naphthodiol under the same reaction conditions resulted in only a 7.5% yield of **5**. By using the mono-benzoate analog of PD, the yield of **5** was improved to 18%, but still not high enough for the synthesis of TERNOL. The construction of the PD bridges to the central naphthyl ring was achieved by the stepwise introduction of the PD units.



Scheme 3.

When a mono-protected central naphthyl unit **6**[5] was reacted with **4** under the same Mitsunobu conditions, the PD tethered product **8** was obtained as the sole product after acid treatment (85% for two steps). The second PD tether was also formed by the reaction of **4** and **8**, which gave **2** in 67% yield.[6] Four chiral centers in **2** were stereochemically pure based on the NMR and HPLC analyses, and should be all (*S*). Here, the substrate for the diastereodifferentiating intramolecular coupling to construct the two axial chiralities was settled upon. Metallo-de-halogenation of **2** for the copper catalyzed oxidation required excess butyllithium, which caused butylation to the naphthalene ring. When *s*-butyllithium was employed instead of butyllithium, the intramolecular coupling of the naphthalene units became a major reaction. A typical experiment was as follows: To a solution of **2** (206 mg) in THF (30 ml), *s*-butyllithium (1.12N in cyclohexane, 1.63 ml) was added dropwise at –78 °C, and after 30 min, a suspension of copper(I) cyanide (168 mg) in THF (15 ml) was added at the same temperature. The mixture was stirred for 30 min and was oxidized by bubbling of dry oxygen for 30 min. After addition of saturate ammonium chloride aqueous solution (5 ml), the product was extracted by ether and purified by MPLC on silica gel (elute 15% ethyl acetate in hexane) to give **3** (63.5 mg, 48% yield).[7] The major by-products of the coupling reaction were the mono- and non-coupled compounds, but no other diastereomers of **3** were detected in the reaction mixture. Ether bond cleavage in **3** to remove the chiral tethers was successful with BBr_3 (in CH_2Cl_2, –78 °C to 0 °C), and the target compound **1** was obtained in 89% after silica gel purification.[8] Based on HPLC analysis[9], the enantio- and diastereomeric purities of **1** proved to be over 99%. Since the circular dichroism spectrum of **1** was superimposable on that of (*R*)-BINOL except for its intensity, the stereochemistry of the obtained **1** was determined to be (*R*,*R*) as expected from the BINOL synthesis using the PD tethered reaction.



6

7. R = MOM
8. R = H (85% for two steps)

$$\xrightarrow[\text{EtOCON=NCOOEt, PBu}_3\ (66.7\%)]{\mathbf{4}} \mathbf{2} \xrightarrow[-78\ ^\circ\text{C}\ (48\%)]{s\text{-BuLi / CuCN / O}_2} \mathbf{3} \xrightarrow[(89\%)]{\text{BBr}_3} (R,R)\text{-}\mathbf{1}$$

Scheme 4.

In this report, enantiomerically pure TERNOL of (*R*,*R*)-**1**, was prepared in six steps under complete selectively, and the total yield was 19% yield. The success of the complete stereocontrol of the concurrently formed two chiral centers proves the high potential of the PD tethered reaction as a stereocontroller.[10] Although oligomeric or polymeric chiral auxiliaries containing BINOL units have been reported,[11] the present compound is the first optically active example to connect BINOL units at the 1,5-positions though a 2,6-naphthodiol unit.[12] One of the characteristics of TERNOL not possessed by BINOL or its known analogs is that the reductive character originated from the central 2,6-naphthodiol unit.[13] In addition, TERNOL is also considered to be a promising synthon for chiral bis-bidentate ligands, since most of the binaphthyl ligands represented by BINAP are prepared from optically active BINOL. The asymmetric reaction using TERNOL as a chiral auxiliary is now on progress.

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References and Notes

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4. The Mitsunobu reaction was carried out with tributylphosphine (1.2 equivalents) and diethyl azodicarboxylate (1.2 eq.) in THF at room temperature.
5. Compound **6** was prepared in five steps from 2,6-naphthodiol; dibromination (Br_2 in acetic acid, 95%), diacetylation (acetic anhydride-pyridine-THF, 98%), mono-de-acetylation (K_2CO_3 in methanol-THF/ r.t./ 2h, 95%), protection of the hydroxyl group (methoxymethyl chloride-K_2CO_3-THF), and de-acetylation (NaOH in methanol, 97% for two steps).
6. Spectral data for **2**: $[\alpha]_D^{20} = +175.5$ (c 0.9, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.3 Hz, 2H), 7.73 (d, J = 9.3 Hz, 2H), 7.50 (t-like, J = 7.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.8 Hz, 2H), 7.25 (t-like, J = 6.6 Hz, 2H), 7.10 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 9.8 Hz, 2H), 5.02–4.90 (m, 4H), 2.21–2.12 (m, 4H), 1.45 (d, J = 5.9 Hz, 6H), 1.36 (d, J = 5.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 151.3, 133.0, 129.8, 129.1, 128.8, 127.7, 127.5, 127.0, 126.1, 124.3, 118.0, 116.8, 110.6, 77.3, 74.1, 73.8, 45.3, 21.2, 20.9.
7. Spectral data for **3**: $[\alpha]_D^{20} = -208.2$ (c 1.0, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.87 (d, J = 8.8 Hz, 2H), 7.82 (d, J = 7.8 Hz, 2H), 7.39 (d, J = 9.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.31 (t-like, J = 7.5 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 7.23 (t-like, J = 8.3 Hz, 2H), 7.09 (d, J = 9.3 Hz, 2H), 4.62 (m, 2H), 4.50 (m, 2H), 1.80–1.73 (m, 4H), 1.30 (d, J = 6.3 Hz, 6H), 1.20 (d, J = 6.4 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 154.9, 153.4, 133.7, 130.4, 130.3, 129.4, 128.0, 127.8, 126.6, 126.2, 124.1, 123.8, 123.3, 119.2, 75.4, 74.7, 42.2, 29.9, 22.7, 22.6.
8. Spectral data for (*R*,*R*)-**1**: $[\alpha]_D^{20} = +75.6$ (c 0.3, THF). mol CD (ethanol) −171 (239 nm), +167 (226 nm). ^1H-NMR ($CDCl_3$) δ 7.94 (d, J = 9.3 Hz, 2H), 7.86 (d, J = 9.3 Hz, 2H), 7.36–7.31 (m, 6H), 7.23–7.18 (m, 4H), 7.12 (d, J = 9.3 Hz, 2H), 5.07 (s, 2H), 4.85 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 152.7, 151.4, 151.3, 133.4, 131.6, 129.5, 128.5, 127.6, 124.3, 124.2, 124.2, 119.1, 119.1, 117.8, 110.9.
9. Chiralpak AD (Daicel Chemical Industry, Ltd.) eluted with hexane/ethanol/trifluoroacetic acid (85/15/0.5, flow rate 0.5 ml/min). An authentic sample of racemic **1** was prepared by copper catalyzed air oxidation (see ref. 12) of a mixture of 2-naphthol and 2,6-naphthodiol followed by silica gel chromatography. Retention time for (*R*,*R*)-**1**, 54 min; for (*S*,*S*)-**1**, 76 min.
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12. Oligomers of 2,6-naphthodiol, see: G. H. Marin, V. Horak J. Org. Chem. 1994;59:4267–4271.
13. $E_{1/2}^{ox}$ of (*R*,*R*)-**1**, 0.71 V vs. Ag^+/Ag in acetonitrile with NBu_4ClO_4.