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The Asymmetric Ullmann Coupling Reaction of (*S*)-2,2′-Bis(1-bromo-2-naphthoyloxy)-1,1′-binaphthyl Revisited. Formation of 24-Membered Optically Pure Cyclic Dimer as Well as 12-Membered Cyclic Monomer

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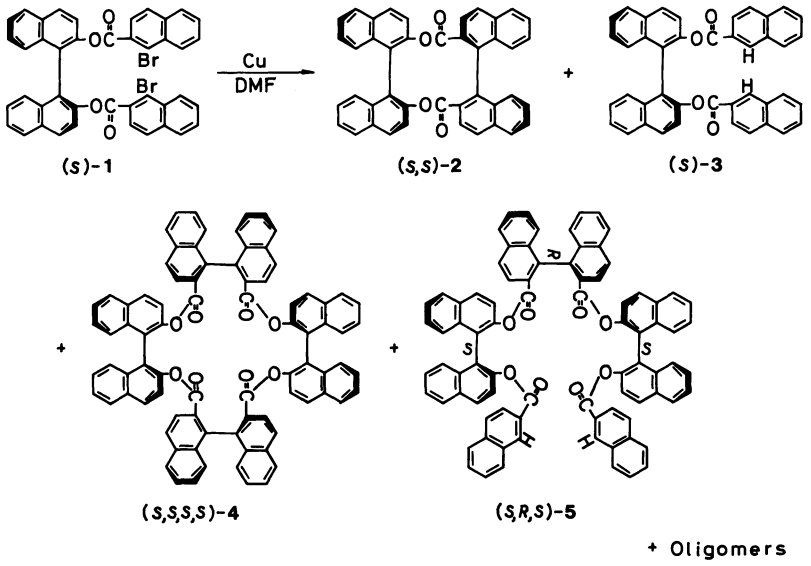
The copper-promoted Ullmann reaction of the title diester proceeded with high stereoselectivity to give 24-membered optically pure cyclic dimer of (*S,S,S,S*)-configuration as well as 12-membered monomeric cycle of (*S,S*)-configuration. The reaction also gave reduced, open-chain dimer enriched in (*S,R,S*)-diastereomer over (*S,S,S*)-counterpart (17% d.e.). Stereochemical course to the cyclic dimer was discussed considering the result that the intermolecular Ullmann coupling of chiral alcohol esters of 1-bromo-2-naphthoic acid poorly induced axial chirality in the joining of the two naphthyl units.

Recently, much attention has been centered on the asymmetric reaction by the use of axially chiral biaryls as the chirality-recognizing auxiliaries,[1] and thus there has been an increasing interest in the construction of the requisite atropisomeric biaryl skeleton via a route other than optical resolution of the racemate.[2]

In our previous papers,[3] we have reported that the Ullmann reaction of axially chiral 1,1′-binaphthyl-2,2′-diol diester (*S*)-**1** proceeds with complete diastereoselectivity to give intramolecularly coupled 12-membered monomeric cycle (*S,S*)-**2** in a 36% isolated yield without formation of (*S,R*)-diastereomer (Scheme 1). It was also implied that 24-membered cyclic dimer **4**, which was obtained only in a small amount from the reaction conducted under dilution conditions, was likely to have a rather high diastereomeric purity (87—100% d.e.) of (*S,S,S,S*)-configuration.[3b] Here we wish to report that the cyclic dimer is obtainable in a 10% yield as a precipitate from a benzene solution of an Ullmann reaction mixture in essentially optically pure state, and also wish to discuss the stereochemical course of the copper-promoted coupling reaction of (*S*)-**1** to the cyclic dimer.



Scheme 1.

Results and Discussion

Isolation of Optically Pure Cyclic Dimer (*S,S,S,S*)-4. In order to gain more information on the stereochemistry of the cyclic dimer, here again we repeated the copper-promoted Ullmann reaction of (*S*)-**1** under conditions intended to promote the intermolecular coupling; a mixture of (*S*)-**1** and an activated copper powder in a small volume of DMF was heated at gentle reflux with vigorous stirring. Debromination was completed within 5 h, and HPLC of the crude reaction mixture showed the presence of several components which had the

