Synthesis of orthogonally protected biaryl amino acid derivatives

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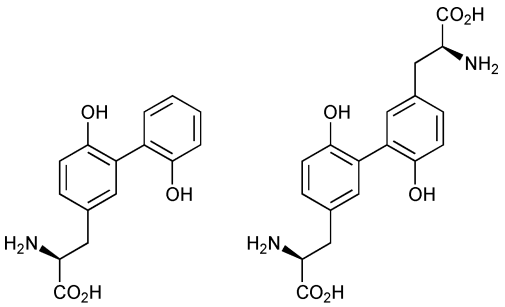
The efficient and direct synthesis of protected biaryl amino acids, including dityrosine (50% overall yield over 3 steps), by Negishi cross-coupling of the serine-derived organozinc reagent **4** with iodo- and di-iodobiaryls, is reported. An improved, although still not perfect, diiodination of 2,2′-biphenol has been achieved using NMe_3BnICl_2–$ZnCl_2$. Protection of phenolic hydroxyl groups as acetates, rather than benzyl ethers, is required for efficient cross-coupling, and evidence for acetyl migration has been observed during debenzylation of a substituted 2-acetoxy-2′-benzyloxybiaryl. Aromatic C–I to C–Cl conversion has been detected as a minor reaction pathway in the palladium-catalyzed coupling of aryl iodide **3b** with organozinc reagent **4**.

Introduction

Biaryl amino acids are present in a variety of natural products, from relatively simple amino acids to complex macrocycles, many of which display a range of biological activities.[1] Of particular interest is the 2,2′-biphenol amino acid **1**, a structural motif commonly found in nature, which in certain circumstances can exhibit atropisomerism.[2] 2,2′-Biphenol derivatives have also found many applications in asymmetric catalysis, for example as the backbone of phosphoramidite ligands which have been used to effect a variety of enantioselective transformations.[3]



Dityrosine **2**[4] occurs naturally and is a member of a larger family which contains, amongst others, isodityrosine,[5,6] trityrosine,[4] isotrityrosine,[7] pulcherosine[8] and di-isodityrosine.[9] The formation of dityrosine was initially reported by Gross and Sizer by the oxidation of tyrosine with aqueous hydrogen peroxide and peroxidase, resulting in dimerisation by formation of the biaryl bond.[10] Andersen then identified the cross-links of resilin, a rubber-like protein present in some of the elastic ligaments of arthropods, as dityrosine and trityrosine.[4] Subsequently, LaBella reported the presence of dityrosine in mammalian collagen[11] and vertebrate elastin,[12] and suggested that the cross-linking of this amino acid was partially responsible for their structural properties. Dityrosine formation was also subsequently shown to be induced by oxidation of a variety of nonstructural proteins.[13]

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In particular, the formation of biphenol amino acid derivatives by the crosslinking of tyrosyl residues on the cell membrane of the sea urchin egg generates a hard fertilisation envelope (HFE), which serves to protect the embryo from disruptive agents, physical forces and polyspermy.[14,15] Similarly, the oocyst cell wall of apicomplexan parasites in their infective form is hardened by the formation of dityrosine cross-links between proteins encapsulating the oocyst, and protects it from the environment.[16]

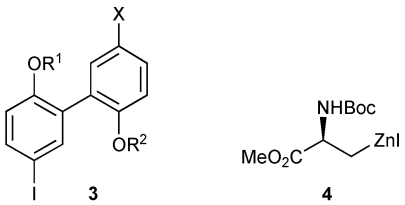
The presence of dityrosine in several proteins is also related to non-specific oxidative damage upon exposure to a variety of agents,[17] including oxygen free-radical species,[18] hydrogen peroxide,[19] nitrogen dioxide[20] and related species[21] and ultraviolet (UV) irradiation.[22] The non-specific formation of tyrosine cross-links has been implicated in several human diseases which include neurodegenerative disorders such as Parkinson's[23,24] and Alzheimer's diseases,[25] atherosclerosis,[26] diabetes,[27] cystic fibrosis[28] and the formation of cataractous lens in humans.[29] During some of these investigations, the urinary levels of dityrosine had been used as a non-invasive biological marker to examine protein oxidative stress *in vivo*,[26,27] since these levels can be easily monitored due to the amino acid **2** possessing an intense 420-nm fluorescence.[17,30] Cross-linked biphenol amino acid derivatives have also been implicated as playing an important role in the oxidative damage of proteins, through the formation of the tyrosyl radical,[31] and that such damaged proteins mediate signals for degradation.[32]

