  Bull. Chem. Soc. Jpn., 61, 3249—3254 (1988)

Asymmetric Synthesis of Axially Chiral, Unsymmetrical Diphenic Acids via Intramolecular Ullmann Coupling Reaction[1)]

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(Received March 22, 1988)

A practical route to unsymmetrical diphenic acids is described. Successive esterification of ethylene glycol with two different 2-halobenzoyl chlorides gave the corresponding mixed diester, which was treated with copper powder in boiling DMF under dilution conditions. Silica-gel column chromatography allowed ready separation of the intramolecularly coupled cyclic diester (30—60% yield) from other by-products accompanying the Ullmann reaction, and alkaline hydrolysis gave unsymmetrical diphenic acid. Axially chiral, unsymmetrical diphenic acids of more than 99% enantiomeric excess were obtained from the reaction of mixed diesters prepared from (*R*)-1,1′-bi-2-naphthol.

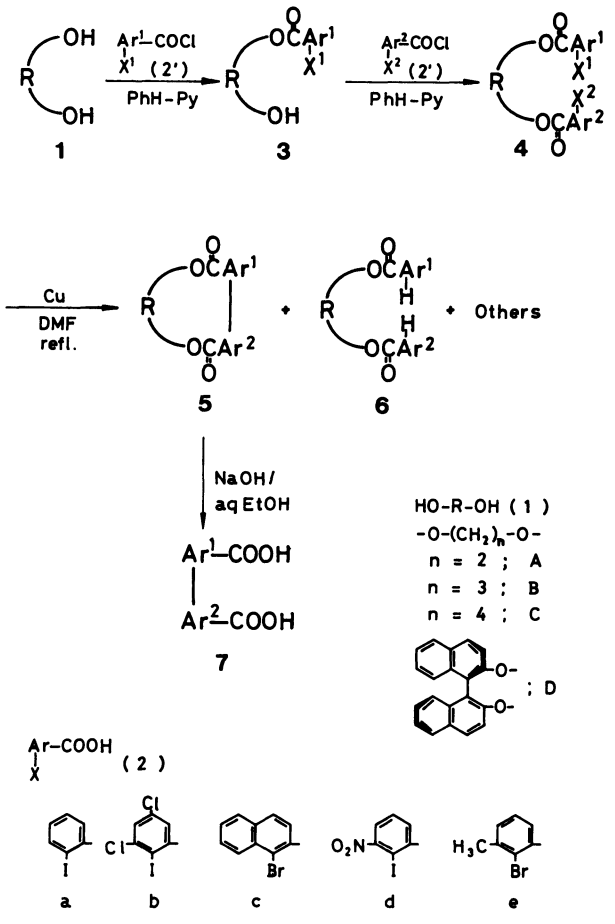
The formation of aryl–aryl bond continues to be an important problem in organic synthesis.[2)] Among a number of methods currently available, nucleophilic addition of aryl Grignard reagents to aryl halides in the presence of nickel–phosphine complex (Kumada-Tamao reaction)[3)] or 2-(*o*-alkoxyaryl)-2-oxazolines (Meyers reaction)[4)] has become widely utilized in the last decade. However, efforts have still been devoted to develop novel methodologies, because procedures are severely limited when one wants regioselective aryl–aryl bond formation between two differently substituted aromatic nuclei bearing substituents such as nitro or carbonyl which are incompatible with organomagnesium reagents.[5)] It is known that, for the aryl halides bearing such functionalities, the Ullmann coupling reaction is complementary to the organometallic routes.[6)] However, when applied to a mixture of two different aryl halides, the reaction rarely works well to give the unsymmetrical biaryl in good yield because of the inevitable formation of the symmetrically coupled products which are difficult to separate from the desired one.[7)]

In the course of our study on the asymmetric reaction by use of axially chiral biaryl auxiliaries, we encountered an occasion where unsymmetrical diphenic acids were needed.[8)] Herein we wish to report that the intramolecular Ullmann coupling reaction of mixed diester of 2-halobenzoic acids provides a convenient route to unsymmetrical diphenic acids, and if desired, with complete axial chirality.

Results and Discussion

Synthesis of Racemic Diphenic Acids. Newman and Cella had tried the synthesis of unsymmetrical diphenic acid via intramolecular Ullmann coupling of a mixed acid anhydride of 2-halobenzoic acids,[9)] but their attempt was not fully realized because of the rapid disproportionation of the anhydride before coupling, resulting in the formation of the corresponding symmetrical diphenic acids along with the unsymmetrical acid in a statistical ratio. Attempted intramolecular coupling of *N*-phenyl-2,2′-dibromodibenzimide or 2,2′-dibromobenzil also failed to cyclize to give *N*-phenyldiphenimide or phenanthrenequinone.

As we had succeeded in the intramolecular Ullmann coupling of diol diesters of 2-halobenzoic acids to give, after hydrolysis, symmetrical diphenic acids,[10)] we tried to extend the reaction to the unimolecular



Scheme 1.