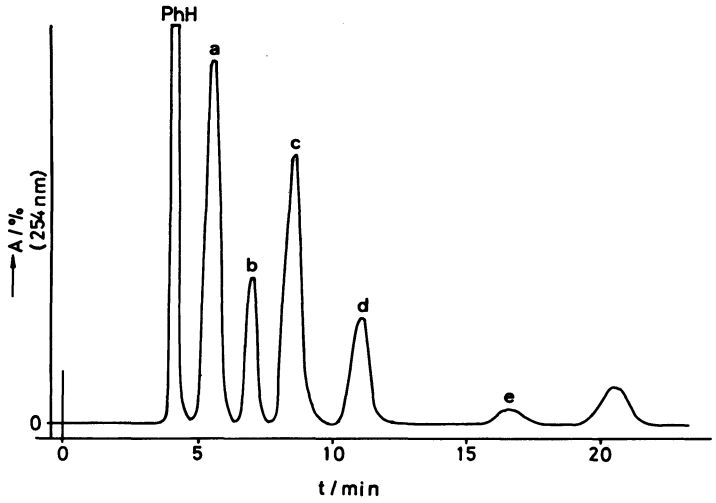


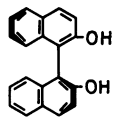
Fig. 1. HPLC of the Ullmann reaction mixture of (*S*)-**1**.
Conditions: microcolumn (0.5 mm (i.d.) × 10 cm) packed with JASCOSIL SC-01 eluted with 2% aq CH_3CN (8 μl/min). **a**, (*S,S*)-**2**; **b**, (*S*)-**3**; **c**, (*S,S,S,S*)-**4**; **d**, (*S,S,S*)- and (*S,R,S*)-**5**; **e**, tentative cyclic trimer(s).

retention volumes identical to those of, in the order of elution, (*S,S*)-**2**, (*S*)-**3**, cyclic dimer **4** obtained in the previous work,[3b] and open-chain dimer **5** (Fig. 1). The authentic sample of **5** was comprised of a 52:48 mixture of (*S,S,S*)- and (*S,R,S*)-**5**,[4] showing that these diastereomers were not differentiated on the HPLC conditions. The component eluting the 5 th on HPLC (**e** in Fig. 1) was tentatively assigned to cyclic trimer(s) (see Experimental).

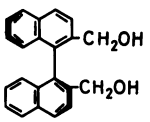
Attempted cryoscopy of the Ullmann reaction mixture in benzene was unsuccessful because of the deposition of a white precipitate on cooling a rather dilute solution. Unexpectedly but to our pleasure, we found that the precipitate showed only one peak on HPLC which had the same retention volume as that of the cyclic dimer **4**. Thus, the component of $[\alpha]_{436}^{24}$ −293±4° (PhH) was isolated in a 10% yield by standing a benzene solution of the reaction mixture at ambient temperature for 2 d followed by filtration of the precipitate deposited. The benzene filtrate was then subjected to silica-gel chromatographies to allow the isolation of (*S,S*)-**2** (12%), an extra amount of cyclic dimer **4** of $[\alpha]_{436}^{24}$ −296±3° (PhH) (1.2%), and open-chain dimer **5** (3.6%).

Discrepancies in optical rotations of the samples of **4** recovered above and the one obtained in the previous work by a column chromatography ($[\alpha]_{436}^{24}$ −291° (PhH)) should be regarded within the limits of the experimental error accompanying the measurement of them. These samples showed IR spectra superimposable on each other. From these results there seemed to be little chance that concentration of a particular stereoisomer among the possible cyclic dimers **4** had occurred during the isolation process.

Stereochemistry of the precipitated cyclic dimer **4** was unequivocally established to be optically pure (*S,S,S,S*)-**4** as follows: Treatment of the sample with lithium aluminium hydride (LAH) gave only two diols, (*S*)-1,1′-binaphthyl-2,2′-diol ((*S*)-**6**) and (*S*)-2,2′-bis(hydroxymethyl)-1,1′-binaphthyl ((*S*)-**7**). Optical



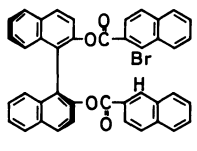
(*S*)-**6**



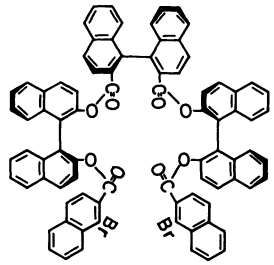
(*S*)-**7**

rotations of these diols compare well with those claimed for enantiomerically pure specimens.[5] The homochirality of (*S*)-**7** was further confirmed by ^1H NMR study of the α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA) ester in the presence of Eu(fod)$_3$ shift reagent.