Previous syntheses of dityrosine derivatives have either relied on oxidative dimerisation of tyrosine, or on methods involving Pd-catalyzed coupling reactions. The enzyme-catalyzed preparation of dityrosine from L-tyrosine using horseradish peroxidase has been reported,[33,34] as well as non-enzymatic oxidative methods using acidic aqueous potassium bromate,[35] or VOF_3 with *N*-benzyloxycarbonyl-L-tyrosine methyl ester.[36] Yamamura and co-workers reported electrolytic phenolic oxidation of a 3,5-diiodotyrosine derivative as the key-step in the synthesis of dityrosine, albeit in low overall yield.[37] Lygo reported a catalytic asymmetric phase transfer alkylation of a glycine-derived imine to install the amino-acid fragments of dityrosine in one high-yielding step.[38] Alternative strategies which employ palladium catalyzed cross-coupling reactions to generate the biaryl link have also been reported. Achab has

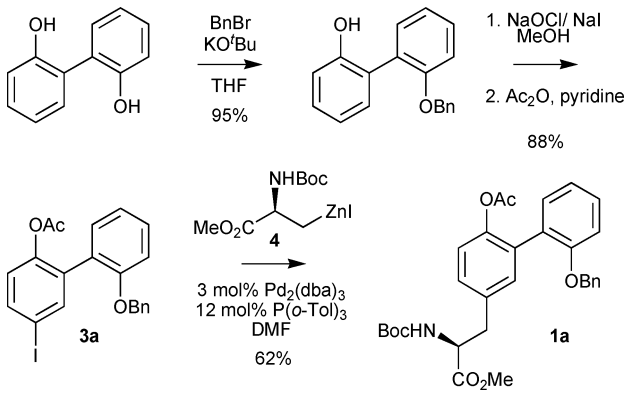
reported that a Stille biaryl-coupling between 3-iodo and 3-stannyl tyrosine derivatives can be achieved in moderate yields,[39] while a Miyaura borylation–Suzuki intermolecular cross-coupling approach has been successfully used by van Vranken[40] and Hutton.[41,42]

Results and discussion

Our approach to the synthesis of the protected biphenol amino acid **1** and dityrosine **2** employs the Negishi cross-coupling reaction of an appropriate iodobiaryl **3** with the organozinc iodide **4**.[43,44] We have previously employed a related strategy in an intramolecular fashion for the synthesis of the macrocyclic tripeptide K13,[45] and intermolecularly in the synthesis of a non-natural, macrocyclic potential protease inhibitor.[46]

