A New Synthesis of 2,2'-Disubstituted Unsymmetrical Biphenyls Based on the Intramolecular Ullmann Coupling Reaction Utilising Salicyl Alcohol as a Template

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A synthesis of 2,2'-disubstituted unsymmetrical biphenyls was examined by using the template-directed intramolecular Ullmann coupling reaction as a key step. The Ullmann coupling reaction of the diesters **1**–**5** showed that the most suitable ring size for the intramolecular Ullmann coupling reaction is an eleven-membered ring. On the basis of these results, salicyl alcohol was selected as a template. Acylations of salicyl alcohol by two different aroyl chlorides proceeded regioselectively in a one-pot procedure to afford the diesters **18** in good yields. The intramolecular Ullmann coupling reaction of **18** by the dropwise-addition method gave the cyclisation products **19** in high yields. Hydrogenolysis of **19** proceeded regioselectively to afford the unsymmetrical biphenyls **21** in quantitative yields, while the regioselective cleavage of the ester bonds of **19** by nucleophilic substitution reactions gave the corresponding 2,2'-disubstituted unsymmetrical biphenyls **22** and **24** in good yields.

The chemistry of 2,2'-disubstituted unsymmetrical biphenyls[1] has attracted considerable interest because of the biological activity of a number of natural products containing these moieties.[2,3] The reported methods for construction of unsymmetrical biphenyl skeletons include those based on the regioselective carbon–carbon bond formation between two different aromatics by transition-metal catalysed cross-coupling reaction of an aryl metal with an aryl halide,[4] the ambient temperature Ullmann coupling reaction,[5] and the Meyers oxazoline method.[6] Because of the unsatisfactory results obtained in the synthesis of highly functionalised unsymmetrical biphenyls using these methods,[7] efforts have recently been devoted to developing a new methodology. Although the Ullmann coupling reaction has been recognised as a useful method for the synthesis of a variety of symmetrical biphenyls,[8] difficulties are encountered in the application of this reaction to a synthesis of unsymmetrical biphenyls because of the concomitant formation of the symmetrical ones.[9] In this paper,[10] we report an efficient synthesis of 2,2'-disubstituted unsymmetrical biphenyls based on the intramolecular Ullmann coupling reaction[11] utilising salicyl alcohol as a template.

Synthetic Strategy.—Our strategy consists of the three steps involving the regioselective acylations of a template, the intramolecular Ullmann coupling reaction and the regioselective removal of the template (Fig. 1). The requirements imposed on the template are three-fold as follows. The template must (i) have two functional groups of differing reactivity, allowing regioselective acylation by two different substituted 2-halogenobenzoyl chlorides; (ii) enable the intramolecular Ullmann coupling reaction to proceed efficiently by stabilising the conformation of a transition state leading to the cyclisation product; (iii) be removed in a stepwise manner from the coupling product, allowing the conversion of each acyl moiety into a different functional group. Thus, our study began with experiments to search for a suitable template.

Selection of a Template.—It is well documented that the yields of the intramolecular cyclisation reactions generally depend on the stability of the ring being formed.[12] In order to select a suitable template for our strategy (Fig. 1), we first examined the effect of the ring size on the yields of the coupling reactions. Thus, we synthesised the diesters **1**–**5** by acylation of the α,ω-alkanediols by using 2 molar equivalents of 2-iodobenzoyl chloride.

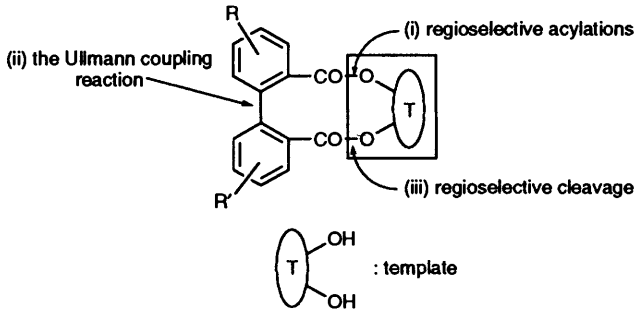
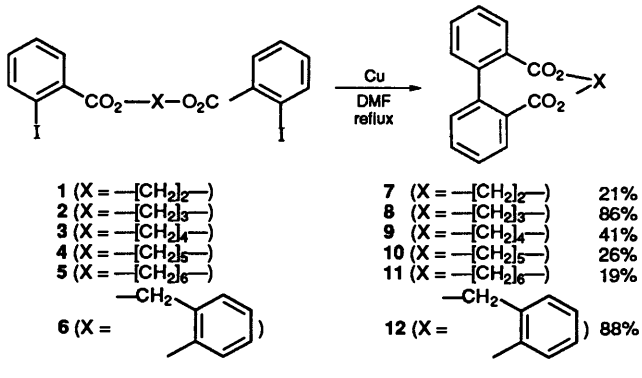


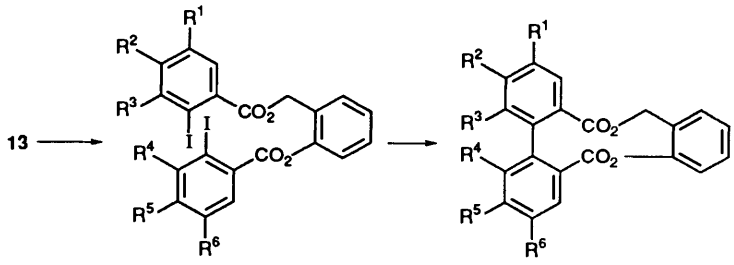
Fig. 1 Synthetic strategy for an unsymmetrical 2,2'-disbustituted biphenyl