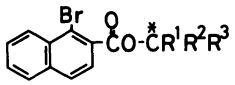
Stereochemical Course of the Ullmann Reaction of (*S*)-1 to (*S,S,S,S*)-4. Reaction path to cyclic dimer **4** inevitably requires initial bimolecular coupling of (*S*)-**1** to open-chain dibromo dimer **8**. It may be reasonable to assume that this kind of intermolecular coupling should afford a diastereomer mixture of (*S,S,S*)- and (*S,R,S*)-**8** (Eq. 1), the former being slightly in excess as a closely related coupling of (*S*)-**9** to **5** induced (*S*)-axial chirality only in a 4% diastereomeric excess (Eq. 2).[4] It was also reported that *C*-chiral alcohol esters (**10**) of 1-bromo-2-naphthoic acid poorly induced axial chirality in the Ullmann coupling of the two naphthyl units.[6]



(*S*)-**9**



(*S,S,S*)-**8**



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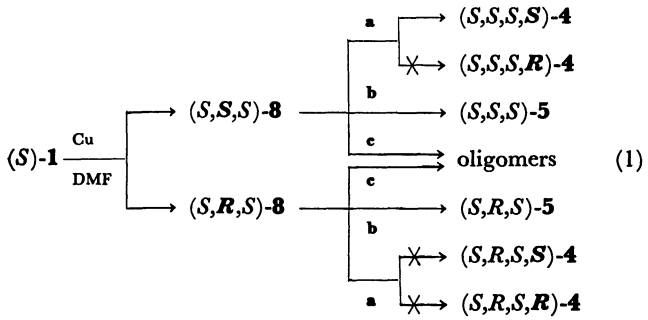
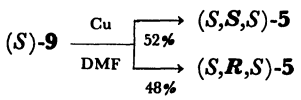


(1)

a: Intramolecular coupling, **b**: Reduction, **c**: Intermolecular reactions. (Bold italic letter indicates newly formed 1,1′-binaphthyl linkage in the said reaction.)



(2)

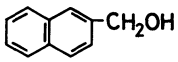
A rational conclusion deduced from the argument above is that intramolecular cyclization of **8** is allowed only for (*S,S,S*)-diastereomer to (*S,S,S,S*)-**4** without forming (*S,S,S,R*)-**4**, but not allowed for (*S,R,S*)-**8** which should give (*S,R,S,S*)- or (*S,R,S,R*)-**4** (Eq. 1). Although it is not easy to unequivocally explain the exclusive formation of (*S,S,S,S*)-**4**, inspection of the CPK molecular models of the intermediate dibromo dimers **8** and the possible cyclic dimers **4** gives some indication.

Conformationally identical 1,1′-binaphthyl axes in (*S,S,S*)-**8** seem to bring the two bromine substituents in a position to allow ring closure to cyclic dimer, while in (*S,R,S*)-**8** the coupling sites are disposed rather separated each other by intervening three 1,1′-binaphthyl moieties.

The models also show that (*S,S,S,S*)-**4** has the most symmetrical, and the least sterically crowded structure among the four possibilities; four sets of 1,1′-binaphthyl moieties are all staggered to each other as schematically illustrated in Fig. 2, which is a top view looking down along the axes of four 1,1′-binaphthyl linkages where the hatched naphthalene rings locate closer to the eyes.

On the other hand, naphthalene planes **a** and **b**, and **c** and **d** in (*S,S,S,R*)-**4** are respectively disposed face to face to each other in a close vicinity, thus imposing steric repulsion between the edges of the rings **c** and **e** (Fig. 3). Similar situation to this is valid for the (*S,R,S,S*)-counterpart. The (*S,R,S,R*)-disposition seems to be the least comfortable because every naphthalene ring faces to another causing four sets of collision among edges of the eight naphthalene rings (Fig. 4).

Stereochemistry of Open-chain Dimer 5. Treatment of the recovered **5** with LAH gave (*S*)-**6**, 2-naphthalenemethanol **11**, and **7**. On the basis of the



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optical rotation of the diol **7**, the diastereomeric excess of the open-chain dimer **5** should be 17% enriched in (*S,R,S*)-**5** over (*S,S,S*)-diastereomer.[7] This stereochemical bias in **5** is qualitatively understandable as follows: Among the plausible reactions of the dibromo dimers **8** are intramolecular ring closure to cyclic dimers **4** and reduction to open-chain dimers **5**, as well as further intermolecular reactions to oligomeric products (Eq. 1). Assuming that the other conditions are equal, (*S,R,S*)-**8** should have more chance than (*S,S,S*)-**8** to be reduced to the open-chain dimer ((*S,R,S*)-**5**), because it lacks the exit to the corresponding cyclic dimer **4** as stated above.