Table 1. Intramolecular Ullmann Coupling of Mixed Diesters of 2-Halobenzoic Acids[a]

	4					5		
	-O-R-O-	$Ar^1(X^1)$-	$Ar^2(X^2)$-	/mmol		Yield/%	IR(KBr)/cm^{-1}	Eluent[b]
4Aab	A	b	a	5.11	**5Aab**	51	1740	PhMe
4Aac	A	c	a	4.88	**5Aac**	43	1740	PhH
4Abc	A	b	c	3.57	**5Abc**	61	1750	PhH
4Abd	A	b	d	3.07	**5Abd**	56	1750	PhH
4Acd	A	c	d	3.77	**5Acd**	38	1745	PhH/EtOAC (4/1)
4Ace	A	e	c	2.24	**5Ace**	28	1740	PhH
4Bce	B	e	c	5.14	**5Bce**	31	1730	PhH
4Cce	C	e	c	3.33	**5Cce**	49	1730	PhH/EtOAc (20/1)
4Dbc	D	b	c	1.89	**5Dbc**	33	1750	Hexane/EtOAc (4/1)
4Dbd	D	b	d	1.92	**5Dbd**	80	1750	Hexane/PhMe (1/3)
4Dcd	D	c	d	1.83	**5Dcd**	44	1740	Hexane/EtOAc (4/1)

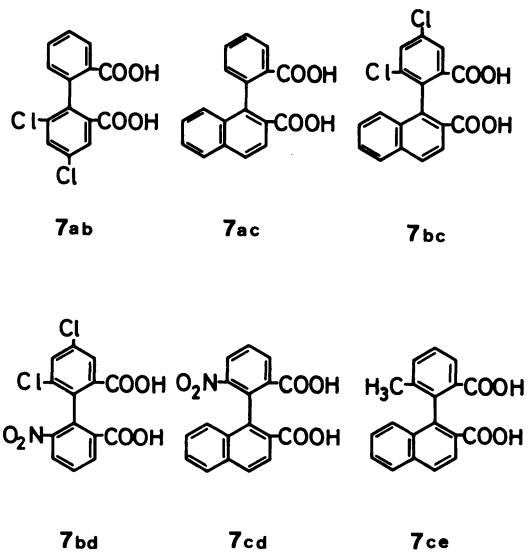
a) A solution of **4** in 40 ml of DMF was added to a vigorously stirred, gently refluxing suspension of Cu powder (20 equiv) in 60 ml of DMF during 6-h period. After the addition, the reaction was continued for 2 h. b) Eluent for the separation of **5** by silica-gel column chromatography; **5** was obtained as the first eluting component.

coupling of mixed diester of two different 2-halobenzoic acids for the synthesis of unsymmetrical diphenic acids (Scheme 1).

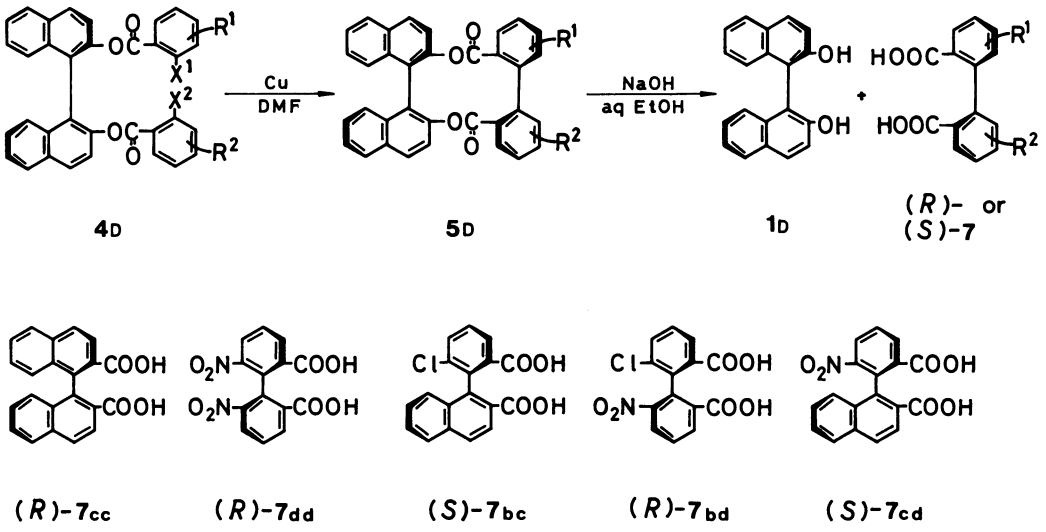
Treatment of a 2-halobenzoyl chloride **2'** with excess diol **1** in benzene–pyridine gave mono ester **3**. After purification by silica-gel column chromatography, **3** was in turn treated with a second 2-halobenzoyl chloride again in benzene–pyridine to give the corresponding unsymmetrical diester **4** in good yields.