Scheme 1

The intramolecular Ullmann coupling reaction was carried out by the dropwise addition of the diester in *N*,*N*-dimethyl-

Table 1 Yield of acylations of salicyl alcohol and the intramolecular Ullmann coupling reaction



18 **19**

	Yield of **18**		Yield of **19**	
Entry	Compound no.[a]	Yield (%)	Compound no.[a]	Yield (%)
1	**18b**	74	**19b**	89
2	**18c**	76	**19c**	75
3	**18d**	79	**19d**	78
4	**18e**	81	**19e**	86
5	**18f**	85	**19f**	89
6	**18g**	72	**19g**	84
7	**18h**	74	**19h**	81
8	**18i**	76	**19i**	76
9	**18j**	79	**19j**	90
10	**18k**	79	**19k**	90
11	**18l**	74	**19l**	81
12	**18m**	74	**19m**	85

[a] **b**: $R^1 = R^4 = H$, $R^2, R^3 = -OCH_2O-$, $R^5 = R^6 = OMe$; **c**: $R^1 = R^4 = H$, $R^2, R^3 = R^5, R^6 = -OCH_2O-$; **d**: $R^1, R^2 = -OCH_2O-$, $R^3 = H$, $R^4 = R^5 = R^6 = OMe$; **e**: $R^1 = H$, $R^2, R^3 = -OCH_2O-$, $R^4 = R^5 = R^6 = OMe$; **f**: $R^1 = R^2 = R^4 = R^5 = R^6 = OMe$, $R^3 = H$; **g**: $R^1 = R^2 = R^5 = H$, $R^3 = NO_2$, $R^4 = R^6 = Cl$; **h**: $R^1 = R^2 = OMe$, $R^3 = R^4 = R^5 = R^6 = H$; **i**: $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = R^6 = Cl$; **j**: $R^1 = R^2 = OMe$, $R^3 = R^5 = R^6 = H$, $R^4 = NO_2$; **k**: $R^1 = R^2 = R^3 = OMe$, $R^4 = NO_2$, $R^5 = R^6 = H$; **l**: $R^1 = R^3 = Cl$, $R^2 = H$, $R^4 = R^5 = R^6 = OMe$; **m**: $R^1 = R^2 = OMe$, $R^3 = R^5 = H$, $R^4 = R^6 = Cl$.

formamide (DMF) to refluxing DMF * containing the activated copper powder.[13] Scheme 1 shows the results of the coupling reactions of the diesters **1**–**5** leading to the corresponding cyclisation products **7**–**11** having 10–14-membered rings. The highest yield was obtained in the coupling reaction of **2**, leading to the cyclisation product **8** having an 11-membered ring, the yields decreasing in the coupling reactions giving 10-, 12-, 13- and 14-membered rings. These results indicate that a three template carbon giving an 11-membered ring is highly suitable for the intramolecular Ullmann coupling reaction.†

The intramolecular Ullmann reaction was examined using salicyl alcohol as a template, which allows differentiation between the phenolic and benzylic hydroxy groups and makes the access of the two reaction sites on the aromatic rings easier than with the propanediol analogue, due to the rigidity of the aromatic ring.[15]

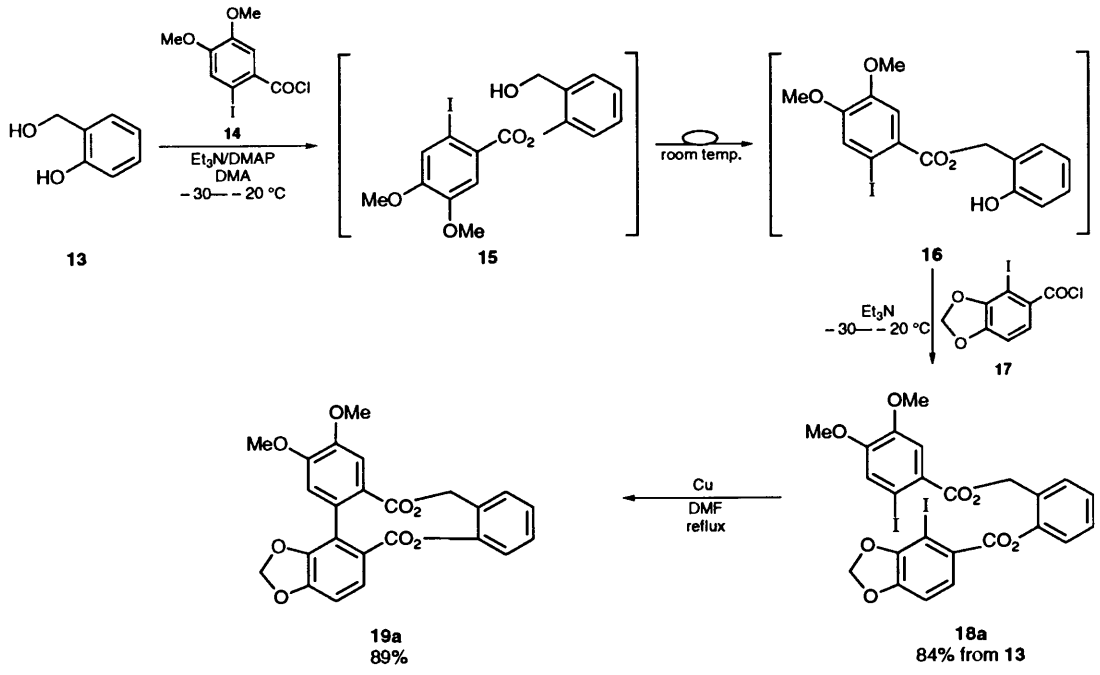
The coupling reaction of the diester **6** was carried out by the dropwise-addition method described to give the coupling product **12** in 88% yield.§ From this result, salicyl alcohol was found to be suitable as a template for realising our strategy.