In conclusion, we have shown here that 24-membered optically pure cyclic dimer (*S,S,S,S*)-**4** is

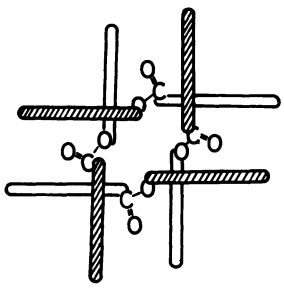

Fig. 2. (*S,S,S,S*)-4.

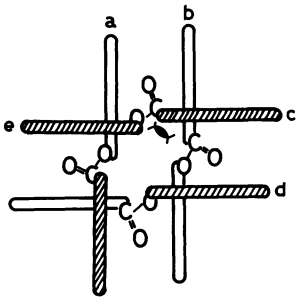

Fig. 3. (*S,S,S,R*)-**4**.

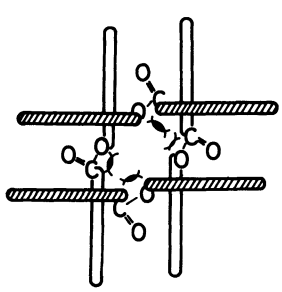

Fig. 4. (*S,R,S,R*)-**4**.

easily obtainable in a 10% yield as a precipitate from a benzene solution of an Ullmann reaction mixture of (*S*)-**1**. Recently, macrocyclic compounds with chiral cavity such as chiral crown ethers and cyclodextrins have been receiving considerable attention because of their high ability for chiral recognition of guest molecules.[8] CPK molecular models show that the 24-membered (*S,S,S,S*)-**4** confines a cavity just fit to accommodate a molecule of the size of benzene nucleus (Fig. 2), and investigation of the host-guest interaction involving the cycle is now under way.

Experimental

General directions are given in Ref. 3b. A JASCO FAMILIC-100 instrument was routinely utilized for the HPLC analyses of various binaphthyl derivatives encountered in this study using a 0.5 mm(i.d.)×10 cm microcolumn packed with JASCOSIL SC-01 (ODS) eluted with CH_3CN–H_2O.

(*S*)-**1** was prepared as before[3b] from (*S*)-**6** ($[\alpha]_D^{22}$ −34.8° (*c* 0.985, THF)) and 1-bromo-2-naphthoyl chloride; mp 178—179 °C (uncor.); $[\alpha]_D^{22}$ +34.3° (*c* 1.13, acetone).

Ullmann Reaction of (*S*)-1. To a mixture of (*S*)-**1** (3.00 g, 3.99 mmol) and activated copper powder (prepared from 3.0 g of Cu (47 mg-atom)) was added 20 ml of DMF. The mixture was magnetically stirred and heated to gentle reflux under nitrogen. After 5 h reaction, the mixture was worked up as before[3b] to give a pale yellow organic residue, 2.31 g (97.7% yield calculated as **2**), $[\alpha]_D^{24}$ −48.6° (*c* 0.803, PhH).

Isolation of (*S,S,S,S*)-4 by Precipitation: A 1.25 g sample of the Ullmann product was dissolved in 30 ml of hot benzene. The solution was allowed to stand for 2 d at ambient temperature to give a white precipitate. The material settled out was recovered by filtration, washed with small portions of benzene, and dried in vacuo (≈100 °C/10^{-1} mmHg) to give (*S,S,S,S*)-**4** as a white powder; 0.133 g (0.112 mmol); $[\alpha]_{436}^{24}$ −293±4° (*c* 0.152, PhH); IR (KBr) 1745 cm^{-1}. Found: C, 84.81; H, 4.43%. Calcd for $C_{84}H_{48}O_8$: C, 85.12; H, 4.08%.

The cyclic dimer (57 mg) was boiled with 0.1 g of LAH in 30 ml of ether for 5 h. After usual work-up, products were separated by preparative TLC (silica gel, $CHCl_3$/AcOEt(4/1)).

(*S*)-**6**: 21 mg; $[\alpha]_D^{24}$ −34.3° (*c* 1.14, THF).

(*S*)-**7**: 25 mg; $[\alpha]_{546}^{24}$ −83.2° (*c* 1.25, acetone). MTPA esters of (*S*)-**7** and racemic **7** were prepared by treatment with (*R*)-MTPA chloride. ^{1}H NMR studies of the esters in $CDCl_3$ in the presence of varying amounts of Eu(fod)$_3$ indicated that the (*S*)-**7** should be more than 98% e.e.[3b]

Stereochemistry of (*S,R,S*)-5: The benzene filtrate, which had been removed of the precipitate of (*S,S,S,S*)-**4**, was subjected to a silica-gel column chromatography ($CHCl_3$ (1% EtOH)) to give 0.157 g of (*S,S*)-**2**, $[\alpha]_D^{24}$ −452° (*c* 0.613, PhH) (lit,[3b] −457.6° (*c* 0.507, PhH)).

