Asymmetric Synthesis of Axially Chiral 1,1'-Biphenyl-2-carboxylates *via* Nucleophilic Aromatic Substitution on 2-Menthoxybenzoates by Aryl Grignard Reagents

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A practical method is presented for an asymmetric synthesis of axially chiral 1,1'-biphenyl-2-carboxylates *via* the ester-assisted nucleophilic aromatic substitution reaction. Thus, upon treatment of 2-*tert*-butylphenyl 2-[(−)-menthoxy]benzoates with an aryl Grignard reagent, chirality of the leaving (−)-menthoxy group is transferred to the newly formed biphenyl linkage with up to 94% optical yield.

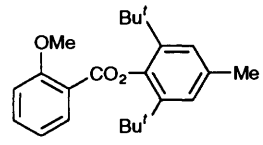
Although a variety of methods exist for the preparation of biphenyls by aryl–aryl bond-forming reactions,[1,2] those which can be used for the asymmetric synthesis of axially chiral biphenyls are severely limited.† Several papers have dealt with induction of axial chirality into the newly formed biphenyl bond by intramolecular coupling of the two aryl halves bonded to chiral templates.[5] As for intermolecular coupling, asymmetric versions of the Ullmann reaction[6] or the oxidative phenolic or non-phenolic coupling reaction[7] have precedence for the synthesis of C_2-symmetric biphenyls. To date, however, the chiral oxazoline-assisted Meyers reaction in which the *ortho* methoxy group in an (*o*-methoxyaryl)oxazoline is displaced by an aryl Grignard reagent[8] is the only one of practical utility for the preparation of axially chiral, unsymmetrical biphenyls.[9,10] Thus, development of a new methodology for the construction of the atropisomeric biphenyl unit is a synthetic challenge because it occurs widely in biologically active natural products,[11] and, more interestingly, these kinds of optically active biphenyls,[12] as well as binaphthyl counterparts,[13] have recently proved to be of potential importance as efficient chiral discriminators in a variety of asymmetric reactions and molecular recognitions.

We have shown in previous papers[3,14] that an ester functionality substantially activates the *ortho* alkoxy group for nucleophilic aromatic substitution (S_NAr); 2,6-dialkylphenyl 2-methoxybenzoic esters (*e.g.* compound **1**) react with aryl Grignard reagents to give the 1,1'-biphenyl-2-carboxylates in good to excellent yields.[15] Herein we describe an extension of the ester-assisted biphenyl coupling reaction to a convenient synthesis of axially chiral biphenyls (see Scheme 2).[16]

Results and Discussion

Ester-assisted Asymmetric Biphenyl Coupling Reaction.—It is known that a minimum of three *ortho* substituents are required for an axially chiral biphenyl to have substantial stability toward racemization under ordinary conditions.[9] We reported that synthesis of binaphthyls can be efficiently achieved in an asymmetric manner by the use of an enantiomeric menthoxy leaving group with isopropoxycarbonyl as the activating group (*e.g.* compound **2**) for the S_NAr reaction.[3] On the other hand, in the case of synthesis of biphenyls, 2,6-di-*tert*-butylphenyl protecting groups are required in general, in order to prevent the addition to the ester carbonyl by the Grignard reagent.[15]

† Several highly stereoselective asymmetric syntheses of axially chiral binaphthyls have been developed in the last decade.[3,4]



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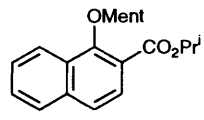

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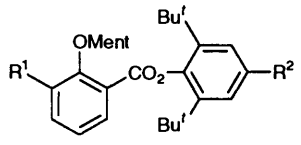
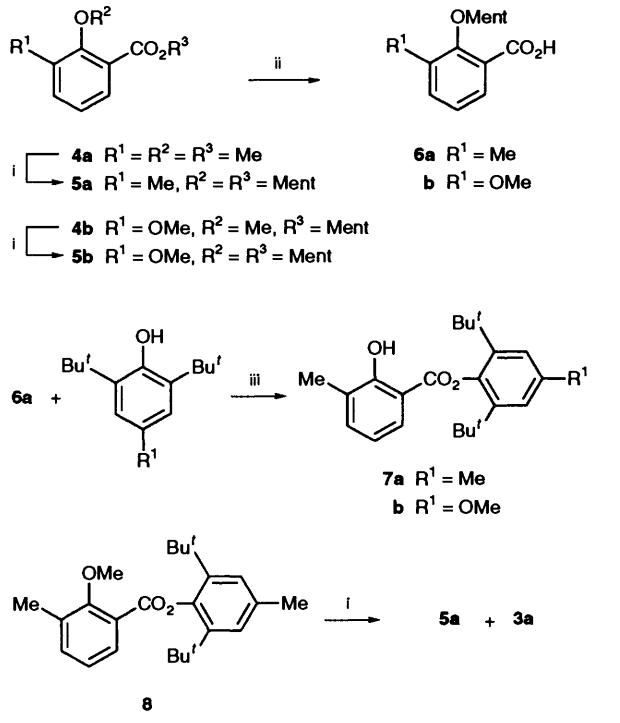


Ment = (−)-menthyl

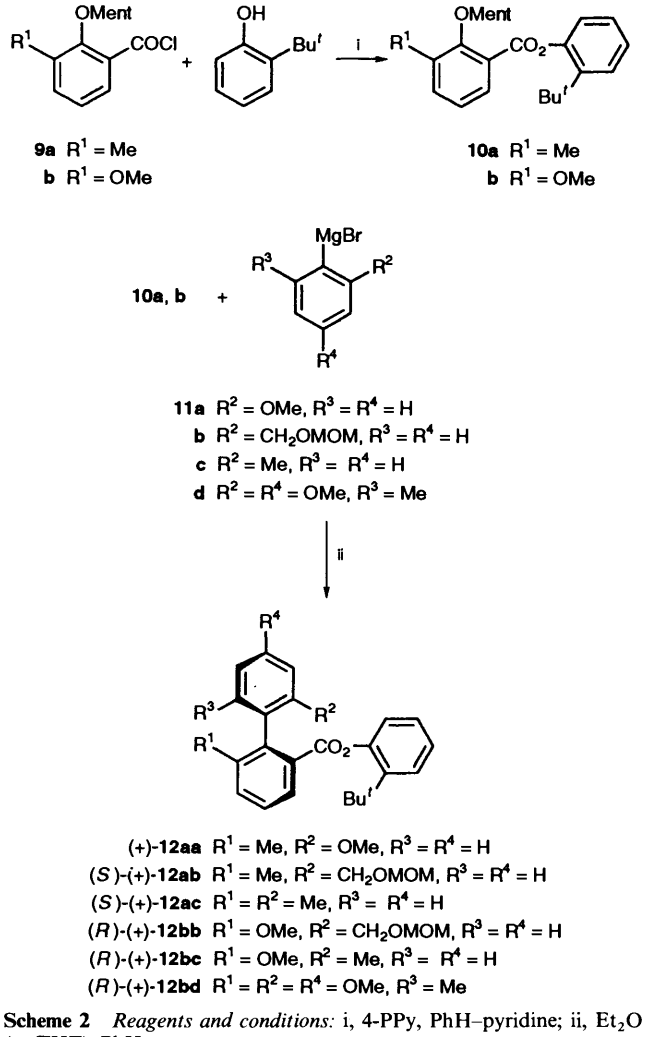
3a R^1 = Me, R^2 = Me
b R^1 = OMe, R^2 = Me

Therefore, our initial effort was directed toward the preparation of 2,6-di-*tert*-butylphenyl 2-[(−)-menthoxy]-benzoic esters **3** as substrates for the asymmetric S_NAr biphenyl synthesis. The requisite 2-[(−)-menthoxy]benzoic acids **6** were easily prepared from the corresponding 2-methoxybenzoates **4** by reaction with sodium menthoxide in dimethylformamide (DMF) followed by alkaline hydrolysis (Scheme 1).[13] However, acid chlorides of compounds **6** failed to react with a 2,6-di-*tert*-butyl-4-methylphenol. Several attempts to esterify 2,6-di-*tert*-butylphenols with 2-[(−)-menthoxy]-3-methylbenzoic acid **6a** in trifluoroacetic anhydride (TFAA) inevitably led to dementhoxylation to give the salicylates **7**. Nucleophilic displacement of the methoxy group of 2,6-di-*tert*-butyl-4-methylphenyl 2-methoxy-3-methylbenzoate **8** by reaction with (−)-menthoxide actually proceeded to give the desired ester **3a** in miserable yield but accompanied by transesterification to regenerate the menthyl ester **5a** as the major product.

As was stated previously, steric compatibility of the bulk of an ester alkyl moiety and that of an attacking Grignard reagent is crucial for the ester-assisted biphenyl coupling to proceed successfully with prevention of the well known Grignard addition to the ester group's carbonyl functionality.[15] Detailed CPK and Dreiding molecular-model inspections suggested that the ester carbonyl of a 2-[(−)-menthoxy]benzoic acid might effectively be protected from nucleophilic attack as a 2-*tert*-butylphenyl ester because the bulky (−)-menthoxy and *tert*-butyl substituent should reside on opposite sides of the plane defined by the relevant benzoate ring due to steric reasons as schematically visualized by stereostructures **10A** and **10B** (see Scheme 5).



Scheme 1 *Reagents and conditions:* i, MentONa, DMF; ii, KOH, aq. EtOH; then conc. HCl; iii, TFAA



Scheme 2 *Reagents and conditions:* i, 4-PPy, PhH–pyridine; ii, Et_2O (or THF)–PhH

The requisite 2-*tert*-butylphenyl esters **10** were readily obtainable in good yield by treatment of acid chlorides **9** with 2-*tert*-butylphenol in benzene–pyridine in the presence of 4-pyrrolidinopyridine (4-PPy) (Scheme 2). To our pleasure, the reaction of 2-*tert*-butylphenyl 2-[(−)-menthoxy]benzoates **10** with several Grignard reagents **11** proceeded nicely upon addition of a solution of Grignard **11** in diethyl ether or tetrahydrofuran (THF) to a benzene solution of an ester **10**; the corresponding biphenyl-2-carboxylates **12** were obtained in good to excellent yields as well as with moderate to good stereoselectivity except in the synthesis of compound **12ac** (see below) (Table 1). It should be noted that the *tert*-butylphenyl protecting group can easily be removed from the coupling products **12** to liberate the free biphenyl-2-carboxylic acids by treatment with potassium hydroxide in aq. ethanol at room temperature. Reaction variables were not necessarily optimized but were chosen so that the coupling reaction could proceed within a practical timescale while keeping the reaction temperature as low as possible. As shown previously, the biphenyl coupling reaction prefers less coordinating solvents, *e.g.* diethyl ether–benzene, rather than strongly coordinating ones, *e.g.* THF.[15] In entries 2 and 4, however, THF was required to solubilize Grignard reagent **11b**. Stoichiometry of the nucleophile **11** to the substrate ester **10** did not matter, as long as an excess of the former was applied; Grignard reagents **11** prepared from 2.0 mol equiv. of the corresponding aryl bromides were applied to ensure the complete use of the 2-menthoxybenzoates **10**.

