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Convenient synthesis and efficient resolution of 3,3′-bis(benzyloxy)-1,1′-binaphthalene-2,2′-diol

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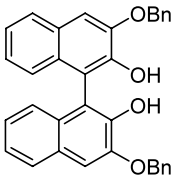
This paper is dedicated to Emeritus Professor Soichi Misumi for his 77th birthday

Abstract—The synthesis and resolution of 3,3′-bis(benzyloxy)-1,1′-binaphthalene-2,2′-diol **1** is described. A diastereomeric mixture of **7** (derived from (±)-**1** and Boc-Ala-OH) was separated using crystallization and column chromatography.

1. Introduction

Over the last few decades BINOL, BINAP, and their derivatives have been widely investigated for asymmetric reactions and supramolecular chemistry. Among these derivatives optically active 3,3′-dioxyfunctionalized-2,2′-dihydroxy-1,1′-binaphthalenes are especially attractive as fundamental compounds for chiral building blocks.[1] Recently, several enantioselective oxidative couplings of 2-naphthols were reported using vanadium,[2] copper,[3] and ruthenium complexes[4] as catalysts, but in multi-gram syntheses of optically active 2,2′-dihydroxy-1,1′-binaphthalenes these syntheses are insufficient due to long reaction times and/or harsh reaction conditions. Previously, we reported the synthesis of optically active **2** through an enzymatic resolution of (±)-**3**,[5] but this route is not applicable to large-scale experiments due to the poor solubility of **3**. This paper reports an alternative synthesis, which is convenient and efficient, of optically active 3,3′-bis(benzyloxy)-1,1′-binaphthalene-2,2′-diol **1** from commercially available 2,3-dihydroxynaphthalene **4** and is applicability to more than 100 g of the starting material **4**.



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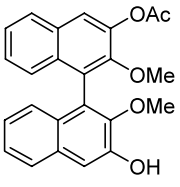

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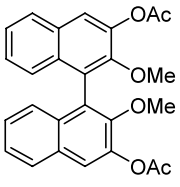

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2. Results and discussion

Scheme 1 outlines a new and improved route to optically active **1**. 3-Benzyloxy-naphthalen-2-ol **5** was synthesized by modifying Weber's procedure[6] without chromatographic purification. Thus, commercially available 2,3-dihydroxynaphthalene **4** was treated with sodium hydrogencarbonate (1.2 equiv.) and benzyl chloride (1.1 equiv.) in DMF at 100°C, which produced a mixture of the desired product **5**, overreacted **6**, and unreacted **4**. After treatment with 6 M sodium hydroxide, **6** was removed by filtration and the solid sodium salts of **4** and **5** were easily separated by extraction between organic layer (diethylether, **5**) and aqueous layer (0.2 M NaOH, **4**). The organic layer was treated with 1 M hydrochloric acid solution to afford **5** in 69% yield. Oxidative coupling under $CuCl_2$/α-methylbenzylamine conditions[7] dimerized 3-benzyloxy-naphthalen-2-ol **5**, giving a 99% yield of (±)-**1**. Crude (±)-**1** was used without further purification.

Next, various resolving reagents of (±)-**1** such as *N*-protected amino acids, (−)-menthyl chloroformate, and cholesteryl chloroformate were screened.[8] The BH_3/proline method[9] and the $B(OH)_3$/α-methylbenzylamine method[10] were also investigated since both have been reported as effective resolution procedures for BINOL