The Ullmann reaction was carried out as before[10] by slowly adding a solution of **4** in *N,N*-dimethylformamide (DMF) to a vigorously stirred suspension of an activated copper powder in DMF heated at reflux. TLC analysis of the reaction mixture showed the presence of intramolecularly coupled cyclic diester **5** and of reduced, open chain diester **6** as the unimolecular reaction products accompanied by several oligomeric products originated from intermolecular coupling. It was shown that the monomeric cycle **5** was the first eluting component on silica-gel column, which enabled ready separation of **5** from the reduction product **6** and other by-products. Table 1 lists the results of the column-chromatographic separation of the intramolecularly coupled products, where yields refer to analytically pure samples.[11] This chromatographic behavior may reflect rather rigid, slightly strained cyclic structure of **5** as judged by higher IR absorption frequencies of the carbonyl function of **5** (1740—1750 cm^{-1}) than that of **6** (ca. 1720 cm^{-1}). CPK molecular models of **5** indicate that linking of two *o,o'*-positions of a biaryl by $-COO(CH_2)_2OCO-$ chain fixes the dihedral angle between the two phenyl rings to ca. 80°,[12] which disposes the $-OCH_2CH_2O-$ protons in diastereotopic positions, placing two of the vicinal protons near the shielding cones of the aromatic planes: ^1H NMR of **5** showed AA'BB' pattern centered at around δ 4.1 and 5.1, while **6** showed a singlet at around δ 4.6 for these protons.

Hydrolytic removal of the bridging ethylenedioxy group from **5** was a trivial procedure, and afforded six unsymmetrical diphenic acids **7ab—7ce** listed.



Steric bulk of the *o,o'*-substituents in biphenyl system is estimated by Adams to be in the order of $H<CH_3<Cl<NO_2$.[13] The inferior result of the reaction of **4Ace** should be ascribed to the electronic effects of the methyl substituent, as is known that electron-donating substituents disfavor the Ullmann coupling. The yield of the intramolecular coupling seems to be improved by the use of somewhat longer methylene chain, which will impose less steric constraints on the cycle (compare the reaction of **4Ace** with that of **4Bce** and **4Cce**). The advantage was offset by the reduced separability of **5Cce** from **6Cce** on silica-gel column; the enlargement of the bridging chain seemed to reduce the difference of the chromatographic behavior between the cycle **5** and the open chain diester **6**.



Scheme 2.

Asymmetric Synthesis of Axially Chiral, Unsymmetrical Diphenic Acids. We have reported virtually complete asymmetric synthesis of axially chiral, symmetrical diphenic acids ((*R*)-**7cc**[14] and (*R*)-**7dd**[10]) via the intramolecular Ullmann coupling of diesters (**4Dcc** and **4Ddd**, respectively) prepared from (*R*)-1,1′-bi-2-naphthol ((*R*)-binaphthol, **1D**) (Scheme 2). The remarkable stereoselectivity in the joining of two aryl rings has been explained on the basis of the steric requirements in assembling the 12-membered cyclic diester **5D** which contains two sets of biaryl skeletons connected each other by -COO- bridges on *o,o′*-positions.[15] This means that the sense of axial chirality of the one biaryl unit determines that of the other in such ring systems, which can be utilized for the determination of axial chirality of relevant biaryl skeletons.[16]

The high stereoselectivity and predictability of the axial chirality were utilized for the synthesis of axially chiral, unsymmetrical diphenic acids of known absolute configurations ((*S*)-**7bc**, (*R*)-**7bd**, and (*S*)-**7cd**) (Scheme 2 and Table 1). Enantiomeric purity of these acids (>99%) were readily confirmed by HPLC analyses carried out on chiral stationary phases prepared from axially chiral binaphthyl derivatives.[8] Further confirmation of the assignment of absolute configurations of these acids by use of ^{1}H NMR spectral studies will be presented elsewhere.

It is known that the Ullmann reaction is susceptible to the reaction conditions, especially the nature of the copper used and accidental moisture, which makes reproducibility difficult. Although we could not fully clarify at present the reason why the reaction of **4Dbd** gave exceptionally good results, we are inclined to say that it was not accidental considering the fact that duplicate runs in this work gave practically analogous results with the deviation range of around ±15%; the combination of two 2-halobenzoic acids as well as the choice of the linking bridge may play a significant role in the reaction.

Previous synthesis of unsymmetrical diphenic acids is only limited.[6] Meyers et al. reported the synthesis of 6-methoxydiphenic acid in high yield by the oxazoline route, which, however, needed somewhat troublesome transformation of the two carboxyl groups to oxazolines for protection and activation, and deprotection after aryl coupling to regenerate them.[17] Although the method disclosed herein needed chromatographic purification, it gave moderate to good yields in the key intramolecular coupling. The procedure is operationally rather simple, and seems to have synthetic utility, especially where the Meyers reaction can not be applied, or where axially chiral diphenic acids are needed.

Experimental

Measurements. IR spectra were measured on a Shimadzu IR-430 grating spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL JNM-FX60 instrument using tetramethylsilane as internal standard and $CDCl_3$ as solvent. Optical rotations were recorded on a Union PM-101 automatic digital polarimeter in a 1-cm cell at 23—25 °C. HPLC was carried out on a JASCO TRIROTAR-III and/or a Shimadzu LC-5A, with UV detection at 254 nm. Melting points were uncorrected.