Determination of the Enantioselectivity of the Biphenyl Coupling Reaction.—The enantiomeric purities of biphenyl-2-carboxylates **12** were determined by initially treating them with $LiAlH_4$ in THF at room temperature to give the 2-hydroxymethyl derivatives, which were then converted into α-methoxy-α-(trifluoromethyl)phenylacetates (MTPA esters). Diastereoisomeric excesses (d.e.s) of the latter were determined by ^1H NMR spectroscopy at 60 MHz with the aid of the lanthanoid shift reagent europium tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionate) [Eu(fod)$_3$].[17] The d.e. values thus determined were cited in Table 1 as the minimum estimation of the enantiomeric excesses (e.e.s) of the biphenyl-2-carboxylates **12** taking into account the axial lability of 2,2′,6-trisubstituted biphenyls and probable racemization during the sequence of treatments (see Experimental section).[9]

Determination of the Absolute Configurations of the Biphenyl Axes.—Although extensive stereochemical data, including chiroptical as well as X-ray crystallographical, have been accumulated for C_2-symmetric optically active biphenyls to allow their configurational assignment,[18] the stereochemistry of unsymmetrical biphenyl atropisomers still remains to be elucidated.

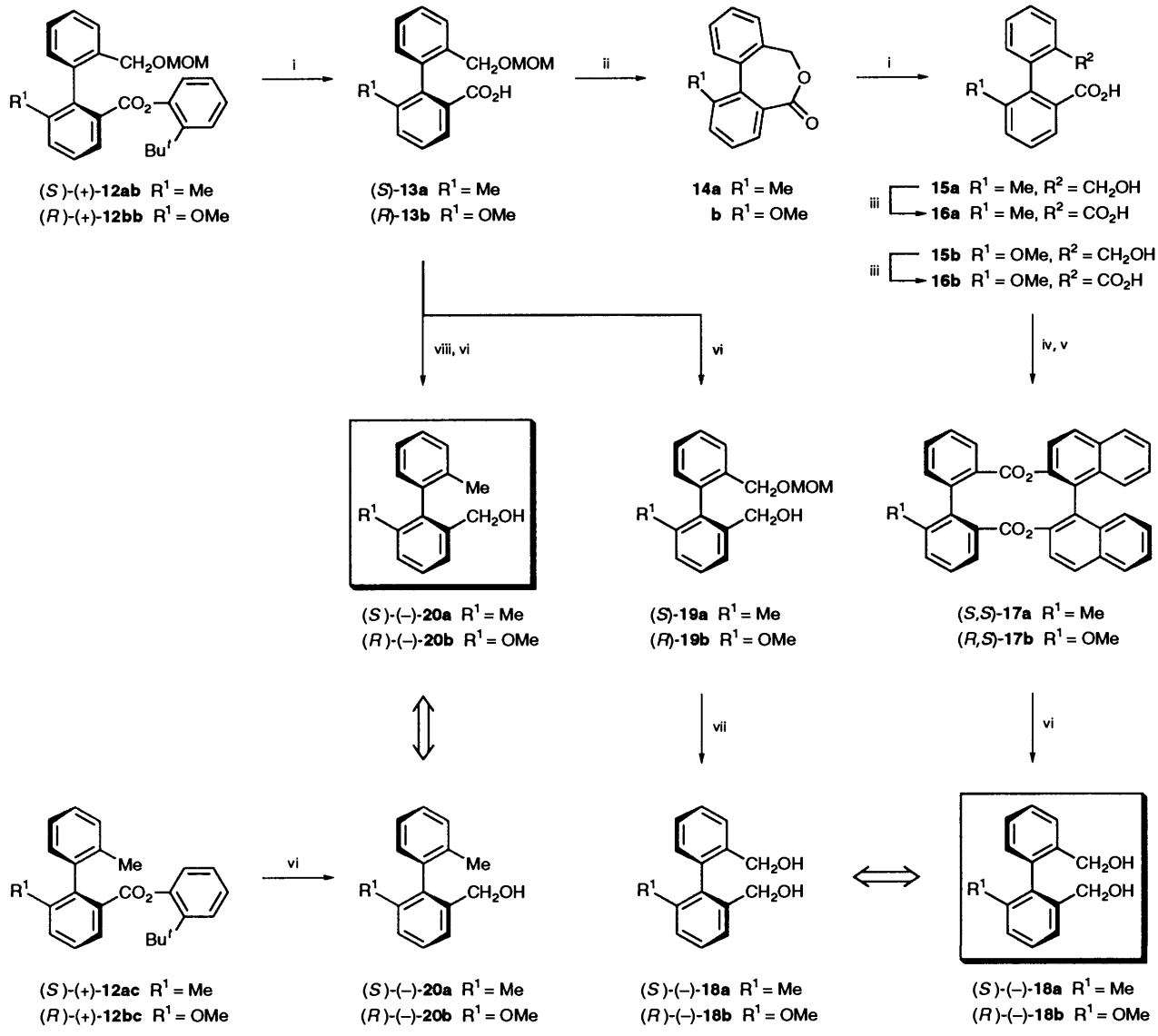
The absolute configurations of the biphenyl coupling products **12ab** and **12ac** were determined by chemical correlation to 2,2′-bis(hydroxymethyl)-6-methyl-1,1′-biphenyl **18a** and 2-hydroxymethyl-2′,6-dimethyl-1,1′-biphenyl **20a**, respectively (Scheme 3). The configurations of 2,2′-bis(hydroxymethyl)-1,1′-biaryls such as compounds **18** could be determined by the axial chirality recognition method developed in this laboratory, which is based on the steric requirement for the formation of a 12-membered cyclic diester, *e.g.* a compound **17**, containing two sets of biaryl units joined by ester-CO_2-linkages between the *ortho,ortho′*-positions.[5d,19]

Compound (+)-**12ab** was hydrolysed to acid **13a**, acidic treatment of which removed the methoxymethyl (MOM) group but caused cyclization with complete racemization to optically inactive lactone **14a**,[20] which was then hydrolysed to racemic 2′-hydroxymethyl-6-methyl-1,1′-biphenyl-2-carboxylic acid **15a**.

Table 1 Asymmetric synthesis of 1,1′-biphenyl-2-carboxylates **12**

Entry	10	11	Solvent[a]	Temp. [time (*t*/*h*)]	Product 12	Yield[b] (%)	E.e. (%)	Configuration
1	**10a**	**11a**	A	*c* [3]	**12aa**	65	62	(*S*)[e]
2	**10a**	**11b**	B	*d* [6]	**12ab**	92	67	*S*
3	**10a**	**11c**	A	*d* [24]	**12ac**	45	22	*S*
4	**10b**	**11b**	B	*c* [7]	**12bb**	95	75	*R*
5	**10b**	**11c**	A	*c* [6]	**12bc**	95	56	*R*
6	**10b**	**11d**	A	*c* [24]	**12bd**	92	94	*R*

[a] Solvent: A, Et_2O–PhH; B, THF–PhH. [b] Isolated yield based on substrate **10**. [c] Room temp. [d] Reflux. [e] Suggested from mechanistic considerations (see text).



Scheme 3 *Reagents and conditions:* i, KOH, aq. EtOH; then conc. HCl; ii, 4 mol dm^{-3} HCl, THF; iii, $KMnO_4$, acetone–water; iv, $SOCl_2$; v, (*S*)-bi-2-naphthol, DMAP, PhH–pyridine; vi, $LiAlH_4$, THF; vii, 6 mol dm^{-3} HCl, THF; viii, 10% Pd/C, EtOH

Oxidation of the hydroxymethyl side chain of compound **15a** gave 6-methyldiphenic acid **16a**. Treatment of the bis(acid chloride) of *rac*-**16a** with (*S*)-bi-2-naphthol allowed cyclization of only the (*S*)-**16a**-derived substrate to give enantiomerically pure cyclic diester (*S*,*S*)-**17a**. Reductive cleavage of diester **17a** with $LiAlH_4$ gave 2,2′-bis(hydroxymethyl)-6-methyl-1,1′-biphenyl (*S*)-(−)-**18a**, the enantiomeric integrity of which was confirmed by ^1H NMR analysis after converting it into the bis-MTPA ester. On the other hand, reduction of the carboxylic function of monoacid **13a** followed by removal of the MOM group *via* compound **19a** gave diol (−)-**18a**. Consequently, the axial chirality of the biphenyl product (+)-**12ab** was determined to be *S*.

Reductive removal of the MOMO group of monoacid (*S*)-**13a** under neutral conditions, followed by reduction of the carboxylic acid function, gave the biphenylylmethanol (*S*)-(−)-**20a**. On the other hand, treatment of the coupling product (+)-**12ac** with $LiAlH_4$ afforded the alcohol (−)-**20a**. Thus, the starting compound (+)-**12ac** should have the *S* axis as shown in Scheme 3. Determination of the absolute configurations of