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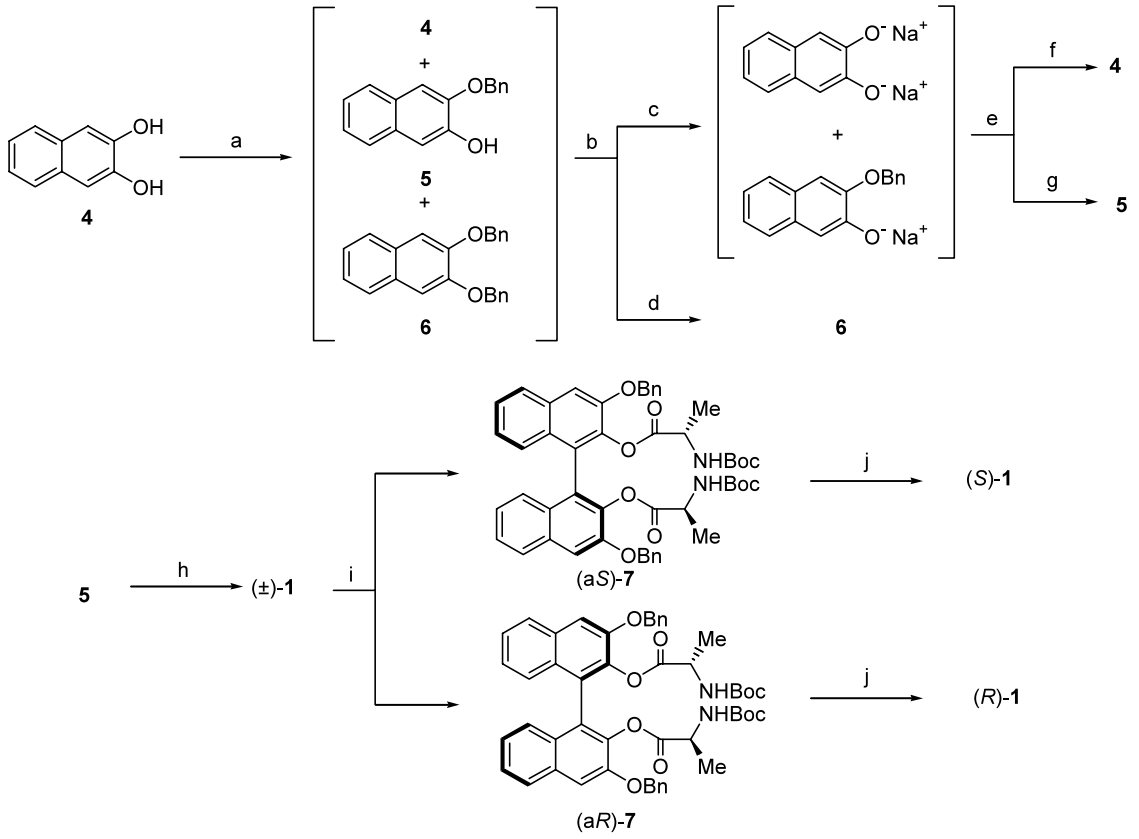

Scheme 1. *Reagents and conditions*: (a) benzyl chloride, $NaHCO_3$; (b) 6 M NaOH; (c) precipitate; (d) filtrate; (e) 0.2 M NaOH; (f) aqueous layer; 1 M HCl; (g) organic layer; 1 M HCl; (h) $CuCl_2$, α-methylphenylamine; (i) Boc-Ala-OH, WSC·HCl, DMAP, then crystallization and column chromatography; (j) 3 M NaOH.

based on different solubilities of diastereomeric complexes. In our trials, TLC analyses (three times developments, *n*-hexane:dichloromethane:ethyl acetate = 12:3:1 as an eluent) indicated that Boc-Ala-OH, Boc-Val-OH, Boc-Ile-OH, and Boc-Met-OH showed relatively large separation factors. Finally, Boc-Ala-OH was selected due to monetary considerations.

Condensation between (±)-**1** and Boc-Ala-OH was conducted by standard WSC/DMAP conditions, which afforded a diastereomeric mixture of (a*S*)-**7** and (a*R*)-**7** in good yield. Furthermore, a portion of (a*S*)-**7** was deposited as a white powder (29% yield) and the residue was separated by column chromatography ((a*S*)-**7**; 16% yield, (a*R*)-**7**; 48% yield). After resolution, hydrolysis of the Boc-Ala moiety afforded (a*R*)- or (a*S*)-**7** in 92 and 91%, respectively, and Boc-Ala-OH was recovered from the aqueous layer without loosing the enantiomeric excess in ~70% yield.

In summary, a convenient and efficient synthesis of optically active 3,3′-bis(benzyloxy)-1,1′-binaphthalene-2,2′-diol **1** was developed and based on **1**, we are currently synthesizing optically active oligo(2,3-dioxy-functionalized)naphthalenes connected at the 1,4-positions as a chiral building block.

3. Experimental

3.1. General

Nuclear magnetic resonance (NMR) spectra were taken at 200 MHz in $CDCl_3$ with chemical shifts being reported as δ ppm from tetramethylsilane as an internal standard and couplings are expressed in hertz. FT-IR and UV spectra was obtained on a JASCO FT/IR-300.