Materials. Analytical TLC was performed using Merck silica gel 60G or $60F_{254}$. Merck silica gel 60H was used for preparative TLC. Silica-gel columns were prepared by use of Wako Gel C-200, while alumina columns by Wako activated alumina (ca. 300 mesh). DMF was distilled from CaH_2 just prior to use under nitrogen. Solvents for experiments requiring anhydrous conditions were purified by the usual methods. Enantiomerically pure (*R*)-binaphthol was obtained as before;[14] $[\alpha]_D$+34.6 ° (*c* 0.905, THF). Copper powder (Junsei Chemical Co., 200 mesh) was

pretreated for activation before the Ullmann reaction.[14]

2-Halobenzoic Acids (2). **2a** was used as purchased. **2b** was prepared according to the literature;[18] mp 179—181 °C (lit,[18] 175—180 °C), IR(KBr) 1705 cm^{-1}. Preparation of **2c**,[19] **2d**,[10] and **2e**[20] were reported before. These acids were converted to acid chlorides **2'** by boiling in thionyl chloride for several hours. After the reaction, volatiles were removed in vacuo, and a small amount of benzene was added and distilled off in vacuo. The latter procedure was repeated two more times, and the remaining acid chlorides were used directly for esterification.

Monoesters 3A—3C of Glycols 1A—1C. The synthesis of 2-(3,5-dichloro-2-iodobenzoyloxy)ethanol (**3Ab**) is representative for the preparation of glycol monoesters. To a stirred mixture of ethylene glycol (**1A**) (30 ml), benzene (30 ml), and pyridine (10 ml) was added dropwise a solution of **2'b** (prepared from 4.50 g of **2b**, 14.2 mmol) in benzene (30 ml). The mixture was stirred overnight at ambient temperature, and then heated at reflux for 3 h. To the cool mixture were added 30 ml of benzene and 100 ml of 2 M† HCl, and phases were separated. Aqueous phase was extracted with portions of benzene. Combined organic phase was washed with 2 M HCl, 1M Na_2CO_3, and water, and then dried over Na_2SO_4. After volatiles were removed in vacuo, the residue was subjected to silica-gel column chromatography eluting with $CHCl_3$ to give 4.72 g of **3Ab** (92%); mp 85—86 °C; IR (KBr) 3250 (br) and 1720 cm^{-1}; ^1H NMR δ=1.9 (1H, s, OH), 3.8—4.2 (2H, m, $\underline{CH_2}$-OH), 4.2—4.6 (2H, m, COO-CH_2), and 7.2—7.9 (2H, m, Ar-H).

3Ac was obtained from **2c** in 87% yield using benzene as the eluent for silica-gel column chromatography; mp 74—76 °C; IR (KBr) 3500 (br) and 1710 cm^{-1}; ^1H NMR δ=2.2 (1H, s, OH), 3.7—4.1 (2H, m, $\underline{CH_2}$-OH), 4.3—4.6 (2H, m, COO-CH_2), and 7.3—8.6 (6H, m, Ar-H).

3Ae was obtained from **2e** as an oil in 82% yield, using chloroform as the eluent for silica-gel column chromatography; IR (liq. film) 3400 (br) and 1720 cm^{-1}; ^1H NMR δ=2.4 (4H, s, OH and CH_3), 3.6—3.9 (2H, m, $\underline{CH_2}$-OH), 4.4—4.7 (2H, m, COO-CH_2), and 7.1—7.6 (3H, m, Ar-H).

3Be was prepared from **2e** and 1,3-propanediol; 83% yield, benzene as the eluent; oil; IR (liq. film) 3400 (br) and 1720 cm^{-1}; ^1H NMR δ=2.0 (1H, s, OH), 2.0 (2H, tt, J_1=J_2=6.0 Hz, $CH_2\underline{CH_2}CH_2$), 2.4 (3H, s, CH_3), 3.77 (2H, t, J_1=6.0 Hz, $\underline{CH_2}$-OH), 4.46 (2H, t, J_2=6.0 Hz, $COOCH_2$), and 7.0—7.6 (3H, m, Ar-H).

3Ce was obtained from **2e** and 1,4-butanediol; 79% yield, benzene-ethyl acetate (3/1) as the eluent; oil; IR (liq. film) 3350 (br) and 1730 cm^{-1}; ^1H NMR δ=1.7 (1H, s, OH), 1.7—2.0 (4H, m, $CH_2(\underline{CH_2})_2CH_2$), 2.42 (3H, s, CH_3), 3.68 (2H, t, J_1=6.0 Hz, $\underline{CH_2}$-OH), 4.34 (2H, t, J_2=6.0 Hz), and 7.0—7.6 (3H, m, Ar-H).

Monoesters 3D of (*R*)-Binaphthol 1D. **3Db:** **2b** (7.50 g, 23.7 mmol) was converted to **2'b**, which was treated with **1D** (5.75 g, 20.1 mmol) as above. The reaction mixture was chromatographed on alumina; after diester **4Dbb** had been eluted out with toluene (0.30 g, 1.7% based on **1D**), elution with toluene-ethanol (10/1) and crystallization from toluene gave **3Db**, 9.94 g (85% based on **1D**); mp 175—177 °C; $[\alpha]_D$ +86.8° (*c* 0.852, $CHCl_3$); IR (KBr) 3450 and 1730 cm^{-1}; ^1H NMR δ=5.0 (1H, s (br), OH) and 7.0—8.2 (14H, m, Ar-H). Found: C, 55.19; H, 2.61; halogen, 34.11%. Calcd for $C_{27}H_{15}Cl_2IO_3$: C, 55.42; H, 2.58; Cl+I, 33.80%.