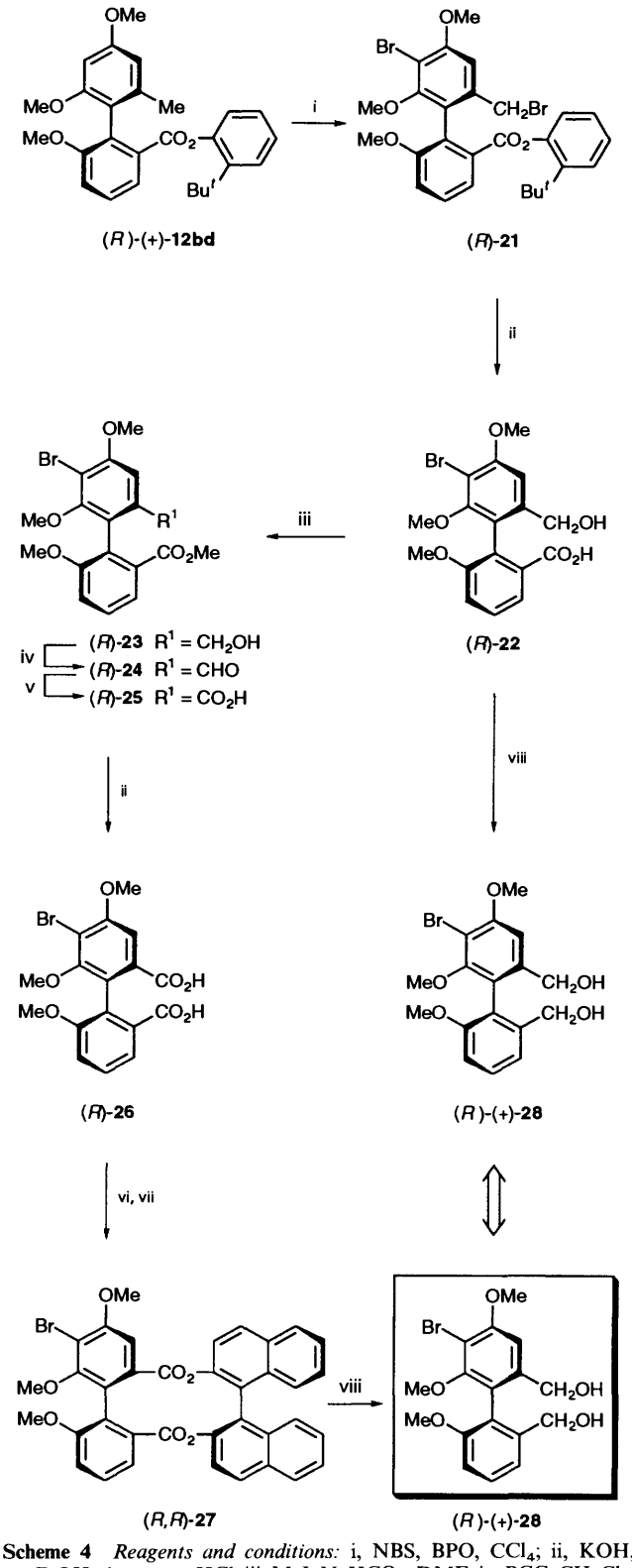
biphenyl products **12bb** and **12bc** followed similar procedures as above (Scheme 3).

Scheme 4 summarizes the determination of the absolute configuration of biphenylcarboxylate (+)-**12bd**. In an intended bromination of the methyl side chain, treatment of carboxylate **12bd** with *N*-bromosuccinimide (NBS) gave the nuclear bromination product preferentially. Then, compound **12bd** was converted into dibromide **21**, which was hydrolysed to carboxylic acid **22**. Attempted direct oxidation of the hydroxymethyl side chain of compound **22** by treatment with potassium permanganate resulted in a complex mixture which contained the desired diphenic acid **26** but only in poor yield.[21] Thus, carboxylic acid **22** was esterified to methyl ester **23**, the 2'-hydroxymethyl substituent of which was first oxidized to aldehyde **24** by treatment with pyridinium chlorochromate (PCC) and this was then subjected to permanganate oxidation to dicarboxylic monoester **25** followed by hydrolysis to diphenic acid **26**.

The bis(acid chloride) of diacid **26** was cyclized with (*R*)-bi-2-naphthol to give cyclic diester **27** which should have (*R*,*R*)-biaryl stereochemistry. This material was reductively cleaved to give diol (*R*)-(+)-**28**. On the other hand, $LiAlH_4$ reduction of biphenylcarboxylic acid **22** gave diol (+)-**28**. These interconversions establish the axis of the *ortho*,*ortho'*-tetrasubstituted biphenyl (+)-**12bd** should be *R*.

Mechanistic Consideration of the Asymmetric Induction in the Biphenyl Coupling Reaction.—In our previous paper, the addition–elimination mechanism proposed by Meyers for the oxazoline-assisted S_NAr reaction[4,10] was modified to the ester-assisted binaphthyl coupling reaction.[3] Essentially the same model can explain the asymmetric induction in the biphenyl coupling reaction (Scheme 5). CPK molecular models suggest that the most strain-free conformers of ester **10** are those in which the carbinyl hydrogen (CHO-) of the menthoxy moiety is disposed toward the pertinent benzoate ring for steric reasons (**10A** and **10B**). Since approach of an aryl Grignard nucleophile from the α-face of a conformer **10A** may cause significant steric repulsion between the organomagnesium species and the (−)-menthyl substituent (chelated complex **29A**), approach from the β-face should be preferred, to form chelated complex **29B**. A reaction sequence comprising phenyl migration to form σ-complexes **30** followed by elimination of menthoxy to give biphenylcarboxylates **12** will determine the axial twist of the biphenyl linkage: Strong intramolecular ligation of the 2-methoxy (MeO) or methoxymethoxymethyl ($MOMOCH_2$) group to the magnesium centre seems to override the steric repulsion between the 6'-R substituent and the phenyl ring undergoing the substitution to give the coupling products **12ab**, **12bb** and **12bd** *via* path a. On the other hand, a phenyl Grignard reagent lacking those ligating substituents (compound **11c**) should prefer path b to give biphenyls **12ac** and **12bc**. Although rotational lability around the biphenyl axis of compound **12aa** prohibited the assignment of its stereochemistry, the mechanistic arguments above strongly suggest that compound (+)-**12aa** should have an *S* axis.

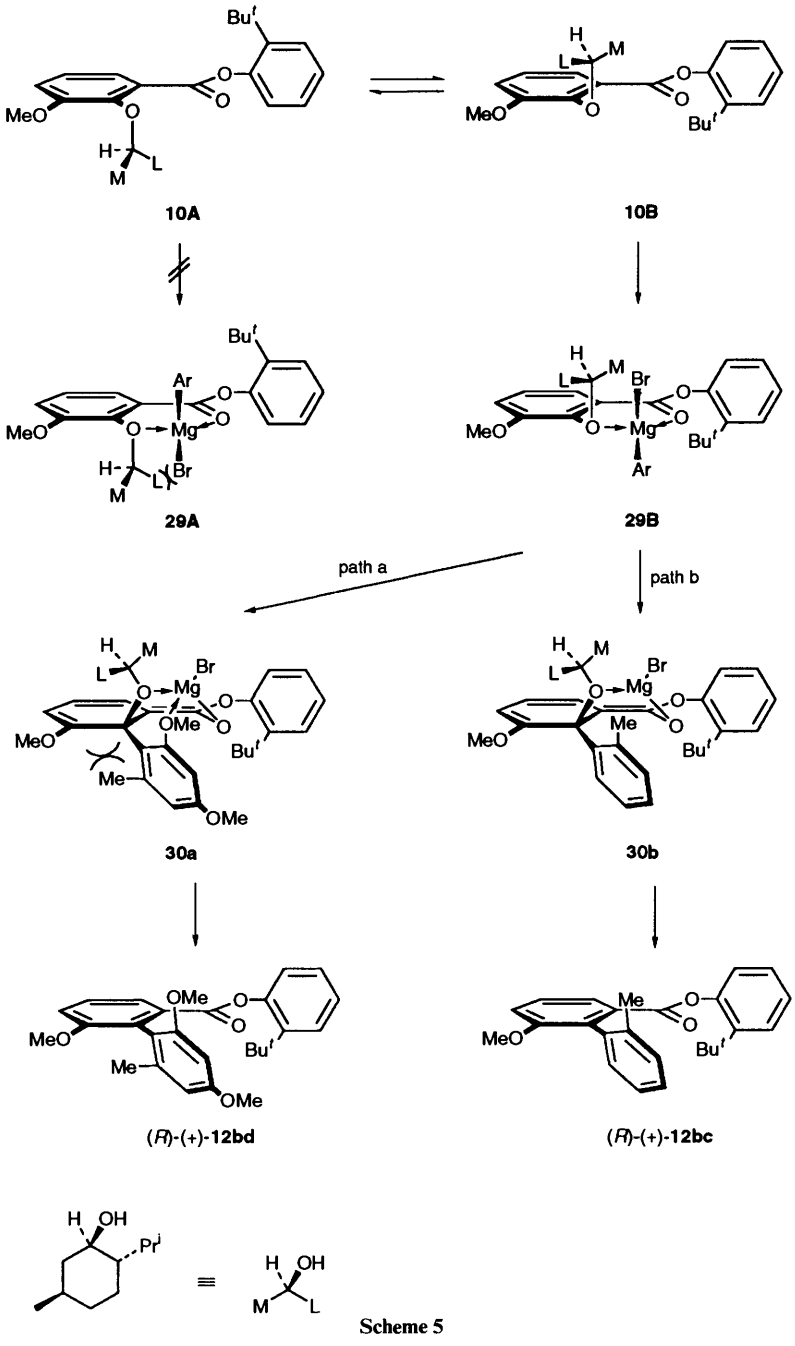
Inspection of the results in Table 1 reveals some interesting trends concerning the apparent steric bulk of the *ortho* substituents on both reagents **11** and substrates **10**. Judging from the yields of the biphenyl products, the apparent bulk of a MeO group seems smaller than that of a Me substituent (entries 3 and 5 compare the effect of the 6-Me and MeO substituent of substrates **10**, and entries 1 and 3 that of the 2-MeO and Me substituent of reagent **11**, respectively). It has been suggested that strong intramolecular ligation of an *ortho* MeO to a magnesium centre reduces the apparent steric bulk of a 2-methoxyphenyl Grignard reagent.[15,22] The mediocre yield and poor stereoselectivity in the synthesis of compound **12ac**



Scheme 4 *Reagents and conditions:* i, NBS, BPO, CCl_4; ii, KOH, aq. EtOH; then conc. HCl; iii, MeI, $NaHCO_3$, DMF; iv, PCC, CH_2Cl_2; v, $KMnO_4$, acetone–water; vi, $SOCl_2$; vii, (*R*)-bi-2-naphthol, DMAP, PhH–pyridine; viii, $LiAlH_4$, THF

may be accounted for by assuming that steric hindrance and lack of ligating substituent retard the formation of a well assembled σ-complex **30**.

In conclusion, a practical method, which rivals the Meyers procedure,[9,10] is presented for the construction of axially chiral biphenyl structures in good to excellent yields and with reasonable stereoselectivity and predictable stereochemistry.