Regioselective Acylations of Salicyl Alcohol.—It is known that the phenolic hydroxy group of salicyl alcohol is acylated far more readily than the benzylic hydroxy group.[16] In order to obtain the diester **18a**, we tried to acylate salicyl alcohol regioselectively by using the two different aroyl chlorides **14** and **17** (Scheme 2). When salicyl alcohol was treated with 1 mol equiv. of acid chloride **14** in *N*,*N*-dimethylacetamide (DMA) in the presence of triethylamine for 1 h at 0–5 °C, a mixture of the monoesters **15** and **16** was obtained. This result indicated that the acyl group on the phenolic hydroxy group of salicyl alcohol migrated slowly to the benzylic hydroxy group under basic conditions. Thus, we examined the reaction conditions to obtain monoester **16** selectively. When the reaction of salicyl alcohol with compound **14** was carried out in DMA in the presence of triethylamine at −30 to −20 °C for 1 h and then at room temp. for 6 h, a single product **16** was obtained in 68% yield. The structure of **16** was determined on the basis of the ^1H NMR spectrum in which the chemical shift of the benzylic protons (δ 5.38) shows almost the same value as that of the benzylic protons (δ 5.40) of compound **11**. We next examined the synthesis of diester **18a** in a one-pot procedure by successive acylations of salicyl alcohol with acid chlorides **14** and **17**. After completion of the first acylation on the benzylic hydroxy group leading to monoester **16**, the second acylation was carried out at −30 to −20 °C by addition of **17** to afford the diester **18a** in 84% yield. This one-pot procedure was applied to the synthesis of the diesters **18b**–**m** having a variety of substituents. In all cases, the reactions proceeded efficiently to give the diesters in good yields. The results are summarised in Table 1. The nature of the substituents on the aroyl chlorides influenced the first acylation step; the migration proceeded more slowly with the

* When a DMF solution containing a diester was refluxed in the presence of copper powder, the yield markedly decreased. The details are shown in the Experimental section.

† It is well documented that the activation energy for an intramolecular cyclisation reflects the strain energy of the ring to be formed, which is dependent on the ring size.[12] In order to evaluate a factor[14] of this type affecting the intramolecular Ullmann coupling reaction, we calculated the strain energies of the cyclisation products **7**–**9** by using MMP2 (87 force field) based on the assumption that the transition structures resemble the cylisation products. Unexpectedly, the strain energy decreased with increment of the ring size; the strain energies of **7**, **8** and **9** were 30.08, 25.14 and 21.81 kcal mol^{-1}, respectively.

§ In the coupling reaction of toluene-α,2-diyl bis(2-bromobenzoate) the yield markedly decreased; in this reaction, the reduction product, toluene-α,2-diyl dibenzoate, formed in 15% yield together with a large amount of polymerisation products.



Scheme 2

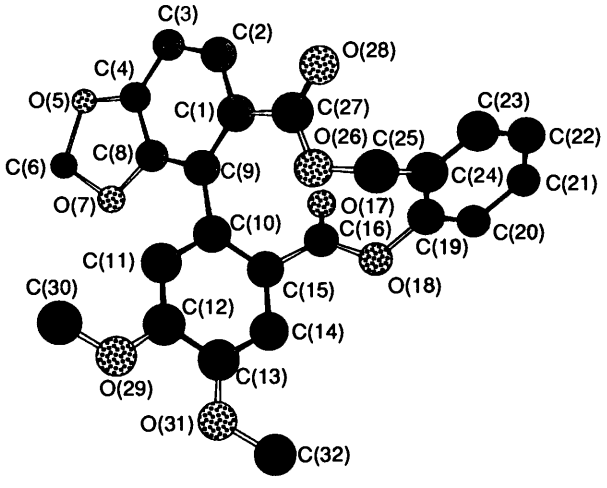


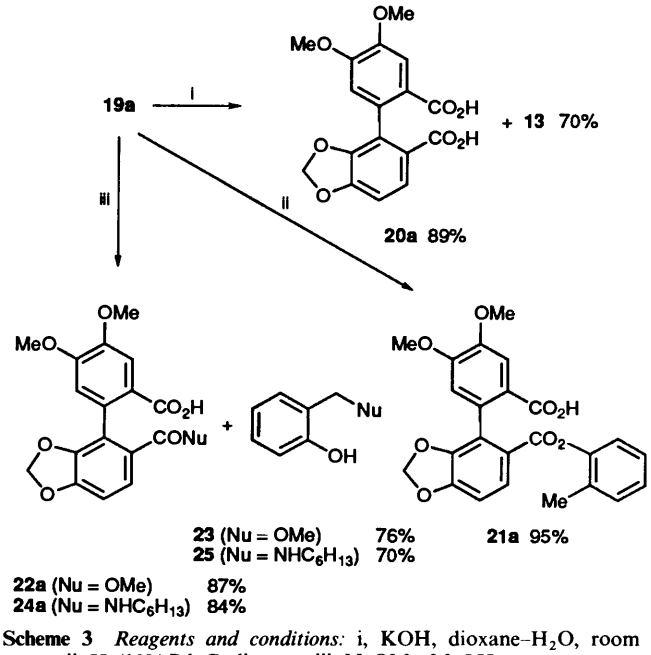
Fig. 2 Perspective view of the structure of **19b** with crystallographic labelling of the atoms

use of aroyl chlorides having electron-donating substituents than those having electron-withdrawing substituents.