3Dc was obtained from **2c** (3.60 g, 14.3 mmol) and **1D** (4.20 g, 14.7 mmol) as above; 6.03 g (81% based on **2c**); mp 192—193 °C (lit,[14] 179—180 °C); $[\alpha]_D$ +33.2° (*c* 0.918, acetone) (lit,[14] $[\alpha]$+ 34.1° (*c* 1.38, acetone)), $[\alpha]_D$ +140.9° (*c* 1.35, $CHCl_3$); IR (KBr) 3400 and 1730 cm^{-1}; ^1H NMR δ=5.4 (1H, s (br), OH) and 6.5—8.4 (18H, m, Ar-H). Found: C, 71.36; H, 3.96; Br, 15.11%. Calcd for $C_{31}H_{19}BrO_3$: C, 71.69; H, 3.69; Br, 15.38%.

Diesters 4. The synthesis of 1-(1-bromo-2-naphthoyloxy)-2-(3,5-dichloro-2-iodobenzoyloxy)ethane (**4Abc**) is representative. A mixture of **2'c** (prepared from 1.50 g (5.98 mmol) of **2c**) and **3Ab** (1.81 g, 5.01 mmol) in benzene (80 ml) and pyridine (10 ml) was stirred overnight at ambient temperature, and then heated at reflux for 3 h. The reaction was worked up as was stated for the synthesis of monoesters. Silica-gel column chromatography eluting with benzene gave 2.68 g of **4Abc** (90%); mp 105—106 °C; IR (KBr) 1720 cm^{-1}; ^1H NMR δ=4.6 (4H, s, $(CH_2)_2$) and 7.0—8.5 (8H, m, Ar-H). Found: C, 40.52; H, 2.38; halogen, 46.52%. Calcd for $C_{20}H_{12}BrCl_2IO_4$: C, 40.44; H, 2.04; Br+Cl+I, 46.75%.

Similar reactions gave the following diesters; silica-gel column was used for purification of the diester unless otherwise noted.

4Aab: 89% yield, toluene as the eluent; mp 52—54 °C; IR (KBr) 1730 and 1700 cm^{-1}; ^1H NMR δ=4.65 (4H, s, $(CH_2)_2$) and 6.9—8.2 (6H, m, Ar-H). Found: C, 32.88; H, 1.89; halogen, 54.72%. Calcd for $C_{16}H_{10}Cl_2I_2O_4$; C, 32.52; H, 1.71; Cl+I, 54.95%.

4Aac: 90% yield, benzene as the eluent; oil; IR (liq. film) 1720 cm^{-1}; ^1H NMR δ=4.65 (4H, s, $(CH_2)_2$) and 6.9—8.6 (10H, m, Ar-H). Found: C, 45.76; H, 3.08; halogen, 39.71%. Calcd for $C_{20}H_{14}BrIO_4$: C, 45.74; H, 2.69; Br+I, 39.38%.

4Abd: 83% yield, cyclohexane-ethyl acetate (20/1) as the eluent; mp 105—108 °C; IR (KBr) 1720 cm^{-1}, ^1H NMR δ=4.65 (4H, s, $(CH_2)_2$) and 7.0—7.8 (5H, m, Ar-H). Found: C, 30.83; H, 1.67; N, 2.20; halogen; 50.56%. Calcd for $C_{16}H_9Cl_2I_2NO_6$: C, 30.22; H, 1.43; N, 2.02; Cl+I, 51.06%. The discrepancy of the elemental analysis seemed to be caused by deiodination during the column chromatography as judged by coloring.

4Acd: 86% yield, benzene as the eluent; mp 110—112 °C; IR (KBr) 1720 cm^{-1}; ^1H NMR δ=4.65 (4H, s, $(CH_2)_2$) and 7.1—8.5 (9H, m, Ar-H). Found: C, 42.56; H, 2.46; N, 2.15; halogen, 36.66%. Calcd for $C_{20}H_{13}BrINO_6$: C, 42.13; H, 2.30; N, 2.46; Br+I, 36.27%.

4Ace: 90% yield, toluene-hexane (3/1) as the eluent; mp 72—73.5 °C; IR (KBr) 1720 cm^{-1}; ^1H NMR δ=2.4 (3H, s, CH_3), 4.6 (4H, s, $(CH_2)_2$), and 7.0—8.6 (9H, m, Ar-H). Found: C, 51.53; H, 3.36; Br, 32.31%. Calcd for $C_{21}H_{16}Br_2O_4$: C, 51.25; H, 3.28; Br, 32.47%.

4Bce: 87% yield, toluene as the eluent; oil; IR (liq. film) 1720 cm^{-1}; ^1H NMR δ=2.1—2.6 (2H, m, CH_2-$\underline{CH_2}$-CH_2), 2.40 (3H, s, CH_3), 4.4—4.7 (4H, m, O$\underline{CH_2}$-$CH_2\underline{CH_2}$O), and 7.0—8.6 (9H, m, Ar-H). Found: C, 52.03; H, 3.72; Br, 31.37%. Calcd for $C_{22}H_{18}Br_2O_4$: C, 52.20; H, 3.58; Br, 31.57%.