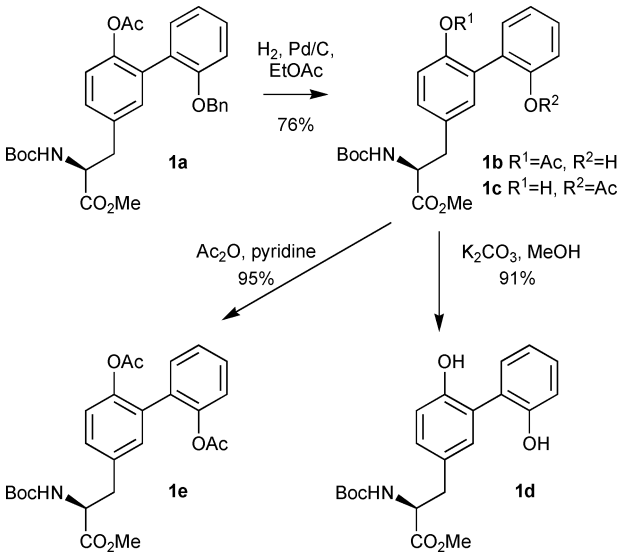


The synthesis of the aromatic iodide coupling partner **3a** used commercially available 2,2′-biphenol, which already has the biaryl linkage installed (Scheme 1). Mono-benzylation of 2,2′-biphenol was achieved efficiently (95% yield), using the conditions originally reported for an analogous transformation of 1,1′-bi-2-naphthol by Oda.[47] Regioselective mono-iodination was subsequently accomplished in high yield, following the procedure reported by Harrowven for a similar substrate,[48] based on earlier work,[49] and subsequent acetylation gave the protected iodobiphenol derivative **3a** (88% over two steps). Coupling of the amino acid-derived organozinc iodide **4** with the differentially protected iodobiphenol derivative **3a** furnished the desired mono-coupled product **1a** in 62% isolated yield (Scheme 1).



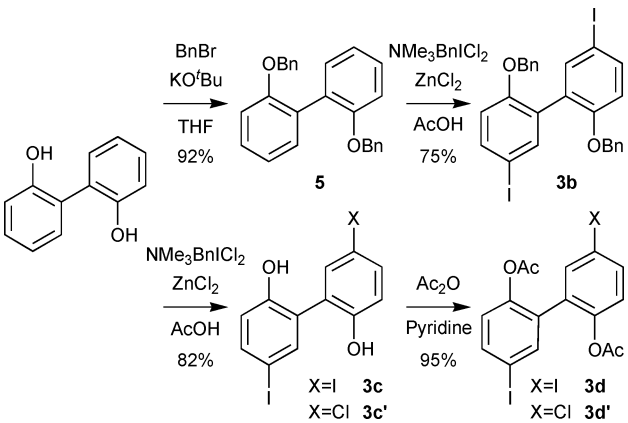
Scheme 1

The differentially protected 2,2′-biphenol **1a** appeared to be a potentially useful intermediate for further elaboration. Debenzylation, however, gave an inseparable 60 : 40 mixture of two compounds (as determined by ^{1}H NMR), which were ultimately identified as the expected phenol **1b**, and the product of acetyl transfer **1c**. Initially, it was suspected that the two sets of signals observed in the ^{1}H NMR spectrum might be the result of diastereoisomers resulting from atropisomerism. However, ^{1}H NMR studies in $CDCl_3$ (at 62 °C), and especially in DMSO (at 27 and 107 °C), which showed exactly the same ratio of signals in each case, instead strongly suggested the presence of two constitutional isomers. Structural assignment was supported by chemical transformations which afforded either the free biphenol derivative **1d** or the diacetylated compound **1e** as single compounds (Scheme 2). In addition, compounds **1d** and **1e** each exhibited a single set of signals in the ^{1}H NMR spectrum. Since neither of these compounds exhibited atropisomerism, it seemed reasonable to deduce that neither would the phenol **1b**. Debenzylation which resulted in acyl migration has been previously reported, although in this case intramolecular transfer occurred between nitrogen substituents.[50]



Scheme 2

Treatment of 2,2′-biphenol with KO′Bu and an excess of benzyl bromide gave the corresponding 2,2′-dibenzyl–biphenol derivative **5** in 92% yield. When the protected biphenol **5** was subjected to the conditions for iodination reported by Kajigaeshi,[51] the desired diiodinated protected biphenol **3b** was obtained in 75% isolated yield (Scheme 3).