The Intramolecular Ullmann Coupling Reaction.—The dropwise addition of diester **18a** in DMF to refluxing DMF containing copper powder over a period of 3 h afforded the coupling product **19a** in 89% yield (Scheme 2); in this reaction, small amounts of polymerisation products were formed. The reaction of **18b** also gave the coupling product **19b**, the regioisomer of **19a**, in 89% yield (Table 1). The structure of compound **19b** was determined by an X-ray crystallographic analysis (Fig. 2). This method was applied to the synthesis of the diesters **19c–m** having a variety of substituents. The results are summarised in Table 1.

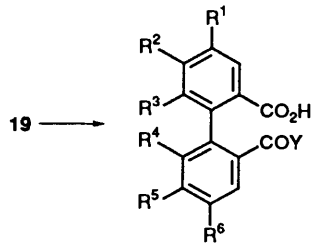
The intramolecular Ullmann coupling reaction proceeds efficiently regardless of the nature of substituents on the aromatic rings: electron-donating substituents on each (**18c–f** → **19c–f**), electron-withdrawing substituents on each (**18g** → **19g**) or an electron withdrawing substituent on one, electron donating on the other (**18j–m** → **19j–m**). Furthermore, it should be emphasised that good results were obtained in the coupling reactions of **18e, g, k** and **l** having substituents at the two *ortho* positions of each of the coupling sites on the two aromatic rings; in the case of the transition-metal catalysed cross-coupling reactions of an arylmetal with an aryl halide having substituents at the two *ortho* positions, the coupling products were obtained in poor yields.[7] The above results show that this template-directed intramolecular Ullmann coupling reaction is effective for the synthesis of highly functionalised biphenyls.

Regioselective Cleavage of the Two Ester Bonds of **19**.—Hydrolysis of the coupling product **19a** readily proceeded under the alkaline conditions to give the diacid **20a** in 89% yield (Scheme 3) with recovered salicyl alcohol **13**. In order to



Scheme 3 *Reagents and conditions:* i, KOH, dioxane–H_2O, room temp.; ii, H_2/10% Pd–C, dioxane; iii, NaOMe–MeOH, room temp. or $C_6H_{13}NH_2$–CH_2Cl_2 room temp.

Table 2 Yield of regioselective cleavage of the ester bonds by hydrogenolysis or nucleophilic substitution reactions

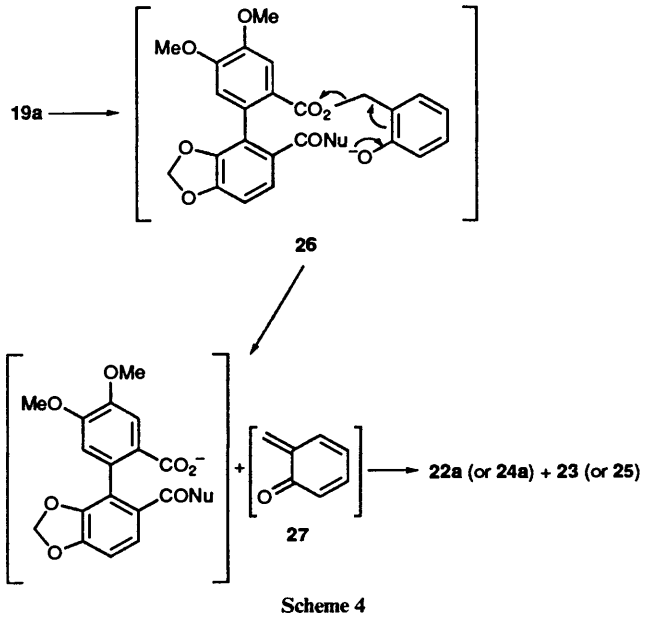


Entry	Substrate[a]	Conditions[b]	Product[a]	Yield (%)
1	**19b**	A	**21b** (Y = *o*-Tolyl)	82
2	**19d**	A	**21d** (Y = *o*-Tolyl)	88
3	**19c**	B	**22c** (Y = OMe)	90
4	**19g**	B	**22g** (Y = OMe)	86
5	**19i**	B	**22i** (Y = OMe)	85
6	**19b**	C	**24b** (Y = NHC_6H_{13})	90
7	**19j**	C	**24j** (Y = NHC_6H_{13})	81
8	**19m**	C	**24m** (Y = NHC_6H_{13})	89

[a] The suffixes **b–d**, **g**, **i**, **j** and **m** represent those substituents shown in Table 1. [b] Conditions A: H_2/10% Pd on charcoal; B: NaOMe–MeOH; C: $C_6H_{13}NH_2$–CH_2Cl_2.

cleave the ester bonds regioselectively, we examined hydrogenolysis of product **19a** using palladium on charcoal to afford the monoester **21a** in 95% yield. The regioisomeric monoester **21b** was also synthesised in a high yield from compound **19b** (Table 2). Hydrogenolysis of the diester **19d** also gave the corresponding monoester **21d** in good yield.