Scheme 5

Experimental

M.p.s were taken using a Yamato MP-21 apparatus and are uncorrected. Optical rotations were measured on a Union Giken PM-101 or JASCO DIP-4S polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Shimadzu IR-460 spectrophotometer. ^1H NMR spectra were recorded on a Bruker AC-250T or JEOL JNM-FX60 spectrometer using tetramethylsilane as internal standard and $CDCl_3$ as solvent unless otherwise stated. *J*-Values are given in Hz. Merck silica gel $60GF_{254}$ was used for analytical and preparative TLC (PLC). Silica gel columns were prepared by use of Nacalai silica gel 60 (70–230 mesh). Water- and air-sensitive reactions were routinely carried out under nitrogen. Diethyl ether, benzene and THF were distilled from sodium diphenylketyl just before use. Other solvents for experiments requiring anhydrous conditions were purified by usual methods. Acetone (2.5 dm^3) was treated with 2% aq. $KMnO_4$ (150 cm^3) and conc. HCl (30 cm^3) at room temperature overnight and then distilled through a Widmer distillation column. Commercial materials were used as purchased. 1-Bromo-2-(methoxymethoxymethyl)benzene, 1-bromo-2,4-dimethoxy-6-methylbenzene and methyl 2-methoxy-3-methylbenzoate **4a** were synthesized according to the literature procedures.[23–25]

Preparation of 2-tert-*Butylphenyl Ester* **10a**.—(−)-*Menthyl* 2-[(−)-*menthoxy*]-3-*methylbenzoate* **5a**. Ester **5a** was prepared by a similar procedure to that described in the previous paper.[3] To sodium (−)-menthoxide obtained by the reaction of (−)-menthol (56.3 g, 360 mmol) with NaH (60% dispersion in mineral oil; 14.4 g, 360 mmol) were added dry DMF (50 cm^3) and the methyl ester **4a** (13.0 g, 72.1 mmol) and the mixture was stirred at 90 °C for 10 h. After the excess of (−)-menthol had been distilled off (66–70 °C/267 Pa), the residue was chromatographed on a silica gel column with hexane–ethyl acetate (9 : 1 to 1 : 1) as the eluent to give menthyl ester **5a** (14.3 g,

46%) as an oil, ν_{max}(neat)/cm^{-1} 1723 (CO); δ_H(60 MHz) 0.77–2.74 (36 H, m, menthyl H), 2.29 (3 H, s, Me), 3.85–4.22 (1 H, m, OCH), 4.75–5.15 (1 H, m, CO_2CH) and 6.80–7.49 (3 H, m, ArH).

2-[(−)-*Menthoxy*]-3-*methylbenzoic acid* **6a**. Ester **5a** (11.5 g, 26.8 mmol) was boiled with KOH (7.10 g) in a mixture of ethanol (60 cm^3) and water (6.0 cm^3) for 10 h. After most of the ethanol had been evaporated off, the residue was dissolved in water and washed with diethyl ether. The aqueous layer was acidified by addition of conc. HCl to liberate the free acid, which was extracted with diethyl ether, and the extract was washed with water and dried over $MgSO_4$. After the solvent had been evaporated off, the residue was dried *in vacuo* to give acid **6a** (7.30 g, 94%) as a yellow oil, ν_{max}(neat)/cm^{-1} 3130 (OH) and 1744 (CO); δ_H(250 MHz) 0.80–1.83 (17 H, m, menthyl H), 2.37 (3 H, s, Me), 2.40–2.61 (1 H, m, menthyl H), 4.28 (1 H, td, *J* 10.8 and 4.1, OCH), 7.16 (1 H, t, *J* 7.7, ArH), 7.39 (1 H, dd, *J* 7.3 and 1.0, ArH), 8.01 (1 H, dd, *J* 7.8 and 1.7, ArH) and 11.5 (1 H, br s, OH).

2-tert-*Butylphenyl* 2-[(−)-*menthoxy*]-3-*methylbenzoate* **10a**. Acid **6a** (3.00 g, 10.3 mmol) was heated under reflux for 2 h in thionyl dichloride (15 cm^3) in the presence of several drops of DMF, and volatiles were removed under reduced pressure to give the chloride **9a**.

The acid chloride **9a** was dissolved in dry benzene (15 cm^3) and the solution was added dropwise to a mixture of 2-*tert*-butylphenol (3.10 g, 20.6 mmol), 4-PPy (3.00 g, 20.2 mmol), benzene (35 cm^3) and pyridine (4.0 cm^3). Then the mixture was refluxed for 2 h. The cooled mixture was diluted with diethyl ether, washed successively with 2 mol dm^{-3} HCl, 2 mol dm^{-3} Na_2CO_3, and water, and dried over $MgSO_4$. After the solvents had been evaporated off, excess of 2-*tert*-butylphenol was distilled off by use of a Kugelrohr (70 °C/200 Pa) and the residue was chromatographed on a silica gel column with hexane–benzene (7 : 3) as the eluent to give *compound* **10a** (3.70 g, 85%) as an oil (Found: C, 79.7; H, 9.0. $C_{28}H_{38}O_3$ requires C, 79.6; H, 9.1%); ν_{max}(neat)/cm^{-1} 1743 (CO); δ_H(250 MHz) 0.75–1.78 (17 H, m, menthyl H), 1.38 (9 H, s, Bu^t), 2.37 (3 H, s, Me), 2.40–2.58 (1 H, m, menthyl H), 4.22 (1 H, td, *J* 10.4 and 4.0, OCH), 7.02–7.49 (6 H, m, ArH) and 7.86 (1 H, dd, *J* 7.9 and 1.6, ArH).

Preparation of 2-tert-*Butylphenyl Ester* **10b**.—This compound was prepared by a similar procedure to that used for the preparation of its analogue **10a** except that (−)-menthyl ester **4b** was used instead of methyl ester **4a**.

(−)-*Menthyl* 2,3-*dimethoxybenzoate* **4b**. 2,3-Dimethoxybenzoyl chloride prepared from 2,3-dimethoxybenzoic acid (25.2 g, 138 mmol) was treated with a solution of (−)-menthol (32.4 g, 207 mmol) in benzene (250 cm^3)–pyridine (56 cm^3) in the presence of 4-(dimethylamino)pyridine (DMAP) (20.3 g, 166 mmol) at room temperature for 1 h. After the usual work-up, distillation under reduced pressure by use of a Kugelrohr (110 °C/133 Pa) gave the ester **4b** (24.8 g) as a pale yellow oil. The residue was chromatographed on a silica gel column eluting with hexane–ethyl acetate (95 : 5) to give an additional crop of ester **4b** (4.20 g) for a total yield of 29.0 g (65%), ν_{max}(neat)/cm^{-1} 1718 (CO); δ_H(60 MHz) 0.75–2.36 (18 H, m, menthyl H), 3.88 (6 H, s, OMe), 4.72–5.14 (1 H, m, CO_2CH) and 6.93–7.37 (3 H, m, ArH).

(−)-*Menthyl* 2-[(−)-*menthoxy*]-3-*methoxybenzoate* **5b**. To sodium (−)-menthoxide obtained by the reaction of (−)-menthol (12.0 g, 76.8 mmol) with NaH (60% dispersion in mineral oil; 3.00 g, 75.0 mmol) were added DMF (70 cm^3) and compound **4b** (16.4 g, 51.2 mmol) and the mixture was stirred at 90 °C for 15 h. Distillation under reduced pressure by use of a Kugelrohr (170 °C/67 Pa) gave compound **5b** (16.2 g, 71%) as a pale yellow oil, ν_{max}(neat)/cm^{-1} 1724 (CO); δ_H(60 MHz) 0.77–2.82 (36 H, m, menthyl H), 3.80 (3 H, s, OMe), 4.07–4.47 (1 H, m, OCH), 4.72–5.13 (1 H, m, CO_2CH) and 6.87–7.36 (3 H, m, ArH).

2-[(−)-*Menthoxy*]-3-*methoxybenzoic acid* **6b**. Ester **5b** (11.0 g, 24.7 mmol) was boiled with KOH (6.50 g) in ethanol (60 cm^3) containing water (6.0 cm^3) for 3 h and the mixture was worked up to give the acid **6b** (7.10 g, 94%) as an oil, ν_{max}(neat)/cm^{-1} 3165 (OH) and 1748 (CO); δ_H(60 MHz) 0.81–2.67 (18 H, m, menthyl H), 3.89 (3 H, s, OMe), 4.55–4.94 (1 H, m, OCH), 7.14 (2 H, d, *J* 5.3, ArH), 7.73 (1 H, t, *J* 5.3, ArH) and 11.48 (1 H, br s, OH).

2-tert-*Butylphenyl* 2-[(−)-*menthoxy*]-3-*methoxybenzoate* **10b**. 2-[(−)-Menthoxy]-3-methoxybenzoyl chloride **9b** prepared from the acid **6b** (5.10 g, 16.6 mmol) was treated with a solution of 2-*tert*-butylphenol (5.00 g, 33.3 mmol) in benzene (50 cm^3)–pyridine (6.5 cm^3) in the presence of 4-PPy (4.90 g, 33.1 mmol) at room temperature for 1 h. After excess of 2-*tert*-butylphenol had been distilled off, the residue was chromatographed on a silica gel column with hexane–benzene (1 : 2) as the eluent to give *ester* **10b** (6.40 g, 88%) as an oil (Found: C, 76.9; H, 8.7. $C_{28}H_{38}O_4$ requires C, 76.7; H, 8.7%); ν_{max}(neat)/cm^{-1} 1750 (CO); δ_H(250 MHz) 0.74–1.78 (17 H, m, menthyl H), 1.36 (9 H, s, Bu^t), 2.41–2.63 (1 H, m, menthyl H), 3.84 (3 H, s, OMe), 4.41 (1 H, td, *J* 10.4 and 4.1, OCH), 7.10–7.32 (5 H, m, ArH), 7.43 (1 H, dd, *J* 7.5 and 1.8, ArH) and 7.52–7.62 (1 H, m, ArH).

Attempted Syntheses of 2,6-*Di*-tert-*butylphenyl* 2-[(−)-*Menthoxy*]*benzoates*.—*Reaction of acid* **6a** *with* 2,6-*di*-tert-*butyl*-4-*methoxyphenol*. A mixture of acid **6a** (2.18 g, 7.51 mmol), 2,6-di-*tert*-butyl-4-methoxyphenol (1.79 g, 7.57 mmol) and TFAA (10 cm^3) was stirred at room temperature for 27 h and was then refluxed for 1 h. After the cooled mixture had been diluted with benzene (100 cm^3), 2 mol dm^{-3} NaOH (100 cm^3) was carefully added. The two layers were separated and the organic layer was washed successively with 2 mol dm^{-3} NaOH and water, and dried over $MgSO_4$. After the solvent had been evaporated off, the residue was recrystallized from ethanol to give ester **7b** (1.06 g, 38%) as crystals, ν_{max}(KBr)/cm^{-1} 3115 (OH) and 1679 (CO); δ_H(60 MHz) 1.32 (18 H, s, Bu^t), 2.30 (3 H, s, Me), 3.82 (3 H, s, OMe), 6.77–8.04 (5 H, m, ArH) and 11.03 (1 H, s, OH).