4Cce: 81% yield, benzene-hexane (4/1) as the eluent; mp 73—77 °C; IR (KBr) 1710 cm^{-1}; ^1H NMR δ=1.7—2.1 (4H, m, CH_2-$(\underline{CH_2})_2$-CH_2), 2.3 (3H, s, CH_3), 4.2—4.6 (4H, m, O$\underline{CH_2}$-$(CH_2)_2$-$\underline{CH_2}$O), and 7.0—8.6 (9H, m, Ar-H). Found:

† 1 M=1 mol dm^{-3}.

C, 53.34; H, 3.95; Br, 30.41%. Calcd for $C_{23}H_{20}Br_2O_4$: C, 53.10; H, 3.88; Br, 30.72%.

4Dbc: The monoester **3Dc** (2.50 g, 4.82 mmol) was treated with **2'b** (prepared from 1.90 g of **2b** (5.99 mmol)) in benzene–pyridine in the presence of 50 mg of 4-(dimethylamino)pyridine to give 2.68 g (68% yield) of **4Dbc**; toluene as the eluent on alumina column; mp 99—102 °C; IR (KBr) 1750 cm^{-1}; $[\alpha]_D$ +29.9° (*c* 0.735, $CHCl_3$). Found: C, 55.78; H, 2.38; halogen, 34.11%. Calcd for $C_{38}H_{20}BrCl_2IO_4$; C, 55.78; H, 2.46; Br+Cl+I, 33.94%.

4Dbd: 93% yield, toluene–hexane (3/1) as the eluent; mp 85-90 °C; IR (KBr) 1745 cm^{-1}; $[\alpha]_D$ +46.0° (*c* 0.891, $CHCl_3$). Found: C, 47.20; H, 2.08; N, 1.58; halogen, 37.94%. Calcd for $C_{34}H_{17}Cl_2I_2NO_6$:C, 47.47; H, 1.99; N, 1.63; Cl+I, 37.74%.

4Dcd: 86% yield, toluene as the eluent; mp 103—106 °C; IR (KBr) 1745 cm^{-1}; $[\alpha]_D$ +29.4° (*c* 0.782, $CHCl_3$). Found: C, 57.81; H, 2.45; N, 1.89; halogen, 25.67%. Calcd for $C_{38}H_{21}BrINO_6$: C, 57.46; H, 2.66; N, 1.76; Br+I, 26.03%.

Synthesis of Unsymmetrical Diphenic Acids 7. General procedure for the Ullmann reaction was the same as that described in the previous paper unless otherwise noted.[10] To a vigorously stirred suspension of the activated copper powder (40—100 mg-atom) in DMF (60 ml) heated at gentle reflux, was added a solution of **4** (2—5 mmol) in 40 ml of DMF over a 6-h period under a nitrogen atmosphere. After 2-h heating at reflux, the reaction was treated as before:[10] The reaction mixture was filtered, products were taken into benzene, worked up as usual, and solvents were removed in vacuo. Organic residue was chromatographed on silica-gel column with eluent depicted in Table 1 to isolate the intramolecularly coupled cycle **5**, which was obtained as the first eluting component. Alkaline hydrolysis of **5** (0.3—1.6 mmol) was performed by boiling with KOH (1—2 g) in ethanol(50 ml)–water(3 ml).

Synthesis of 7ab: The treatment of **4Aab** (3.02 g) with 6.5 g of copper powder gave, after usual workup, 1.60 g of organic residue, which was chromatographed on silica-gel column with toluene as the eluent to give 0.878 g of **5Aab** (R_f=0.41 on Merck 60G/toluene) and 50 mg of **6Aab** (R_f=0.31). **5Aab**; mp, 165—167 °C; ^1H NMR δ=3.8—4.3 (2H, m, C<u>H</u>H-C<u>H</u>H), 4.8—5.3 (2H, m, CH<u>H</u>-CH<u>H</u>), and 7.1—8.0 (6H, m, Ar-H). Found: C, 57.17; H, 3.22; Cl, 21.34%. Calcd for $C_{16}H_{10}Cl_2O_4$: C, 57.00; H, 2.99; Cl, 21.03%. **6Aab**: IR (KBr) 1720 cm^{-1}; ^1H NMR δ=4.6 (4H, s, $(CH_2)_2$) and 7.1—8.0 (8H, m, Ar-H).

After a sample of **5Aab** (0.50 g, 1.48 mmol) had been boiled with KOH (1 g) in aq ethanol for 4 h, the mixture was diluted with water, and most of the ethanol was removed under reduced pressure. The aqueous phase was extracted with ether, made acidic by adding concd HCl, and then extracted with ether. After the usual workup, evaporation of the solvent afforded **7ab** as white powder; 0.41 g, 89% yield; mp 204—205 °C; IR (KBr) 2900 (br), 1690, 1400, 1260, 1080, 1000, 800, and 700 cm^{-1}. Found: C, 53.91; H, 2.65; Cl, 23.03%. Calcd for $C_{14}H_8Cl_2O_4$: C, 54.05; H, 2.59; Cl, 22.79%.