Furthermore, we examined the regioselective cleavage of the ester bonds by nucleophilic substitution reactions. The diester **19a** was treated with sodium methoxide in methanol at room temp. to afford acid **22a** in 87% yield with the concomitant formation of phenol **23** (Scheme 3). The reaction of diester **19a** with hexylamine in dichloromethane at room temp. also gave the monoamide **24a** in 84% and also amine **25**. The structures of compounds **22a** and **24a** were confirmed by comparison with authentic samples which were prepared by treatment of **21a** with sodium methoxide and hexylamine, respectively. The phenol derivatives **23** and **25** would be formed by the Michael additions of the nucleophiles to *o*-quinone methide **27** generated from **26** (Scheme 4).[17] This method could be applied to a synthesis of monoesters and monoamides having a variety of substituents on the benzene rings. The results are summarised in Table 2.



Scheme 4

Experimental

Melting points were determined in open capillary tubes on a Yamato MP-21 melting point apparatus and were uncorrected. IR spectra were obtained using a Perkin-Elmer 1640 infrared spectrometer. NMR spectra were recorded on a Hitachi R-90 or a Bruker AC-200 instrument using Me_3Si as the internal standard. *J* Values are given in Hz. Mass Spectra were obtained on a Hitachi M-60 or Hitachi M-2000A spectrometers. Thin layer chromatography (TLC) was carried out on silica gel (Merck type 60H). DMF and DMA were dried over 4 Å molecular sieves and used without further purification. All other solvents were used as received. Copper powder was purchased from Katayama Chemical Industries (Japan).

Preparation of Benzoyl Chlorides.—2-Iodo-3,4-methylenedioxybenzoic acid,[18] 2-iodo-3,4,5-trimethoxybenzoic acid,[19] 2-iodo-3-nitrobenzoic acid,[20] 2-iodo-4,5-methylenedioxybenzoic acid,[21] 2-iodo-4,5-dimethoxybenzoic acid[22] and 3,5-dichloro-2-iodobenzoic acid[23] were prepared according to reported methods. The benzoic acids were converted into the benzoyl chlorides as follows. A benzoic acid (50 mmol) was treated with thionyl chloride (15 cm^3) in dioxane (15 cm^3) with refluxing for 30 min. The mixture was evaporated to dryness under reduced pressure. Toluene was added to the residue (50 cm^3) and the solvent was evaporated to dryness under reduced pressure. This evaporation procedure was repeated twice, and the residue was used in the next step without further purification.

Preparation of Compounds **1–6**.—To a solution of ethane-1,2-diol (620 mg, 10 mmol), triethylamine (3.34 cm^3, 24 mmol) and 4-dimethylaminopyridine (12 mg, 0.1 mmol) in methylene chloride (50 cm^3) was added 2-iodobenzoyl chloride (5.7 g, 22 mmol) with vigorous stirring at 0–10 °C. The reaction mixture was stirred at room temp. for 14 h. The mixture was washed with aqueous sodium hydrogen carbonate and water and dried over $MgSO_4$. The organic layer was evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate–hexane) to give ethylene bis(2-iodobenzoate) **1** (4.7 g, 90%) as colourless crystals, m.p. 49–50 °C (Found: C, 37.0; H, 2.25; I, 48.7.

$C_{16}H_{12}I_2O_4$ requires C, 36.8; H, 2.3; I, 48.6%); ν_{max}(KBr)/cm^{-1} 1722 (CO); δ_H(200 MHz; $CDCl_3$) 4.70 (4 H, s, CH_2CH_2), 7.14 (2 H, dt, *J* 1.9 and 7.7, ArH), 7.40 (2 H, dt, *J* 1.1 and 7.7, ArH), 7.86 (2 H, dd, *J* 7.7 and 1.9, ArH) and 8.00 (2 H, dd, *J* 7.7 and 1.1, ArH); *m/z* 522 (M^+, 22%), 275 (87), 231 (100), 203 (37) and 76 (88). The compounds **2–6** were prepared under the same reaction conditions as above. The analytical data and spectral details of these compounds have been deposited as a Supplementary Publication [Supp. No. 56950 (6 pp)].*

The Ullmann Coupling Reaction of Compounds **1–6**.—A solution of toluene-α,2-diyl bis(2-iodobenzoate) **6** (1.17 g, 2.0 mmol) in DMF (10 cm^3) was added dropwise over a period of 3 h to refluxing DMF (10 cm^3) in the presence of activated copper powder[13] (20 mmol). After complete addition, the reaction mixture was refluxed for a further 1 h, allowed to cool and the insoluble materials were filtered off. The solvent was evaporated to dryness under reduced pressure. Ethyl acetate (50 cm^3) was added to the residue and the solution was washed with water and dried over $MgSO_4$. After the solution has been evaporated to dryness under reduced pressure, the residue was purified by silica gel column chromatography to afford toluene-α,2-diyl biphenyl-2,2′-dicarboxylate **12** (580 mg, 88%) as colourless crystals, m.p. 185–186 °C (Found: C, 76.5; H, 4.2. $C_{21}H_{14}O_4$ requires C, 76.4; H, 4.3%); ν_{max}(Nujol)/cm^{-1} 1744 (CO); δ_H(90 MHz; $CDCl_3$) 4.64 (1 H, d, *J* 12, $ArCH_2$), 6.19 (1 H, d, *J* 12, $ArCH_2$) and 7.1–7.9 (12 H, m, ArH); *m/z* 330 (M^+, 39%), 189 (89) and 106 (100).