Reaction of compound **8** *with sodium* (−)-*menthoxide*. This reaction was performed by a similar procedure to that used for the preparation of compound **5a** from its analogue **4a**. To sodium (−)-menthoxide obtained by the reaction of (−)-menthol (293 mg, 1.87 mmol) with NaH (60% dispersion in mineral oil; 71.0 mg, 1.78 mmol) were added DMF (4.0 cm^3) and ester **8** (106 mg, 288 μmol) and the mixture was stirred at 60 °C for 3 h. PLC with hexane–benzene (4 : 1) as the developer gave the following two products.

Ester **5a** (42.4 mg, 34%) as an oil, spectral data of which were identical with those of compound **5a** obtained from its analogue **4a**.

Ester **3a** (13.7 mg, 10%) as crystals, ν_{max}(KBr)/cm^{-1} 1742 (CO); δ_H(60 MHz) 0.72–2.34 (18 H, m, menthyl H), 1.33 (18 H, s, Bu^t), 2.33 (6 H, s, Me), 4.18–4.62 (1 H, m, OCH), 6.94–7.48 (4 H, m, ArH) and 8.14 (1 H, dd, *J* 7.6 and 1.8, ArH).

Asymmetric Synthesis of Biphenyl-2-carboxylates **12**. *General Procedure*.—General procedure for Grignard reaction was similar to that described in the previous paper.[3] To a solution of an ester **10** (1.00 mmol) in dry benzene (3.5 cm^3) was added a Grignard reagent **11** which had been prepared from the corresponding aryl bromide (2.00 mmol) and magnesium turnings (80.0 mg) in dry diethyl ether or THF (3.5 cm^3) and dissolved by addition of benzene (3.5 cm^3). The mixture was stirred for 3–24 h at appropriate temperature. See Table 1 for reaction conditions and the yield of the corresponding product

12. PLC with hexane–ethyl acetate as the developer was used for purification of the products.

The following compounds were obtained by this procedure.

2-tert-*Butylphenyl 2'-methoxy-6-methyl-1,1'-biphenyl-2-carboxylate* **12aa**. As *crystals*, m.p. 88.1–89.0 °C (Found: C, 80.1; H, 7.1. $C_{25}H_{26}O_3$ requires C, 80.2; H, 7.0%); $[\alpha]_D^{23}$ +33.6 (*c* 0.88, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1739 (CO); δ_H(250 MHz) 1.27 (9 H, s, Bu^t), 2.11 (3 H, s, Me), 3.70 (3 H, s, OMe), 6.62–6.71 (1 H, m, ArH), 6.87–7.51 (9 H, m, ArH) and 7.93 (1 H, d, *J* 7.7, ArH).

2-tert-*Butylphenyl 2'-methoxymethoxymethyl-6-methyl-1,1'-biphenyl-2-carboxylate* **12ab**. As an *oil* (Found: C, 77.3; H, 7.3. $C_{27}H_{30}O_4$ requires C, 77.5; H, 7.2%); $[\alpha]_D^{18}$ +19.1 (*c* 0.64, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1747 (CO); δ_H(250 MHz) 1.29 (9 H, s, Bu^t), 2.06 (3 H, s, Me), 3.23 (3 H, s, OMe), 4.29 (2 H, s, CH_2), 4.52 (2 H, s, CH_2), 6.52–6.61 (1 H, m, ArH), 7.02–7.55 (9 H, m, ArH) and 7.94 (1 H, dd, *J* 7.9 and 1.1, ArH).

2-tert-*Butylphenyl 2',6-dimethyl-1,1'-biphenyl-2-carboxylate* **12ac**. As an *oil* (Found: C, 83.5; H, 7.4. $C_{25}H_{26}O_2$ requires C, 83.8; H, 7.3%); $[\alpha]_D^{23}$ +4.4 (*c* 6.60, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1748 (CO); δ_H(250 MHz) 1.29 (9 H, s, Bu^t), 2.04 (3 H, s, Me), 2.06 (3 H, s, Me), 6.40–6.50 (1 H, m, ArH), 7.02–7.57 (9 H, m, ArH) and 7.88 (1 H, d, *J* 7.7, ArH).

2-tert-*Butylphenyl 6-methoxy-2'-methoxymethoxymethyl-1,1'-biphenyl-2-carboxylate* **12bb**. As an *oil* (Found: C, 74.8; H, 7.0. $C_{27}H_{30}O_5$ requires C, 74.6; H, 7.0%); $[\alpha]_D^{17}$ +18.8 (*c* 1.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1747 (CO); δ_H(250 MHz) 1.28 (9 H, s, Bu^t), 3.26 (3 H, s, OMe), 3.76 (3 H, s, OMe), 4.39 (2 H, q, *J* 22.1 and 12.4, CH_2), 4.56 (2 H, q, *J* 11.5 and 6.6, CH_2), 6.48–6.58 (1 H, m, ArH), 7.02–7.58 (9 H, m, ArH) and 7.64 (1 H, dd, *J* 7.8 and 0.9, ArH).

2-tert-*Butylphenyl 6-methoxy-2'-methyl-1,1'-biphenyl-2-carboxylate* **12bc**. As *crystals*, m.p. 82.5–83.3 °C (Found: C, 80.3; H, 7.1. $C_{25}H_{26}O_3$ requires C, 80.2; H, 7.0%); $[\alpha]_D^{23}$ +12.7 (*c* 1.50, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1730 (CO); δ_H(250 MHz) 1.27 (9 H, s, Bu^t), 2.12 (3 H, s, Me), 3.77 (3 H, s, OMe), 6.38–6.46 (1 H, m, ArH), 7.02–7.34 (8 H, m, ArH), 7.47 (1 H, t, *J* 7.9, ArH) and 7.59 (1 H, dd, *J* 7.7 and 1.3, ArH).

2-tert-*Butylphenyl 2',4',6-trimethoxy-6'-methyl-1,1'-biphenyl-2-carboxylate* **12bd**. As *crystals*, m.p. 140–141 °C (Found: C, 74.5; H, 7.1. $C_{27}H_{30}O_5$ requires C, 74.6; H, 7.0%); $[\alpha]_D^{21}$ +47.2 (*c* 1.39, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1741 (CO); δ_H(250 MHz) 1.28 (9 H, s, Bu^t), 2.01 (3 H, s, Me), 3.63 (3 H, s, OMe), 3.77 (3 H, s, OMe), 3.78 (3 H, s, OMe), 6.32 (1 H, d, *J* 2.2, ArH), 6.39 (1 H, d, *J* 2.2, ArH), 6.61–6.67 (1 H, m, ArH), 7.04–7.15 (2 H, m, ArH), 7.20 (1 H, dd, *J* 8.3 and 0.6, ArH), 7.28–7.36 (1 H, m, ArH), 7.46 (1 H, t, *J* 8.0, ArH) and 7.71 (1 H, dd, *J* 8.0 and 0.8, ArH).

Determination of the Optical Purity of the Coupling Product **12**. *General Procedure*.—To a solution of an ester **12** (~0.1 mmol) in THF (1.5 cm^3) was added a suspension of $LiAlH_4$ (38.0 mg, 1.00 mmol) in THF (1.5 cm^3) at 0 °C and the mixture was stirred at room temperature for 6–12 h. Then the mixture was cooled to 0 °C and quenched by successive addition of ethyl acetate (2.0 cm^3), water (2.0 cm^3) and 2 mol dm^{-3} HCl (15 cm^3). After the resulting mixture had been allowed to warm to room temperature, it was extracted with diethyl ether, and the extracts were washed with water and dried over $MgSO_4$. PLC with hexane–ethyl acetate as the developer gave the 2-hydroxymethyl derivative in greater than 70% yield, which was treated with 1.5 equiv. of the acid chloride of (*S*)-MTPA in benzene–pyridine in the presence of 3.0 mol equiv. of DMAP at room temperature for 12 h. PLC with hexane–ethyl acetate as the developer gave the MTPA ester almost quantitatively. ^{1}H NMR analysis of the sample in C_6D_6 differentiated well the methoxy signals of MTPA moieties of (*S,S*)- and (*R,S*)-ester by successive addition of Eu(fod)$_3$.[17]

Determination of the Absolute Configuration of the Coupling Product **12ab**.—*Hydrolysis of ester* **12ab** *to 2'-methoxymethoxymethyl-6-methyl-1,1'-biphenyl-2-carboxylic acid* **13a**. A mixture of ester **12ab** (5.80 g, 13.9 mmol), KOH (5.00 g), ethanol (50 cm^3) and water (5.0 cm^3) was stirred at room temperature for 6 h and worked up as mentioned for the preparation of acid **6a** except that conc. HCl was added at 0 °C to give acid **13a** (3.70 g, 93%) as a yellow oil, $[\alpha]_D^{22}$ −26.8 (*c* 1.53, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2935 (OH) and 1690 (CO); δ_H(250 MHz) 1.98 (3 H, s, Me), 3.09 (3 H, s, OMe), 4.29 (2 H, q, *J* 20.4 and 11.0, CH_2), 4.44 (2 H, q, *J* 26.2 and 6.7, CH_2), 7.03–7.53 (6 H, m, ArH) and 7.71 (1 H, d, *J* 6.1, ArH).

Acidic treatment of acid **13a** *to 1-methyl-5,7-dihydrodibenzo*[c,e]*oxepin-5-one* **14a**. To a solution of acid **13a** (3.40 g, 11.9 mmol) in THF (20 m^3) was added 4 mol dm^{-3} HCl (17 cm^3) and the mixture was stirred at room temperature for 10 h. To it was added further 2 mol dm^{-3} HCl (10 cm^3) and the mixture was extracted with diethyl ether. The organic layer was washed successively with 2 mol dm^{-3} Na_2CO_3 and water, and dried over $MgSO_4$. After the solvents had been evaporated off, the residue was dried *in vacuo* to give crude tricycle **14a** (2.10 g), a sample (30.4 mg) of which was purified by PLC with hexane–ethyl acetate (4:1) as the eluent to give an analytical sample (27.8 mg, 72%) as crystals, m.p. 96.5–97.3 °C; ν_{max}(KBr)/cm^{-1} 1708 (CO); δ_H(250 MHz) 2.45 (3 H, s, Me), 4.96 (2 H, q, *J* 36.0 and 11.8, CH_2), 7.39–7.70 (6 H, m, ArH) and 7.74 (1 H, d, *J* 7.6, ArH).