3.2. 3-Benzyloxy-naphthalen-2-ol 5

To a solution of 2,3-dihydroxynaphthalene **4** (100.0 g, 0.62 mol) in DMF (600 mL), sodium hydrogencarbonate (55.0 g, 0.66 mol) was added portionwise at 100°C and stirred for 30 min. A solution of benzyl chloride (72 mL, 0.62 mol) was added dropwise to the mixture and stirred at 100°C for 4 h. Additional sodium hydrogencarbonate (11.0 g, 0.13 mol) and benzyl chloride (7.2 mL, 0.06 mol) were successively added to the reaction mixture and stirred for a further hour. The reaction mixture was poured into the mixed solvent of ether (1 L) and water (1 L). The aqueous layer was extracted with ether (1 L). The organic layers were combined and washed successively with water (1 L, three times) and brine. Aqueous solution of sodium

hydroxide (6.0 M, 104 mL, 0.62 mol) was slowly added to the organic layer at 0°C and stirred for 30 min. White precipitate was collected by filtration and washed with ether (150 mL, twice). The precipitate was added to a mixed solvent of ether (1.5 L) and hydrochloric acid solution. The organic layer was separated and washed successively with 0.2 M aqueous sodium hydroxide solution (500 mL, twice), 1.0 M hydrochloric acid solution, and brine. After being dried over sodium sulfate, the solvent was evaporated in vacuo to afford crude **5** as a pale brown solid (107.1 g, 69% yield). Crude **5** was directly used for the next step without further purification. The characterization data have been reported.[6]

3.3. 3,3′-Bis(benzyloxy)-1,1′-binaphthalene-2,2′-diol (±)-1

To a solution of $CuCl_2$ (107.6 g, 0.8 mol) in methanol (600 mL), (±)-α-methylbenzylamine (129 mL, 1.0 mol) was added under ice-bath cooling and stirred for 40 min (yellow–green solid was formed). A solution of crude **5** (100 g, 0.4 mol) in dichloromethane (400 mL) was added to the suspension at rt (the yellow–green solid temporally dissolved and then large amount of brown solid was deposited). The suspension was stirred for 7 h. The solvent was evaporated under reduced pressure and iced water (1 L) and conc. HCl (300 mL) were successively added to the residue and extracted with ethyl acetate (1.5 L). The organic layer was separated, and the aqueous layer was washed with ethyl acetate (1.5 L). The organic layer were combined and washed with 1.0 M hydrochloric acid solution (1 L) and brine. After being dried over sodium sulfate, the solvent was evaporated in vacuo to afford crude (±)-**1** as a pale brown solid (99.4 g, 99% yield). Crude (±)-**1** was directly used for the next step without further purification. A small part of the sample was subjected to the further purification by column chromatography (SiO_2, *n*-hexane/ethyl acetate = 5/1) to give an analytical sample. Mp 178–180°C (from ethyl acetate and ether); IR ($CHCl_3$) 3532, 3067, 1463, 1445, 1380, 1011 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.33 (s, 4H), 6.10 (s, 2H), 7.16 (d, J = 4.8 Hz, 4H), 7.22–7.52 (m, 14H), 7.77 (d, J = 8.1 Hz, 2H); HRMS calcd for $C_{34}H_{26}O_4$: 498.1831. Found: 498.1816. Anal. calcd for $C_{34}H_{26}O_4$: C, 81.91; H, 5.26. Found: C, 81.67; H, 5.19.

3.4. 2-*tert*-Butoxycarbonylamino-propionic acid 3,3′-bis(benzyloxy)-2′-(2-*tert*-butoxycarbonylamino-propionyloxy)-1,1′-binaphthalenyl-2-yl ester. (a*S*)-7 and (a*R*)-7

To a solution of (±)-**1** (99.0 g, 0.20 mol), Boc-Ala-OH (94.0 g, 0.50 mol), and DMAP (1.0 g) in DMF (600 mL), WSC·HCl (114.4 g, 0.60 mol) was added portionwise under water-bath cooling and stirred for over night. The reaction mixture was poured into the mixed solvent of ether (1 L) and water (1.5 L). The aqueous layer was extracted with ether (1 L). The organic layers were combined and washed successively with aqueous hydrochloric acid solution (0.1 M, 1 L), water (1 L, twice), and brine. After being dried over sodium sulfate, the solvent was evaporated in vacuo to give a residue. Ether (50 mL) and petroleum ether (150 mL) were added to the residue and allowed to stand for 2 days to afford (a*S*)-**7** as a white powder (47.9 g, 30% yield). The residue obtained from the mother liquor was purified by column chromatography (SiO_2, 2 kg, *n*-hexane/chloroform/ethyl acetate = 6/3/1) to successively gave (a*S*)-**7** (17.1 g), a mixture (38.3 g) of (a*S*)-**7** and (a*R*)-**7** and (a*R*)-**7** (59.1 g). The mixture was again purified by column chromatography to give (a*S*)-**7** (13.2 g), a mixture (14.5 g), and (a*R*)-**7** (7.8 g). The third chromatography of the mixture (14.5 g) of (a*S*)-**7** and (a*R*)-**7** gave (a*S*)-**7** (0.6 g), a mixture (1.1 g), and (a*R*)-**7** (12.9 g). Total yields of (a*S*)-**7** and (a*R*)-**7** were 75.8 g (45%) and 79.8 g (48%), respectively.