The Ullmann coupling reaction of toluene-α,2-diyl bis(2-bromobenzoate) (0.98 g, 2.0 mmol) was carried out under the same reaction conditions as above, and the reaction mixture was purified by silica gel column chromatography. The first major fraction was collected and identified as toluene-α,2-diyl dibenzoate (100 mg, 15%), a colourless oil (Found: C, 75.8; H, 4.9. $C_{21}H_{16}O_4$ requires C, 75.9; H, 4.85%); ν_{max}(Nujol)/cm^{-1} 1725 (CO); δ_H(200 MHz; $CDCl_3$) 5.79 (2 H, s, $ArCH_2$), 7.2–7.75 (10 H, m, ArH) and 8.1–8.25 (4 H, m, ArH); *m/z* 332 (M^+, 8%) and 105 (100). The second major fraction was collected and identified as compound **12** (250 mg, 38%).

The compounds **7–11** were prepared under the same reaction conditions as above. The analytical data and spectral details of these compounds have been deposited as a Supplementary Publication [Supp. No.: 56950 (6 pp.)].

When the reaction was carried out under the following reaction conditions, the yield markedly decreased; when a solution of diester **6** (1.17 g, 2.0 mmol) dissolved in DMF (10 cm^3) containing copper powder (1.27 g, 20 mmol) was refluxed for 3 h, **12** (244 mg, 37%) was obtained.

o-*Hydroxybenzyl* 2-*Iodo*-4,5-*dimethoxybenzoate* **16**.—To a solution of salicyl alcohol **13** (1.24 g, 10 mmol), triethylamine (3.34 cm^3, 24 mmol) and 4-dimethylaminopyridine (12 mg, 0.1 mmol) in DMA (50 cm^3) was added in portions 2-iodo-4,5-dimethoxybenzoyl chloride **14** (3.27 g, 10 mmol) over a period of 30 min at −30 to −20 °C. The reaction mixture was warmed to room temp. and stirred for 6 h then poured into 10% aqueous citric acid (300 cm^3) and extracted with ethyl acetate (3 × 100 cm^3). The organic layer was dried over $MgSO_4$ and evaporated to dryness under reduced pressure. The residue was crystallised from diisopropyl ether to afford **16** (2.8 g, 68%) as colourless crystals, m.p. 94–95 °C (Found: C, 46.4; H, 3.6. $C_{16}H_{15}IO_5$ requires C, 46.4; H, 3.65%); ν_{max}(KBr)/cm^{-1} 3496 (OH) and 1728 (CO); δ_H(200 MHz; $CDCl_3$) 3.88 (3 H, s, OMe), 3.90 (3 H, s, OMe), 5.38 (2 H, s, $ArCH_2$), 6.85–7.05 (2 H, m, ArH), 7.25–7.45 (2 H, m, ArH), 7.38 (1 H, s, ArH), 7.45 (1 H, s, ArH) and 7.85 (1 H, s, OH); *m/z* 414 (M^+, 32%), 308 (96) and 106 (100).

Preparation of the Diesters **18a–m**.—To a solution of salicyl alcohol **13** (1.24 g, 10 mmol), triethylamine (3.34 cm^3, 24 mmol) and 4-dimethylaminopyridine (12 mg, 0.1 mmol) in DMA (50 cm^3) was added in portions 2-iodo-4,5-dimethoxybenzoyl chloride **14** (3.27 g, 10 mmol) over a period of 30 min at −30 to −20 °C. The reaction mixture was warmed to room temp. and stirred for 6 h then cooled again to −30 to −20 °C. To the mixture was added in portions 2-iodo-3,4-methylenedioxybenzoyl chloride **17** (3.1 g, 10 mmol) over a period of 30 min at −30 to −20 °C. The reaction mixture was warmed to room temp. and stirred for 14 h, then poured into water (300 cm^3) and extracted with ethyl acetate (3 × 200 cm^3). The combined organic phase was washed with aqueous sodium hydrogen carbonate and brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by crystallisation from diethyl ether to afford 2-(2-iodo-4,5-dimethoxybenzoyloxymethyl)phenyl 2-iodo-3,4-methylenedioxybenzoate **18a** (5.8 g, 84%) as colourless crystals, m.p. 135–136 °C (Found: C, 41.7; H, 2.6. $C_{24}H_{18}I_2O_8$ requires C, 41.9; H, 2.65%); ν_{max}(KBr)/cm^{-1} 1730 (CO); δ_H(90 MHz; $CDCl_3$) 3.81 (3 H, s, OMe), 3.87 (3 H, s, OMe), 5.37 (2 H, s, $ArCH_2$), 6.10 (2 H, s, OCH_2O), 6.78 (1 H, d, *J* 8, ArH), 7.15–7.65 (6 H, m, ArH) and 7.75 (1 H, d, *J* 8, ArH); *m/z* 688 (M^+, 15%) and 275 (100).

The diesters **18b–m** were prepared under the same reaction conditions as above. The analytical data and spectral details of compounds **18b–m** are included in the Supplementary Publication [Supp. No. 56950 (6 pp.)].