Hydrolysis of compound **14a** *to 2'-hydroxymethyl-6-methyl-1,1'-biphenyl-2-carboxylic acid* **15a**. A mixture of crude lactone **14a** (1.80 g), KOH (2.00 g), ethanol (20 cm^3) and water (2.0 cm^3) was stirred at room temperature for 8 h and worked up as mentioned for the preparation of acid **6a** except that conc. HCl was added at 0 °C to give acid **15a** (1.80 g, 63% based on diether **13a**) as pale yellow crystals, m.p. 129–130 °C; ν_{max}(KBr)/cm^{-1} 3195 (OH) and 1674 (CO); δ_H(250 MHz) 1.91 (3 H, s, Me), 4.28 (2 H, s, CH_2), 6.41 (2 H, br s, OH), 6.94 (1 H, d, *J* 7.3, ArH), 7.26–7.48 (5 H, m, ArH) and 7.67 (1 H, d, *J* 7.4, ArH).

A sample of acid **15a** (14.7 mg, 60.7 μmol) was esterified by treatment with an excess of diazomethane in diethyl ether at room temperature to give methyl 2'-hydroxymethyl-6-methyl-1,1'-biphenyl-2-carboxylate. Optical purity of the ester was determined to be no more than 2% e.e. by ^{1}H NMR spectroscopy in C_6D_6 in the presence of Eu(fod)$_3$ after conversion into the (*S*)-MTPA ester.

Oxidation of hydroxy acid **15a** *to 6-methyl-1,1'-biphenyl-2,2'-dicarboxylic acid* **16a**. To a refluxing solution of acid **15a** (1.60 g, 6.60 mmol) in acetone (100 cm^3) was added dropwise aq. $KMnO_4$ (3.10 g, 19.6 mmol in 100 cm^3) over a period of 30 min and the mixture was refluxed for 3 h. To the cooled brown suspension were added 2 mol dm^{-3} Na_2SO_3 (50 cm^3) and 4 mol dm^{-3} H_2SO_4 (50 cm^3) to form a clear solution with evolution of SO_2 gas. After most of the acetone had been evaporated off, the residue was dissolved in 2 mol dm^{-3} NaOH (150 cm^3) and washed with diethyl ether. The aqueous layer was acidified by addition of conc. HCl to liberate the free acid, which was extracted with diethyl ether, and this extract was washed with water and dried over $MgSO_4$. After the solvent had been evaporated off, benzene (50 cm^3) was added to the residue and the mixture was heated under reflux. After 30 min the mixture was filtered hot and the insoluble solid was dried *in vacuo* to give diacid **16a** (904 mg, 53%), m.p. 224–226 °C; ν_{max}(KBr)/cm^{-1} 2995 (OH) and 1688 (CO); δ_H(250 MHz; [$^2H_6$]acetone) 1.94 (3 H, s, Me), 7.09 (1 H, dd, *J* 7.8 and 1.2, ArH), 7.30–7.61 (4 H, m, ArH), 7.82 (1 H, d, *J* 7.4, ArH), 8.07 (1 H, d, *J* 7.6, ArH) and 9.60 (2 H, br s, OH).

Treatment of diacid rac-**16a** *with* (S)-*bi-2-naphthol to afford cyclic diester* (S,S)-*16-methyl-12,21-dihydrodibenzo*[h,j]*dinaphtho*[2,1-b:1,2-d]-*1,6-dioxacyclododecapentaene-12,21-dione* (S,S)-**17a**. Racemic diacid **16a** (650 mg, 2.54 mmol) was heated under reflux for 3 h in thionyl dichloride (15 cm^3) in the presence of several drops of DMF, and volatiles were then

removed under reduced pressure. The acid chloride was dissolved in benzene (150 cm^3). Also prepared was a solution of (*S*)-bi-2-naphthol (740 mg, 2.58 mmol) in benzene (150 cm^3). To a well stirred, boiled solution of DMAP (611 mg, 5.00 mmol) in benzene (100 cm^3)–pyridine (10 cm^3) were added dropwise the two solutions at the same rate over a period of 1 h. After addition was complete, the mixture was refluxed for a further 1 h and was then worked up as mentioned for the preparation of ester **10a**. PLC with hexane–dichloromethane (1:1) as developer gave *heptacycle* (S,S)-**17a** (120 mg, 9%) as crystals, m.p. 253–255 °C (Found: C, 82.9; H, 4.5. $C_{35}H_{22}O_4$ requires C, 83.0; H, 4.4%); $[\alpha]_D^{20}$ −205.6 (*c* 1.67, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1752 (CO); δ_H(250 MHz) 2.14 (3 H, s, Me), 7.00 (2 H, t, *J* 9.2, ArH), 7.12–7.58 (12 H, m, ArH), 7.67 (1 H, d, *J* 8.3, ArH) and 7.82–7.97 (4 H, m, ArH).

Reductive cleavage of compound (S,S)-**17a** *to* (S)-2,2′-*bis*-(*hydroxymethyl*)-6-*methyl*-1,1′-*biphenyl* (S)-**18a**. To a solution of compound (*S,S*)-**17a** (106 mg, 209 μmol) in THF (10 cm^3) was added $LiAlH_4$ (111 mg, 2.92 mmol) portionwise at 0 °C and the mixture was stirred at room temperature for 12 h before being cooled to 0 °C and quenched by successive additions of ethyl acetate (4.0 cm^3), water (2.0 cm^3), and 2 mol dm^{-3} HCl (14 cm^3). After the resulting mixture had warmed to room temperature, it was extracted with diethyl ether, and the extracts were washed with water and dried over $MgSO_4$. PLC with hexane–dichloromethane (1:2) as developer gave laevorotatory *diol* (S)-**18a** (39.5 mg, 83%) as crystals, m.p. 108–110 °C (Found: C, 78.85; H, 7.05. $C_{15}H_{16}O_2$ requires C, 78.9; H, 7.1%); $[\alpha]_D^{22}$ −58.0 (*c* 0.79, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3255 (OH); δ_H(250 MHz) 1.92 (3 H, s, Me), 2.50 (2 H, br s, OH), 4.17–4.35 (4 H, m, CH_2) and 7.03–7.57 (7 H, m, ArH).

The enantiopurity of the sample was confirmed by ^1H NMR spectroscopy in C_6D_6 in the presence of Eu(fod)$_3$ after conversion into the bis-MTPA ester.

Reduction of acid **13a** *to* 2-*hydroxymethyl*-2′-*methoxymethoxymethyl*-6-*methyl*-1,1′-*biphenyl* **19a**. Reduction of acid **13a** was performed by a similar procedure to that used for bis-lactone (*S,S*)-**17a**. Acid **13a** (241 mg, 842 μmol) was treated with $LiAlH_4$ (160 mg, 4.22 mmol) in THF (10 cm^3) at room temperature for 12 h. PLC with hexane–ethyl acetate (2:1) as the developer gave the alcohol **19a** (200 mg, 87%) as an oil, ν_{max}(neat)/cm^{-1} 3410 (OH); δ_H(60 MHz) 1.94 (3 H, s, Me), 3.13 (3 H, s, OMe), 4.22 (2 H, s, CH_2), 4.24 (2 H, s, CH_2), 4.44 (2 H, q, *J* 8.7 and 6.7, CH_2) and 6.82–7.79 (7 H, m, ArH).

2,2′-*Bis*(*hydroxymethyl*)-6-*methyl*-1,1′-*biphenyl* **18a** *from mono-alcohol* **19a**. To a solution of compound **19a** (193 mg, 709 μmol) in THF (5.0 cm^3) was added 6 mol dm^{-3} HCl (3.0 cm^3) and the mixture was stirred at room temperature for 40 h. Water (10 cm^3) was added and the mixture was extracted with diethyl ether. The organic layer was washed with brine and dried over $MgSO_4$. After the solvents had been evaporated off, the residue was purified by PLC with hexane–ethyl acetate (7:3) to give diol **18a** (120 mg, 74%) as crystals, m.p. 97.5–98.7; $[\alpha]_D^{22}$ −39.2 (*c* 2.46, $CHCl_3$).

The negative sign of the specific rotation of the sample indicated its axial chirality to be *S*. Thus, the axial chirality of the coupling product **12ab** was determined to be *S*.

Determination of the Absolute Configuration of the Coupling Product **12ac**.—*Reduction of acid* (S)-**13a** *to* (S)-2-*hydroxymethyl*-2′,6-*dimethyl*-1,1′-*biphenyl* (S)-**20a**. Acid **13a**, whose axial chirality was determined to be *S* by the above procedure, was used for this transformation. A suspension of palladium on carbon (10 w/w %, 100 mg) in ethanol (1.0 cm^3) was stirred at room temperature under hydrogen for 1 h. To this mixture was added a solution of acid **13a** (110 mg, 384 μmol) in ethanol (1.0 cm^3) and the mixture was stirred at room temperature. The reaction was monitored by TLC, and another suspension of palladium on carbon (50.0 mg) in ethanol (1.0 cm^3) was added every 4 h. After 24 h, the catalyst was filtered off, the filtrate was evaporated, and the residue was dried *in vacuo* to give an oil, which was dissolved in THF (10 cm^3). To this solution was added $LiAlH_4$ (210 mg, 5.53 mmol) at 0 °C and the mixture was stirred at room temperature for 10 h. After the same work-up as mentioned for bis-lactone (*S,S*)-**17a**, PLC with hexane–ethyl acetate (2:1) gave laevorotatory alcohol (*S*)-**20a** (28.5 mg, 35%) as an oil, $[\alpha]_D^{20}$ −6.6 (*c* 1.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3335 (OH); δ_H(250 MHz) 1.96 (3 H, s, Me), 1.97 (3 H, s, Me), 4.28 (2 H, s, CH_2) and 6.98–7.55 (7 H, m, ArH).

Optical purity of the sample was determined to be 50% e.e. by ^1H NMR spectroscopy in C_6D_6 in the presence of Eu(fod)$_3$ after conversion into the MTPA ester. This means that at least 17% racemization had occurred during the hydrogenolysis as evidenced by comparison with the result in Table 1 (entry 2).

2-*Hydroxymethyl*-2′,6-*dimethyl*-1,1′-*biphenyl* **20a** *from the coupling product* **12ac**. Reduction of compound **12ac** was performed by the general procedure used for determination of the optical purity of coupling products **12**, to give *compound* (−)-**20a** as an oil (Found: C, 84.95; H, 7.7. $C_{15}H_{16}O$ requires C, 84.9; H, 7.6%); $[\alpha]_D^{23}$ −2.2 (*c* 4.70, $CHCl_3$).

The negative sign of the specific rotation of the sample indicated its axial chirality to be *S*. Thus, the axial chirality of the coupling product **12ac** was determined to be *S*.

Determination of the Absolute Configuration of the Coupling Product **12bb**.—The same procedure as mentioned for the analogue **12ab** was employed unless otherwise noted.