Synthesis of 7ac: Treatment of 2.56 g of **4Aac** gave 0.667 g of **5Aac**; mp 58—59 °C; ^1H NMR δ=3.8—4.4 (2H, m, C<u>H</u>H-C<u>H</u>H), 4.8—5.4 (2H, m, CH<u>H</u>-CH<u>H</u>), and 7.1—8.2 (10H, m, Ar-H). Found: C, 75.31; H, 4.30%. Calcd for $C_{20}H_{14}O_4$: C, 75.46; H, 4.43%.

Hydrolysis of 0.50 g of **5Aac** gave 0.39 g of **7ac**; 85% yield; mp 228—230 °C; IR (KBr) 2900 (br), 1680, 1400, 1280, 1240, and 750 cm^{-1}. Found: C, 73.81; H, 4.20%. Calcd for $C_{18}H_{12}O_4$: C, 73.96; H, 4.14%.

Synthesis of 7bc: Treatment of 2.12 g of **4Abc** gave 0.843 g of **5Abc**; mp 60—61 °C; ^1H NMR δ=3.8—4.4 (2H, m, C<u>H</u>H-C<u>H</u>H), 4.9—5.3 (2H, m, CH<u>H</u>-CH<u>H</u>), and 7.1—8.1 (8H, m, Ar-H). Found: C, 61.66; H, 3.26; Cl, 17.98%. Calcd for $C_{20}H_{12}Cl_2O_4$: C, 62.04; H, 3.12; Cl, 18.31%.

Hydrolysis of 0.55 g of **5Abc** gave 0.46 g of **7bc**: 89% yield; mp 238—239 °C; IR (KBr) 2950 (br), 1690, 1280, 1250, 1080, 1010, and 790 cm^{-1}. Found: C, 59.57; H, 2.94; Cl, 19.34%. Calcd for $C_{18}H_{10}Cl_2O_4$: C, 59.86; H, 2.79; Cl, 19.63%.

Synthesis of 7bd: Treatment of 1.95 g of **4Abd** gave 0.661 g of **5Abd**; mp 172—173 °C; ^1H NMR δ=3.7—4.3 (2H, m, C<u>H</u>H-C<u>H</u>H), 4.7—5.4 (2H, m, CH<u>H</u>-CH<u>H</u>), and 7.0—8.3 (5H, m, Ar-H). Found: C, 50.58; H, 2.57; N, 3.45; Cl, 18.25%. Calcd for $C_{16}H_9Cl_2NO_6$: C, 50.29; H, 2.37; N, 3.67; Cl, 18.55%.

Hydrolysis of 0.50 g of **5Abd** gave 0.45 g of **7bd**; 96% yield; mp 276—277 °C; IR (KBr) 2900 (br), 1690, 1530, 1280, 1240, 820, and 690 cm^{-1}. Found: C, 47.63; H, 2.21; N, 3.65; Cl, 20.19%. Calcd for $C_{14}H_7Cl_2NO_6$: C, 47.22; H, 1.98; N, 3.93; Cl, 19.91%.

Synthesis of 7cd. Treatment of 2.15 g of **4Acd** gave 0.520 g of **5Acd**; 260—262 °C; ^1H NMR δ=3.8—4.4 (2H, m, C<u>H</u>H-C<u>H</u>H), 4.8—5.5 (2H, m, CH<u>H</u>-CH<u>H</u>), and 7.2—8.3 (9H, m, Ar-H). Found: C, 65.76; H, 3.66; N, 3.99%. Calcd for $C_{20}H_{13}NO_6$: C, 66.12; H, 3.61; N, 3.86%.

Hydrolysis of 0.35 g of **5Acd** gave 0.31 g of **7cd**: 95% yield, mp 249—250 °C; IR (KBr), 2950 (br), 1690, 1530, 1350, 1280, 1070, and 790 cm^{-1}. Found: C, 63.76; H, 3.63; N, 3.91%. Calcd for $C_{18}H_{11}NO_6$: C, 64.10; H, 3.29; N, 4.15%.

Synthesis of 7ce: Treatment of 1.10 g of **4Ace** gave 0.212 g of **5Ace**; mp, 196—199 °C; ^1H NMR δ=1.92 (3H, s, CH_3), 3.8—4.4 (2H, m, C<u>H</u>H-C<u>H</u>H), 4.7—5.4 (2H, m, CH<u>H</u>-CH<u>H</u>), and 7.1—8.0 (9H, m, Ar-H). Found: C, 76.10; H, 4.94%. Calcd for $C_{21}H_{16}O_4$: C, 75.89; H, 4.85%.

Hydrolysis of 0.15 g of **5Ace** gave 0.12 g of **7ce**; 87% yield; mp 211—215 °C; IR (KBr) 3000 (br), 1690, 1400, 1290, 1250, and 760 cm^{-1}. Found: C, 74.42; H, 4.81%. Calcd for $C_{19}H_{14}O_4$: C, 74.50; H, 4.61%.