(a*S*)-**7**; mp = 167–168°C (from ethyl acetate and *n*-hexane); $[\alpha]_D^{20} = -59$ (*c* 1.04, $CHCl_3$); IR (KBr) 3450, 2979, 1772, 1712, 1621 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.4–1.0 (br, 6H), 1.39 (s, 18H), 4.2–4.4 (m, 2H), 5.0–5.3 (m, 2H), 5.29 (s, 4H), 7.15 (d, J = 5.4 Hz, 4H), 7.25–7.47 (m, 14H), 7.77 (d, J = 7.8 Hz, 2H); MS (+APCI) 841.8 $(M+1)^+$. Anal. calcd for $C_{50}H_{52}N_2O_{10}$: C, 71.41; H, 6.23; N, 3.33. Found: C, 71.46; H, 6.20, N, 3.33.

(a*R*)-**7**; pale yellow viscous oil, $[\alpha]_D^{20} = -24$ (*c* 1.50, $CHCl_3$); IR (KBr) 3422, 2978, 1769, 1719, 1624 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.4–0.8 (br, 6H), 1.35 (s, 18H), 4.2–4.4 (m, 2H), 4.8–5.0 (m, 2H), 5.28 (s, 4H), 7.16 (d, J = 4.0 Hz, 4H), 7.25–7.48 (m, 14H), 7.78 (d, J = 8.4 Hz, 2H); MS (+APCI) 841.8 $(M+1)^+$. Anal. calcd for $C_{50}H_{52}N_2O_{10}$: C, 71.41; H, 6.23; N, 3.33. Found: C, 71.22; H, 6.29, N, 3.28.

3.5. (*S*)-3,3′-Bis(benzyloxy)-1,1′-binaphthalene-2,2′-diol (*S*)-1

A solution of (a*S*)-**7** (65.4 g, 77.8 mmol) in THF (460 mL) and aqueous sodium hydroxide (3.0 M, 78 mL, 0.23 mol) was stirred at 60°C for 11 h under an argon atmosphere. The solvent was evaporated off (about 300 mL), ethyl acetate (650 mL) and water (650 mL) were added to the residue and separated. The aqueous layer was extracted with ethyl acetate (650 mL). The organic layers were combined and washed successively with water (500 mL), aqueous hydrochloric acid solution (0.1 M, 500 mL), water (500 mL) and brine (100 m). After being dried over sodium sulfate, the solvent was evaporated in vacuo to give a residue as pale yellow viscous oil. The residue was crystallized and triturated with ether (25 mL) and *n*-hexane (45 mL) to give (*S*)-**1** as a pale yellow powder (35.3 g, 91%). mp = 131–133°C; $[\alpha]_D^{20} = -56$ (*c* 1.02, $CHCl_3$), $[\alpha]_D^{20} = -74$ (*c* 1.81, THF) for >99% ee, [lit.,[3a] $[\alpha]_D^{23} = +22.0$ (*c* 0.80, THF) 38% ee *R*]; HPLC t_R 21.7 min (*S*) (Chiralcel AS, *i*-PrOH/*n*-hexane = 20/80, 1.25 mL/min, λ = 254 nm). The first aqueous layer was acidified with hydrochloric acid and extracted with ethyl acetate (500 mL, twice). The organic layer was washed successively with water (500 mL) and brine (100 m). After dried over sodium sulfate, the solvent was evaporated in vacuo to give a residue as a pale colorless viscous oil. The residue was crystallized and triturated with *n*-hexane (20 mL) to give Boc-Ala-OH as a white powder (23.3 g, 79%). $[\alpha]_D^{20} = -26$ (*c* 1.50, AcOH) (pure Boc-Ala-OH, $[\alpha]_D^{20} = -26$ (*c* 1.78, AcOH)).

3.6. (*R*)-3,3′-Bis(benzyloxy)-1,1′-binaphthalene-2,2′-diol (*R*)-1

In the same way as above, the optically active (*R*)-**1** (41.5 g, 92%, mp = 147–148°C; $[\alpha]_D^{20} = +51$ (*c* 1.23, $CHCl_3$), $[\alpha]_D^{20} = +68$ (*c* 2.04, THF) for 94% ee; HPLC t_R 21.7 min (*S*) and t_R 29.7 min (*R*) (Chiralcel AS, *i*-PrOH/*n*-hexane = 20/80, 1.25 mL/min, $\lambda = 254$ nm) and Boc-Ala-OH (25.0 g, 73%, $[\alpha]_D^{20} = -26$ (*c* 1.25, AcOH)) were obtained from (a*R*)-**7** (76.3 g).

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