Hydrolysis of coupling product **12bb** *to* 6-*methoxy*-2′-*methoxymethoxymethyl*-1,1′-*biphenyl*-2-*carboxylic acid* **13b**. Starting from coupling product **12bb** (5.40 g, 12.4 mmol), compound **13b** (3.50 g, 93%) was obtained as a pale yellow oil, ν_{max}(neat)/cm^{-1} 2950 (OH) and 1699 (CO); δ_H(250 MHz) 3.10 (3 H, s, OMe), 3.70 (3 H, s, OMe), 4.28–4.58 (4 H, m, CH_2), 7.04–7.55 (7 H, m, ArH) and 9.86 (1 H, br s, OH).

Acidic treatment of compound **13b** *to give* 1-*methoxy*-5,7-*dihydrodibenzo*[c,e]*oxepin*-5-*one* **14b**. Starting from compound **13b** (3.20 g, 10.6 mmol), crude lactone **14b** (3.80 g) was obtained, a sample (38.5 mg) of which was purified by PLC to give an analytical sample (22.0 mg, 85%) as crystals, m.p. 147 °C; ν_{max}(KBr)/cm^{-1} 1708 (CO); δ_H(250 MHz) 3.85 (3 H, s, OMe), 4.97 (2 H, q, *J* 37.5 and 11.9, CH_2), 7.20 (1 H, dd, *J* 7.8 and 1.4, ArH), 7.34–7.58 (5 H, m, ArH) and 7.84 (1 H, dd, *J* 6.4 and 1.8, ArH).

Hydrolysis of lactone **14b** *to* 2′-*hydroxymethyl*-6-*methoxy*-1,1′-*biphenyl*-2-*carboxylic acid* **15b**. Starting from crude lactone **14b** (3.6 g), compound **15b** (2.10 g, 77% based on acid **13b**) was obtained as crystals, m.p. 145–146 °C; ν_{max}(KBr)/cm^{-1} 3020 (OH) and 1702 (CO); δ_H(250 MHz; [$^2H_6$]acetone) 3.70 (3 H, s, OMe), 4.40 (2 H, q, *J* 16.0 and 12.6, CH_2), 6.97 (1 H, dd, *J* 7.3 and 1.5, ArH) and 7.20–7.58 (6 H, m, ArH).

The sample was found to be a racemic modification by ^1H NMR spectroscopy in C_6D_6 in the presence of Eu(fod)$_3$ after conversion into the MTPA ester of methyl 2′-hydroxymethyl-6-methoxy-1,1′-biphenyl-2-carboxylate, which had been prepared from acid **15b** (23.1 mg, 89.4 μmol).

Oxidation of acid **15b** *to* 6-*methoxy*-1,1′-*biphenyl*-2,2′-*dicarboxylic acid* **16b**. Starting from hydroxy acid **15b** (2.00 g, 7.74 mmol), diacid **16b** (800 mg, 38%) was obtained as crystals, m.p. 217–219 °C; ν_{max}(KBr)/cm^{-1} 3005 (OH) and 1687 (CO); δ_H(250 MHz; [$^2H_6$]acetone) 3.67 (3 H, s, OMe), 7.11 (1 H, d, *J* 7.3, ArH), 7.20 (1 H, d, *J* 8.1, ArH), 7.40 (2 H, t, *J* 8.5, ArH), 7.53 (2 H, t, *J* 8.5, ArH), 8.03 (1 H, d, *J* 7.6, ArH) and 10.81 (2 H, br s, OH).

Treatment of diacid rac-**16b** *with* (S)-*bi*-2-*naphthol to give cyclic diester* (R,S)-16-*methoxy*-12,21-*dihydrodibenzo*[h,j]*dinaphtho*[2,1-b:1,2-d]-1,6-*dioxacyclododecapentaene*-12,21-*dione* (R,S)-**17b**. Starting from diacid *rac*-**16b** (600 mg, 2.20 mmol), *bis-lactone* (R,S)-**17b** (253 mg, 22%) was obtained as crys-

tals, m.p. 282–283 °C (Found: C, 80.5; H, 4.2. $C_{35}H_{22}O_5$ requires C, 80.45; H, 4.2%); $[\alpha]_D^{20}$ −237 (*c* 1.01, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1748 (CO); δ_H(250 MHz) 3.76 (3 H, s, OMe), 6.98 (2 H, t, *J* 7.5, ArH), 7.05–7.59 (12 H, m, ArH), 7.66 (1 H, d, *J* 7.7, ArH) and 7.82–7.96 (4 H, m, ArH).

Reductive cleavage of bis-lactone (R,S)-**17b** *to* (R)-2,2′-*bis*-(*hydroxymethyl*)-6-*methoxy*-1,1′-*biphenyl* (R)-**18b**. Starting from bis-lactone (*R,S*)-**17b** (153 mg, 293 μmol), laevorotatory *diol* (R)-**18b** (62.8 mg, 88%) was obtained as crystals after PLC with hexane–ethyl acetate (2:1) as developer, m.p. 110–112 °C (Found: C, 73.9; H, 6.7. $C_{15}H_{16}O_3$ requires C, 73.75; H, 6.6%); $[\alpha]_D^{20}$ −65.1 (*c* 0.43, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3210 (OH); δ_H(250 MHz) 2.76 (2 H, br s, OH), 3.70 (3 H, s, OMe), 4.20–4.38 (4 H, m, CH_2), 6.93 (1 H, d, *J* 8.3, ArH) and 7.05–7.55 (6 H, m, ArH).

Reduction of acid **13b** *to* 2-*hydroxymethyl*-6-*methoxy*-2′-*methoxymethoxymethyl*-1,1′-*biphenyl* **19b**. Starting from acid **13b** (252 mg, 834 μmol), compound **19b** (221 mg, 92%) was obtained as an oil, ν_{max}(neat)/cm^{-1} 3425 (OH); δ_H(250 MHz) 2.34 (1 H, br s, OH), 3.10 (3 H, s, OMe), 3.69 (3 H, s, OMe), 4.26 (2 H, q, *J* 22.7 and 11.9, CH_2), 4.29 (2 H, s, CH_2), 4.44 (2 H, q, *J* 32.2 and 6.7, CH_2), 6.91 (1 H, d, *J* 8.3, ArH) and 7.09–7.53 (6 H, m, ArH).

2,2′-*Bis*(*hydroxymethyl*)-6-*methoxy*-1,1′-*biphenyl* **18b** *from mono-alcohol* **19b**. Starting from **19b** (188 mg, 652 μmol), compound **18b** (126 mg, 79%) was obtained as crystals, m.p. 96.2–98.0 °C; $[\alpha]_D^{20}$ −53.2 (*c* 0.57, $CHCl_3$).

The negative sign of the specific rotation of the sample indicated its axial chirality to be *R*. Thus, the axial chirality of the coupling product **12bb** was determined to be *R*.

Determination of the Absolute Configuration of the Coupling Product **12bc**.—The same procedure as mentioned for coupling product **12ac** was employed unless otherwise noted.

Reduction of acid (R)-**13b** *to* (R)-2-*hydroxymethyl*-6-*methoxy*-2′-*methyl*-1,1′-*biphenyl* (R)-**20b**. Starting from acid **13b** (151 mg, 499 μmol), laevorotatory alcohol (*R*)-**20b** (34.3 mg, 30%) was obtained as an oil, $[\alpha]_D^{20}$ −25.0 (*c* 1.01, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3265 (OH); δ_H(250 MHz) 1.44 (1 H, br s, OH), 2.02 (3 H, s, Me), 3.72 (3 H, s, OMe), 4.32 (2 H, s, CH_2), 6.93 (1 H, d, *J* 7.8, ArH), 7.04–7.32 (5 H, m, ArH) and 7.38 (1 H, t, *J* 8.0, ArH).

Optical purity of the sample was determined to be 62% e.e. by ^{1}H NMR spectroscopy in C_6D_6 in the presence of Eu(fod)$_3$ after conversion into the MTPA ester. This means that at least 13% racemization had occurred during the hydrogenolysis as evidenced by comparison with the result in Table 1 (entry 4).

2-*Hydroxymethyl*-6-*methoxy*-2′-*methyl*-1,1′-*biphenyl* **20b** *from the coupling product* **12bc**. Starting from compound **12bc** (123 mg, 328 μmol), the *alcohol* **20b** (65.1 mg, 87%) was obtained as an oil (Found: C, 78.7; H, 7.2. $C_{15}H_{16}O_2$ requires C, 78.9; H, 7.1%); $[\alpha]_D^{23}$ −20.1 (*c* 0.8, $CHCl_3$).

The negative sign of the specific rotation of the sample indicated its axial chirality to be *R*. Thus, the axial chirality of the coupling product **12bc** was determined to be *R*.

Determination of the Absolute Configuration of the Coupling Product **12bd**.—*Dibromination of compound* **12bd** *to give* 2-*tert*-*butylphenyl* 3′-*bromo*-6′-*bromomethyl*-2′,4′,6-*trimethoxy*-1,1′-*biphenyl*-2-*carboxylate* **21**. To a solution of compound **12bd** (4.30 g, 9.90 mmol) in CCl_4 (100 cm^3) were added NBS (7.30 g, 41.0 mmol) and dibenzoyl peroxide (BPO) (240 mg, 991 μmol), and the mixture was refluxed for 5 h. After the mixture had cooled to room temperature, precipitates were filtered off and the filtrate was evaporated to dryness. Chromatography on a silica gel column with hexane–ethyl acetate (4:1) as the eluent gave *dibromide* **21** (5.10 g, 87%) as crystals, m.p. 91.2–92.8 °C (Found: C, 54.8; H, 4.8; Br, 26.7. $C_{27}H_{28}Br_2O_5$ requires C, 54.75; H, 4.8; Br, 27.0%); $[\alpha]_D^{21}$ +22.8 (*c* 2.00, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1739 (CO); δ_H(250 MHz) 1.31 (9 H, s, Bu^t), 3.66 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.89 (3 H, s, OMe), 4.34 (2 H, q, *J* 21.0 and 9.8, CH_2), 6.48 (1 H, s, ArH), 6.79 (1 H, dd, *J* 7.0 and 2.1, ArH), 7.06–7.19 (2 H, m, ArH), 7.26 (1 H, td, *J* 3.7 and 0.9, ArH), 7.35 (1 H, dd, *J* 6.8 and 2.4, ArH), 7.56 (1 H, t, *J* 8.1, ArH) and 7.90 (1 H, dd, *J* 7.9 and 0.9, ArH).