The Ullmann Coupling Reaction of **18**.—The Ullmann coupling reaction of diester **18a** (1.38 g, 2.0 mmol) was carried out under the reaction conditions described for diester **6** to afford toluene-α(2),2(2′)-diyl 4,5-dimethoxy-5′,6′-methylenedioxybiphenyl-2′,2′-dicarboxylate **19a** (770 mg, 89%) as colourless crystals, m.p. 217–219 °C (Found: C, 66.7; H, 4.1. $C_{24}H_{18}I_2O_8$ requires C, 66.4; H, 4.2%); ν_{max}(Nujol)/cm^{-1} 1740 (CO) and 1705 (CO); δ_H(90 MHz; $CDCl_3$) 3.85 (3 H, s, OMe), 3.88 (3 H, s, OMe), 4.77 (1 H, d, *J* 12, $ArCH_2$), 5.97 (1 H, d, *J* 12, $ArCH_2$), 5.99 (1 H, d, *J* 1, OCH_2O), 6.09 (1 H, d, *J* 1, OCH_2O), 6.85 (1 H, d, *J* 8, ArH) and 7.0–7.55 (7 H, m, ArH); *m/z* 434 (M^+, 57%), 328 (92), 284 (100) and 269 (73).

The compounds **19b–m** were prepared under the same reaction conditions as above. The analytical data and spectral details of **19b–m** are included in the Supplementary Publication [Supp. No. 56950 (6 pp.)].

X-Ray Structure Determination of **19b**.—Crystal data. $C_{24}H_{18}O_8 \cdot C_4H_8O$ (obtained crystal contained equimolar THF), M = 506.51, A = 16.808(3), B = 9.107(1), C = 16.0949(3) Å, β = 99.11(1)°, U = 2425.6(7) Å^3, monoclinic, $P2_1/a$, Z = 4, D_x = 1.39 g cm^{-3}, $F(000)$ = 1064, μ(CuKα) = 8.80 cm^{-1}. The diffraction experiment was carried out using a colourless transparent prism, which was recrystallised from THF, with dimension of 0.5 × 0.4 × 0.3 mm. The diffractometer AFC/5 (RIGAKU) was used with graphite-monochromated CuKα radiation (λ = 1.5418 Å). The unit cell dimensions were determined from angular setting of 25 reflections (2θ values in the range of 30–60°). 3628 Unique refractions ($2\theta \leqslant 120°$) were measured, of which 2920 with $|F_o| \geqslant 2.67\ \sigma(F_o)$ were considered as observed. No absorption correction was applied. The structure was solved by a direct method using MULTAN 80[24] and difference Fourier method. The refinement of atomic parameters were carried out using full matrix least-squares methods with anisotropic temperature factors. Eighteen hydrogen atoms were located on the difference Fourier maps

* For details of the Supplementary Publication Scheme, see *J. Chem. Soc., Perkin Trans. 1*, 1993, Issue 1.

and refined with isotropic temperature factors. The positions of residual hydrogen atoms were assumed geometrically, and fixed. Throughout the refinement the function $\Sigma w(|F_o| - |F_c|)^2$ was minimised. The weighting scheme of $\sqrt{W} = 1/\sigma(F_o)$ was used during the final refinement stage. The atomic scattering factors were taken from 'International Tables for X-ray crystallography'.[25] The final R value is 0.071 (R_w = 0.078). Refined coordinates, thermal parameters, bond lengths and bond angles have been deposited with the Cambridge Crystallographic Data Centre.*

4,5-Dimethoxy-5',6'-methylenedioxybiphenyl-2,2'-dicarboxylic Acid **20a**.—To a solution of diester **19a** (870 mg, 2.0 mmol) in dioxane (10 cm^3) and water (5 cm^3) was added potassium hydroxide (2.0 g), and the mixture was stirred for 3 h at room temp. The mixture was evaporated to about 5 cm^3 under reduced pressure and the pH of the solution was adjusted to 0–1 by addition of 10% hydrochloric acid. The resulting mixture was extracted with ethyl acetate (3 × 100 cm^3). The combined organic layer was dried over $MgSO_4$ and evaporated to dryness under reduced pressure. The residue was crystallised from diethyl ether to afford diacid **20a** (620 mg, 89%) as colourless crystals, m.p. 207–211 °C (Found: C, 59.1; H, 4.0. $C_{17}H_{14}O_8$ requires C, 59.0; H, 4.1%); ν_{max}(Nujol)/cm^{-1} 3050, 2620 (OH) and 1695 (CO); δ_H(90 MHz; [$^2H_6$]Me_2SO) 3.4 (2 H, br s, COOH), 3.73 (3 H, s, OMe), 3.81 (3 H, s, OMe), 5.9–6.1 (2 H, m, OCH_2O), 6.70 (1 H, s, ArH), 6.89 (1 H, d, *J* 8, ArH), 7.46 (1 H, s, ArH) and 7.50 (1 H, d, *J* 8, ArH); *m/z* 346 (M^+, 70%) and 301 (100). The mother liquor was evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography to afford salicyl alcohol **13** (174 mg, 70%).