Column effluent fractions which were mostly comprised of cyclic dimer **4** and open-chain dimer **5** were further subjected to TLC separation (silica gel, $CHCl_3$ (1% EtOH)) to give (*S,S,S,S*)-**4** (15 mg, $[\alpha]_{436}^{24}$ −296±3° (*c* 0.147, PhH)) and (*S,R,S*)-**5** (46 mg). The latter was treated with LAH to give (*S*)-**6** (18 mg, $[\alpha]_D^{24}$ −34.2° (*c* 0.352, THF), (*S*)-**7** (11 mg, $[\alpha]_{546}^{24}$ +14.6° (*c* 0.518, acetone), and **11** (6 mg).

Similar preparative TLC of another fraction of the column effluent gave the component corresponding to **e** in Fig. 1, 14 mg, $[\alpha]_D^{24}$ +26.3° (*c* 0.909, PhH), which was tentatively assigned to cyclic trimer(s) on the basis of the HPLC elution pattern, a chemical transformation, and IR spectral studies: The cyclic structure was confirmed by the fact that LAH treatment of the sample gave only two spots on TLC (silica gel, $CHCl_3$/AcOEt(4/1)) which corresponded to (*RS*)-**6** (R_f 0.18) and (*RS*)-**7** (R_f 0.67), respectively. IR absorption (KBr disk) of the ester carbonyl function was precisely compared with those of cyclic monomer and dimer as follows, and it seemed that release of ring strain reduced the absorption frequency of the cyclic trimer(s).

(*S,S*)-**2**	1752.4 cm^{-1}
(*S,S,S,S*)-**4**	1744.7 cm^{-1}
Tentative cyclic trimer(s)	1742.9 cm^{-1}

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References

1) Recent examples; a) K. Yamamoto, H. Fukushima, Y. Okamoto, K. Hatada, and M. Nakazaki, *J. Chem. Soc., Chem. Commun.*, **1984**, 1111; b) Y. Kawakami, J. Hiratake, Y. Yamamoto, and J. Oda, ibid., **1984**, 779; c) R. Noyori, I. Tomino, Y. Tanimoto, and M. Nishizawa, *J. Am. Chem. Soc.*, **106**, 6709 (1984); d) K. Tani, T. Yamagata, S. Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, R. Noyori, and S. Otsuka, ibid., **106**, 5208 (1984); e) A. Miyashita, H. Takaya, T. Souchi, and R. Noyori, *Tetrahedron*, **40**, 1245 (1984).

2) Recent examples; a) F. Sannicolo, *Tetrahedron Lett.*, **26**, 119 (1985); b) J. M. Wilson and D. J. Cram, *J. Org. Chem.*, **49**, 4930 (1984); c) K. Yamamoto, H. Fukushima, and M. Nakazaki, *J. Chem. Soc., Chem. Commun.*, **1984**, 1490; d) A. I. Meyers and D. G. Wettlaufer, *J. Am. Chem. Soc.*, **106**, 1135, (1984).

3) a) S. Miyano, M. Tobita, M. Nawa, S. Sato, and H. Hashimoto, *J. Chem. Soc., Chem.. Commun.*, **1980**, 1233; b) S. Miyano, M. Tobita, and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, **54**, 3522 (1981).

4) The sample was in fact comprised of a 52:48 mixture of (*R,R,R*)- and (*R,S,R*)-**5**, as it was obtained in Ref. 3b by the Ullmann reaction of (*R*)-**9**. For the sake of clarity, however, we will discuss here as if the reaction had been carried out with (*S*)-**9**.

5) See Ref. 3b: (*S*)-**6**: $[\alpha]_D^{22}$ −35.0° (*c* 1.18, THF). (*S*)-**7**: $[\alpha]_{546}^{24}$ −86.0° (*c* 1.43, acetone).

6) S. Miyano, M. Tobita, S. Suzuki, Y. Nishikawa, and H. Hashimoto, *Chem. Lett.*, **1980**, 1027.

7) The (*S,S,S*)-**5** in Scheme 3 in Ref. 3b) should now be read (*S,R,S*)-**5**.

8) "Inclusion Compounds," ed by J. L. Atwood, J. E. D. Davies, and D. D. MacNicol, Academic Press, London (1984) Vol. 2.