Hydrolysis of dibromide **21** *to* 3′-*bromo*-6′-*hydroxymethyl*-2′,4′,6-*trimethoxy*-1,1′-*biphenyl*-2-*carboxylic acid* **22**. A mixture of dibromide **21** (4.50 g, 7.60 mmol), KOH (20.0 g), ethanol (200 cm^3) and water (20 cm^3) was stirred at room temperature for 20 h and worked up as mentioned for the preparation of acid **6a** except that conc. HCl was added at 0 °C to give hydroxy acid **22** (2.50 g, 83%) as crystals, m.p. 176–177 °C; ν_{max}(KBr)/cm^{-1} 3150 (OH) and 1720 (CO); δ_H(250 MHz; [$^2H_6$]acetone) 2.91 (1 H, br s, OH), 3.66 (3 H, s, OMe), 3.72 (3 H, s, OMe), 3.96 (3 H, s, OMe), 4.43 (2 H, q, *J* 83.6 and 10.9, CH_2), 6.78 (1 H, s, ArH), 7.27 (1 H, dd, *J* 7.5 and 2.1, ArH) and 7.41–7.52 (2 H, m, ArH).

Esterification of acid **22** *to methyl* 3′-*bromo*-6′-*hydroxymethyl*-2′,4′,6-*trimethoxy*-1,1′-*biphenyl*-2-*carboxylate* **23**. To a solution of acid **22** (2.00 g, 5.03 mmol) in dry DMF (70 cm^3) was added $NaHCO_3$ (423 mg, 5.04 mmol) and the mixture was stirred at 50 °C for 2 h. To the cooled mixture was added iodomethane (620 mm^3, 9.96 mmol) and the resulting mixture was stirred at room temperature for 16 h. It was poured into 2 mol dm^{-3} HCl and extracted with ethyl acetate. The extracts were washed successively with 2 mol dm^{-3} HCl, 1 mol dm^{-3} Na_2SO_3, and water, and dried over $MgSO_4$. After volatiles were evaporated off, the residue was chromatographed on a silica gel column with hexane–ethyl acetate (2:1) as the eluent to give ester **23** (1.50 g, 72%) as crystals, m.p. 189 °C (Found: C, 52.85; H, 4.75; Br, 19.7. $C_{18}H_{19}BrO_6$ requires C, 52.6; H, 4.7; Br, 19.4%); $[\alpha]_D^{18}$ +48.4 (*c* 0.62, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3475 (OH) and 1719 (CO); δ_H(250 MHz) 2.67 (1 H, br s, OH), 3.66 (6 H, s, OMe), 3.72 (3 H, s, OMe), 3.95 (3 H, s, OMe), 4.44 (2 H, q, *J* 36.2 and 11.4, CH_2), 6.53 (1 H, s, ArH), 7.15 (1 H, d, *J* 8.1, ArH), 7.42 (1 H, t, *J* 7.8, ArH) and 7.52 (1 H, dd, *J* 7.8 and 1.0, ArH).

Oxidation of hydroxy ester **23** *to methyl* 3′-*bromo*-6′-*formyl*-2′,4′,6-*trimethoxy*-1,1′-*biphenyl*-2-*carboxylate* **24**. A solution of compound **23** (1.40 g, 3.40 mmol) and PCC (1.10 g, 5.10 mmol) in dichloromethane (30 cm^3) was stirred at room temperature for 6 h. The mixture was poured into 2 mol dm^{-3} HCl and extracted with diethyl ether. The extracts were washed with water and dried over $MgSO_4$. After the solvents had been evaporated off, the residue was chromatographed on a silica gel column with hexane–ethyl acetate (4:1) as the eluent to give compound **24** (1.00 g, 72%) as crystals, m.p. 195–197 °C; ν_{max}(KBr)/cm^{-1} 1709 (CO); δ_H(250 MHz) 3.65 (3 H, s, OMe), 3.70 (6 H, s, OMe), 3.98 (3 H, s, OMe), 6.72 (1 H, s, ArH), 7.09 (1 H, d, *J* 8.2, ArH), 7.41 (1 H, t, *J* 8.0, ArH), 7.61 (1 H, d, *J* 7.8, ArH) and 10.09 (1 H, s, CHO).

Oxidation of aldehyde **24** *to* 2′-*methyl* 2-*hydrogen* 5-*bromo*-4,6,6′-*trimethoxy*-1,1′-*biphenyl*-2,2′-*dicarboxylate* **25**. A solution of $KMnO_4$ (1.00 g, 6.33 mmol) in water (50 cm^3) was added at 50 °C to a stirred solution of compound **24** (881 mg, 2.15 mmol) in acetone (50 cm^3) and the mixture was stirred for 2 h at 50 °C. To the cooled brown suspension were added 2 mol dm^{-3} of Na_2SO_3 (30 cm^3) and 4 mol dm^{-3} H_2SO_4 (50 cm^3) to form a clear solution. After most of the acetone had been evaporated off, the residue was dissolved in 2 mol dm^{-3} NaOH (100 cm^3) and washed with diethyl ether. The aqueous layer was acidified by addition of conc. HCl at 0 °C to liberate the free acid, which was extracted with ethyl acetate, and the extract was washed with water and dried over $MgSO_4$. After the solvent had been evaporated off, the residue was dried *in vacuo* to give compound **25** (549 mg, 60%) as crystals, m.p. 202–204 °C; ν_{max}(KBr)/cm^{-1} 2950 (OH), 1728 and 1705 (CO); δ_H(250 MHz; [$^2H_6$]acetone) 3.59 (3 H, s, OMe), 3.69 (3 H, s, OMe), 3.74 (3 H, s, OMe), 3.99 (3 H, s, OMe), 4.61 (1 H, br s, OH), 6.85 (1 H, s, ArH), 7.22 (1 H, dd, *J* 8.1 and 1.2, ArH), 7.41 (1 H, t, *J* 8.0, ArH) and 7.50 (1 H, dd, *J* 7.8 and 1.3, ArH).

Hydrolysis of mono-ester **25** *to* 5-*bromo*-4,6,6′-*trimethoxy*-1,1′-*biphenyl*-2,2′-*dicarboxylic acid* **26**. A mixture of partial ester **25** (502 mg, 1.18 mmol), KOH (710 mg), ethanol (10 cm^3) and water (1 cm^3) was stirred at room temperature for 12 h and worked up as mentioned for the preparation of acid **6a** except that conc. HCl was added at 0 °C and the liberated acid was extracted with ethyl acetate to give crude diacid **26** (340 mg, 70%) as yellow crystals, δ_H(250 MHz; [$^2H_6$]acetone) 3.69 (3 H, s, OMe), 3.72 (3 H, s, OMe), 3.97 (3 H, s, OMe), 5.12 (2 H, br s, OH), 6.83 (1 H, s, ArH), 7.23 (1 H, dd, *J* 8.2 and 1.2, ArH), 7.42 (1 H, t, *J* 8.0, ArH) and 7.54 (1 H, dd, *J* 7.8 and 1.0, ArH).

Treatment of diacid **26** *with* (R)-*bi*-2-*naphthol to cyclic diester* (R,R)-15-*bromo*-14,16,17-*trimethoxy*-12,21-*dihydrodibenzo*-[h,j]*dinaphtho*[2,1-b:1,2-d]-1,6-*dioxacyclododecapentaene*-12,-21-*dione* (R,R)-**27**. This transformation was performed by the same procedure as mentioned for compound **16a** except that crude product was purified by chromatography on a silica gel column with hexane–ethyl acetate (3:1) as the eluent. Starting from diacid **26** (340 mg, 827 μmol) and (*R*)-bi-2-naphthol (238 mg, 831 μmol) the *heptacycle* (R,R)-**27** (192 mg, 35%) was obtained as crystals, m.p. 220 °C (Found: C, 67.2; H, 3.8; Br, 12.2. $C_{37}H_{25}BrO_7$ requires C, 67.2; H, 3.8; Br, 12.1%); $[\alpha]_D^{20}$ +315 (*c* 0.92, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1754 (CO); δ_H(250 MHz) 3.72 (3 H, s, OMe), 3.78 (6 H, s, OMe), 6.59 (1 H, s, ArH), 6.84 (2 H, t, *J* 8.2, ArH), 7.03–7.43 (6 H, m, ArH), 7.49 (1 H, d, *J* 8.9, ArH) and 7.83–8.01 (6 H, m, ArH).

Reductive cleavage of diester (R,R)-**27** *to* (R)-3-*bromo*-2′,6-*bis*(*hydroxymethyl*)-2,4,6′-*trimethoxy*-1,1′-*biphenyl* (R)-**28**. To a solution of diester (*R,R*)-**27** (143 mg, 216 μmol) in THF (10 cm^3) was added $LiAlH_4$ (90.3 mg, 2.38 mmol) portionwise at 0 °C and the mixture was stirred at room temperature for 10 h. After the same work-up as mentioned for diester (*S,S*)-**17a**, except that ethyl acetate was used for extraction, PLC with hexane–ethyl acetate (1:1) as the developer gave dextrorotatory diol (*R*)-**28** (67.8 mg, 82%) as crystals, m.p. 187–189 °C; $[\alpha]_D^{20}$ +59.0 (*c* 0.80, THF); ν_{max}(KBr)/cm^{-1} 3370 (OH); δ_H(250 MHz; [$^2H_6$]acetone) 3.67 (3 H, s, OMe), 3.70 (3 H, s, OMe), 3.98 (3 H, s, OMe), 4.09–4.29 (4 H, m, CH_2 and OH), 4.40–4.58 (2 H, m, CH_2), 6.82 (1 H, s, ArH), 7.00 (1 H, d, *J* 8.3, ArH), 7.13 (1 H, d, *J* 7.0, ArH) and 7.36 (1 H, t, *J* 7.9, ArH).

3-*Bromo*-2′,6-*bis*(*hydroxymethyl*)-2,4,6′-*trimethoxy*-1,1′-*biphenyl* **28** *from acid* **22**. In the same way as mentioned for diester (*R,R*)-**27**, treatment of acid **22** (163 mg, 410 μmol) with $LiAlH_4$ (150 mg, 3.95 mmol) in THF (10 cm^3) at room temperature for 12 h gave *diol* **28** (143 mg, 91%), m.p. 184–185 °C (Found: C, 53.5; H, 5.0; Br, 20.7. $C_{17}H_{19}BrO_5$ requires C, 53.3; H, 5.0; Br, 20.85%); $[\alpha]_D^{20}$ +53.6 (*c* 0.84, THF).

The positive sign of the specific rotation of the sample indicated its axial chirality to be *R*. Thus, the axial chirality of the coupling product **12bd** was determined to be *R*.

Acknowledgements

This work was supported in part by Sumitomo Seika Chemicals Co., Ltd.

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Paper 4/01557F
Received 15*th March* 1994
Accepted 18*th April* 1994