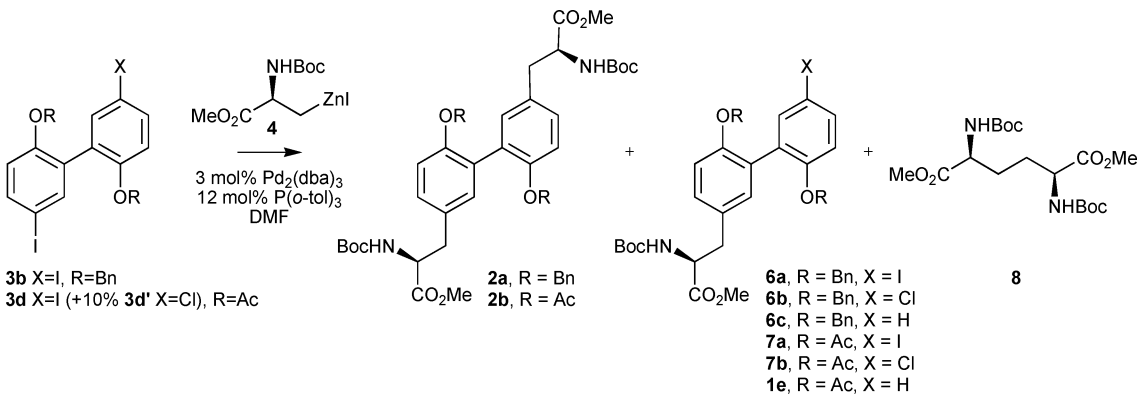
Scheme 3

Use of 2,2′-biphenol as a substrate for this reaction gave the corresponding unprotected diiodide derivative **3c** in 82% yield. Upon close inspection of the mass spectrum, it was apparent that the isolated material was an approximately 10 : 1 mixture of the diiodide **3c** and the corresponding mono-iodinated, mono-chlorinated product 5-chloro-5′-iodo-2,2′-biphenol **3c′**, as suggested by the relative intensities of the respective molecular ions. Efforts to separate the compounds by column chromatography proved unsuccessful. No competing chlorinated product was observed in the formation of the dibenzyl diiodide **3b**, presumably due to the less reactive nature of the dibenzyl ether precursor **5**. It is noteworthy that, although diiodination of 2,2′-biphenol with NMe_3BnICl_2–$ZnCl_2$[51] was not completely clean, giving small amounts of **3c′**, previous attempts to effect controlled iodination using a variety of iodination procedures gave complicated mixtures of mono- and poly-iodinated phenols, which proved difficult to separate and purify, an observation also made by Harrowven during attempted mono-iodination.[48] Treatment of the diiodide **3c** with acetic anhydride gave the acetylated derivative **3d** in 95% yield, again as a 10 : 1 mixture with the 5-chloro-5′-iodo derivative **3d′** (Scheme 3). The composition of this mixture was again determined by the relative intensities of the two corresponding molecular ions (EI+) and, in this case, also by the elemental analysis of the product mixture. The self-consistent results that were obtained from each method validated the earlier assessment of the **3c** : **3c′** ratio.

Previous studies established that 4-iodophenol, possessing an unprotected phenolic OH group, is compatible with the Negishi cross-coupling reaction of the organozinc iodide **4**.[52] Attempted cross-coupling reaction of the unprotected biphenol derivative **3c**, however, resulted in substantial amounts of alanine, presumably due to the increased acidity of the biphenolic derivative **3c** arising from a co-operative effect of hydrogen-bonding interactions between the OH substituents (PhOH $pK_a = 10.0$, 2,2′-biphenol $pK_{a1} = 7.6$ in water).[53–55]

The dibenzyl (**3b**) and diacetyl (**3d**) protected biphenol derivatives reacted under palladium catalysis with the organozinc reagent **4** to afford the expected bis-coupled products **2a** and **2b**, respectively, together with varying amounts of the mono-coupled (**6** and **7**) and the homo-coupled (**8**) products (Scheme 4 and Table 1). Use of an excess of zinc reagent **4** resulted in a satisfactory overall yield (65%) of the desired product **2b**.

The initial products of mono-coupling are the species **6a** and **7a**, which possess an iodine substituent at the 5′ position, and can then each, therefore, undergo a second cross-coupling reaction to afford the protected dityrosine derivative **2a** and **2b**, respectively. Compounds **6c** and **1e**, may arise from insertion of excess zinc, present in the reaction mixture, into the aromatic C–I bond, followed by protonation. Alternatively, compounds **6c** and **1e** could arise from initial insertion of zinc into one of the carbon–iodine bonds of **3b** or **3d**, respectively, prior to cross-coupling with the zinc reagent **4**. In an effort to minimise this side reaction, the solution of organozinc reagent **4** was transferred into a separate flask containing the electrophile. Although this allowed the isolation of the mono-coupled product **7a** (Table 1, entry 4) it did not prevent the formation of the reduced by-product **1e** when a large excess of the organozinc reagent **4** was employed (Table 1, entry 5). The mass balance in all these reactions suggested that, in the absence of an excess of the zinc reagent **4** (Table 1, entries 2 and 4), a substantial amount of the diiodide **3d** was consumed by non-productive side reactions. The crude NMR spectra did