Hydrogenolysis of **19**.—A solution of diester **19a** (870 mg, 2.0 mmol) in dioxane (50 cm^3) containing 10% palladium on carbon (100 mg) was shaken for 5 h under a hydrogen atmosphere (2.0 kg cm^{-2}). The insoluble materials were filtered off. The filtrate was evaporated to dryness under reduced pressure. The residue was crystallised from diisopropyl ether to give 4,5-dimethoxy-5',6'-methylenedioxy-2'-(2-methylphenoxycarbonyl)biphenyl-2-carboxylic acid **21a** (830 mg, 95%) as colourless crystals, m.p. 185–186 °C (Found: C, 66.0; H, 4.6. $C_{24}H_{20}O_8$ requires C, 66.05; H, 4.6%); ν_{max}(Nujol)/cm^{-1} 2600 (OH), 1735 (CO) and 1685 (CO); δ_H(90 MHz; $CDCl_3$) 2.02 (3 H, s, ArMe), 3.85 (3 H, s, OMe), 3.87 (3 H, s, OMe), 5.9–6.0 (2 H, m, OCH_2O), 6.7–7.3 (6 H, m, ArH), 7.58 (1 H, s, ArH), 7.86 (1 H, d, *J* 8, ArH) and 8.0 (1 H, br s, COOH); *m/z* 436 (M^+, 1%), 328 (49), 285 (100), 269 (32), 241 (31) and 108 (33).

The compounds **21b** and **d** were prepared under the same reaction conditions as above. The analytical data and spectra details of these compounds are included in the Supplementary Publication [Supp. No. 56950 (6 pp.)].

Regioselective Cleavage of the Ester Groups of **19** *by Sodium Methoxide in Methanol*.—To a solution of diester **19a** (870 mg, 2.0 mmol) in methanol (40 cm^3) was added sodium methoxide (270 mg, 5.0 mmol) at 5 °C and the mixture was stirred for 1 h. The mixture was poured into aqueous 10% aqueous citric acid (200 cm^3) and extracted with ethyl acetate (3 × 100 cm^3). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness under reduced pressure. The residue was crystallised from diisopropyl ether to give 4,5-dimethoxy-2'-methoxycarbonyl-5',6'-methylenedioxybiphenyl-2-carboxylic acid **22a** (630 mg, 87%) as colourless crystals, m.p. 184–186 °C (Found: C, 60.1; H, 4.5. $C_{18}H_{16}O_8$ requires C, 60.0; H, 4.5%); ν_{max}(Nujol)/cm^{-1} 2600 (OH), 1710 (CO_2Me) and 1680 (CO_2H); δ_H(90 MHz; $CDCl_3$) 3.58 (3 H, s, CO_2Me), 3.87 (3 H, s, OMe), 3.94 (3 H, s, OMe), 5.8–6.15 (2 H, m, OCH_2O), 6.63 (1 H, s, ArH), 6.81 (1 H, d, *J* 8, ArH), 7.62 (1 H, s, ArH), 7.62 (1 H, d, *J* 8, ArH) and 8.5 (1 H, br s, CO_2H); *m/z* 360 (M^+, 100%), 315 (56), 301 (50) and 285 (46). The mother liquor was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 2-methoxymethylphenol **23** (210 mg, 76%).

The compounds **22c**, **g** and **i** were prepared under the same reaction conditions as above. The analytical data and spectral details of these compounds are included in the Supplementary Publication [Supp. No. 56950 (6 pp.)].

Regioselective Cleavage of the Ester Groups of **19** *by Hexylamine*.—To a solution of diester **19a** (870 mg, 2.0 mmol) in methylene chloride (40 cm^3) was added hexylamine (2.0 g, 20 mmol) at 5 °C and the mixture was stirred for 4 days at room temp. The reaction mixture was poured into aqueous 10% citric acid solution (100 cm^3) and extracted with methylene chloride (2 × 100 cm^3). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness under reduced pressure. The residue was crystallised from hexane to give 2'-(*N*-hexylcarbamoyl)-4,5-dimethoxy-5',6'-methylenedioxybiphenyl-2-carboxylic acid **24a** (770 mg, 1.8 mmol) as colourless crystals, m.p. 144–145 °C (Found: C, 63.95; H, 6.4; N, 3.0. $C_{23}H_{27}NO_7$ requires C, 64.3; H, 6.3; N, 3.3%); ν_{max}(Nujol)/cm^{-1} 3380 (CO_2H) and 1686 (CO); δ_H(200 MHz; $CDCl_3$) 0.84 (3 H, t, *J* 6.6, CH_2CH_3), 1.0–1.4 (8 H, m, $CH_3CH_2CH_2CH_2CH_2$), 2.95–3.45 (2 H, m, NCH_2), 3.83 (3 H, s, OMe), 3.94 (3 H, s, OMe), 5.8 (1 H, br s, CO_2H), 5.85–5.95 (2 H, m, OCH_2O), 6.11 (1 H, bt, *J* 7, NH), 6.65 (1 H, s, ArH), 6.81 (1 H, d, *J* 8, ArH), 7.16 (1 H, d, *J* 8, ArH) and 7.43 (s, 1 H); *m/z* 429 (M^+, 52%), 384 (76), 300 (43) and 285 (100). The mother liquor was evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography to afford 2-(hexylaminomethyl)phenol **25**[26] (300 mg, 70%) as a colourless oil.

The compounds **24b**, **j** and **m** were prepared under the same reaction conditions as above. The analytical data and spectral details of these compounds are included in the Supplementary Publication [Supp. No. 56950 (6 pp.)].

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