From 2.60 g of **4Bce** was obtained 0.55 g of **5Bce**; mp, 180—182.5 °C; ^1H NMR δ=1.9 (3H, s, CH_3), 1.8—2.4 (2H, m, $CH_2\underline{CH_2}CH_2$), 3.7—5.0 (4H, m, $O\underline{CH_2}CH_2\underline{CH_2}O$), and 7.2—8.0 (9H, m, Ar-H). Found: C, 76.53; H, 5.26%. Calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24%.

From 1.73 g of **4Cce** was obtained 0.59 g of **5Cce**; mp, 165—168.5 °C; ^1H NMR δ=1.6—2.0 (4H, m, $CH_2(\underline{CH_2})_2CH_2O$), 1.9 (3H, s, CH_3), 3.8—4.6 (4H, m, $O\underline{CH_2}(CH_2)_2\underline{CH_2}O$), and 7.1—8.0 (9H, m, Ar-H). Found: C, 76.23; H, 5.81%. Calcd for $C_{23}H_{20}O_4$: C, 76.65; H, 5.59%.

Synthesis of (*R*)-7bd: Treatment of 1.65 g of **4Dbd** gave 0.93 g of **5Dbd**; mp 195—198 °C; $[\alpha]_D$ +151.3° (*c* 0.840, $CHCl_3$). Found: C, 67.46; H, 2.81; N, 2.02; Cl, 11.95%. Calcd for $C_{34}H_{17}Cl_2NO_6$: C, 67.34; H, 2.83; N, 2.31; Cl, 11.69%.

A portion of the **5Dbd** (0.53 g, 0.875 mmol) was treated with KOH in aq ethanol as above. The reaction mixture was diluted with 50 ml of water, and most of ethanol was removed in vacuo. The residue was extracted with ether, and the aqueous phase was made acidic with concd HCl, followed by extraction with diethyl ether. Ether extracts were combined, and then extracted with 2 M sodium hydrogencarbonate solution, leaving binaphthol in ether

phase. The diphenic acid and binaphthol were recovered by the usual procedure. Recovered (*R*)-binaphthol (0.22 g, 88%) showed no sigh of racemization as judged by its optical rotation; $[\alpha]_D$ +35.0° (*c* 0.813, THF).

(*R*)-**7bd:** 0.28 g (90% yield); mp 237—238°C; $[\alpha]_D$ +35.0° (*c* 0.485, 95% EtOH); IR (KBr) 3000 (br), 1700, 1530, 1350, 1280, 1240, 820, and 790 cm^{-1}. Found: C, 47.63; H, 2.21; N, 3.65; Cl, 20.19%. The enantiomeric purity of the acid (>99% ee) was confirmed by HPLC analysis by comparing the corresponding racemic acid; the details of the experiment have been reported.[8]

Diphenic acids were converted to *N,N'*-dibutyldiphenamides for HPLC analysis as follows: A mixture of a diphenic acid (5—10 mg) in 0.5 ml of thionyl chloride in a screw-capped bottle was stirred under sonication for 1.5 h at 60 °C. Excess thionyl chloride was removed in vacuo, and then 0.5 ml of butylamine was added. After the mixture had been stirred for 1 h at ambient temperature, excess amine was removed in vacuo. The residue was purified by preparative TLC (ethyl acetate–hexane (2/1)).

Synthesis of (*S*)-7bc: Treatment of 1.55 g of **4Dbc** gave 0.38 g of **5Dbc**; mp 205—208 °C; $[\alpha]_D$+272° (*c* 2.22, $CHCl_3$). Found: C, 75.01; H, 2.94; Cl, 11.35%. Calcd for $C_{38}H_{20}Cl_2O_4$: C, 74.64; H, 3.30; Cl, 11.60%.

Hydrolysis of 0.20 g of **5Dbc** gave 0.11 g of (*S*)-**7bc**; 93% yield; mp 238—239 °C; $[\alpha]_D$ −1.3° (*c* 1.57, THF), −18.6° (*c* 1.02, $CHCl_3$); IR (KBr) 2900 (br), 1700, 1440, 1400, 1270, 1230, 790, and 760 cm^{-1}. Found: C, 59.41; H, 2.73; Cl, 19.26%.

Synthesis of (*S*)-7cd: Treatment of 1.45 g of **4Dcd** gave 0.47 g of **5Dcd**; mp 324—326 °C; $[\alpha]_D$ +201° (*c* 0.762, $CHCl_3$). Found: 78.04; H, 4.01; N,2.26%. Calcd for $C_{38}H_{21}NO_6$: C, 77.68; H, 3.60; N, 2.38%.

Hydrolysis of 0.25 g of **5Dcd** gave 0.13 g of (*S*)-**7cd**; 91% yield; mp 210—212 °C; $[\alpha]_D$ +42.0° (*c* 1.95, THF), +30.4° (*c* 0.520, 95% EtOH); IR (KBr) 2900 (br), 1690, 1530, 1345, 1300, 1070, 1010, 790, 770, and 750 cm^{-1}. Found: C, 64.10, H, 3.19; N, 4.09%.

This work was partly supported by a Grant-in-Aid for Scientific Research No. 62550539 from the Ministry of Education, Science and Culture.

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