3b X=I, R=Bn
3d X=I (+10% **3d'** X=Cl), R=Ac

2a, R = Bn
2b, R = Ac

6a, R = Bn, X = I
6b, R = Bn, X = Cl
6c, R = Bn, X = H
7a, R = Ac, X = I
7b, R = Ac, X = Cl
1e, R = Ac, X = H

8

Scheme 4

Table 1 Palladium catalyzed double cross-coupling reactions

Entry	Equivalents of reagent **4**	Diiodide	Products (%)[a]		
1	2.4	**3b**	**2a**, 22	**6a** + **6b**, 14[b]	**6c**, 19
2	1.2	**3d**	**2b**, 36	**7b**, 4	**1e**, 15
3	2.1	**3d**	**2b**, 50	**7b**, 4	**1e**, 15
4[c]	1.2	**3d**	**2b**, 19	**7b**, —[d]	**7a**, 25
5[c]	4.0	**3d**	**2b**, 65	**7b**, 5	**1e**, 16

[a] Yields are calculated with respect to diiodide derivative **3**, isolated after column chromatography. In all cases the homo-coupled product **8** was obtained in 4–8% isolated yield. [b] A 4 : 1 ratio of **6a** to **6b** was observed by ES+. [c] The solution of organozinc iodide **4** was added to a separate flask containing the diiodo biphenol derivative **3d**. [d] Not isolated.

contain evidence of additional aromatic by-products, but no other compounds were isolated.

A small amount of the mono-coupled product **7b**, which contains a chloro substituent at the 5′ position, was observed in entries 2, 3 and 5 (Table 1). This is not unexpected, since the diacetate derivative **3d** was accompanied by the corresponding 5′-chloro-5-iodo derivative **3d′**, which underwent a single selective cross coupling reaction at the 5-iodo position. It is interesting to note that a mixture of **6a** and **6b** was *also* obtained with the dibenzyl protected derivative **3b**, even though the starting material was devoid of any chlorinated biphenol (Table 1, entry 1). Compound **6b** could arise by a palladium-catalyzed aromatic Finkelstein reaction, in which the necessary chloride anions are produced during the zinc activation process (which uses Me_3SiCl); aromatic Finkelstein reactions have been previously reported using both copper[56] and nickel catalysts,[57] and an analogous fortuitous observation resulted in the discovery of the copper-catalyzed process.[56] Further experiments to investigate this preliminary observation of a palladium-catalyzed halide exchange appear warranted.

Conclusions

In summary, the expedient synthesis of a range of enantiomerically pure, novel biphenol amino acid derivatives is reported, which could find application in asymmetric catalysis and as useful synthetic intermediates. The synthesis of orthogonally protected dityrosine derivative **2b** (50% yield over 3 steps from commercially available materials) is also reported, in which the key step is a palladium catalyzed double cross-coupling reaction of the amino acid-derived organozinc reagent **4** and the diiodide **3d**.

Experimental

All moisture/air sensitive reactions were conducted under a positive pressure of nitrogen in flame dried or oven dried glassware. All reagents used were purchased from commercial sources or prepared and purified according to literature procedure. Dry DMF was distilled from calcium hydride and stored over 4 Å molecular sieves. Dry dichloromethane was distilled from calcium hydride. Dry THF was distilled from potassium benzophenone ketyl. Petroleum ether refers to the fraction with a boiling point between 40–60 °C.

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC-250, Bruker AMX2–400 or a Bruker DRX-500 NMR spectrometer at room temperature. Chemical shifts were measured relative to residual solvent and are expressed in parts per million (δ). Coupling constants (J) are given in Hertz and the measured values are rounded to one decimal place. High-resolution mass spectra were recorded using a MicroMass LCT operating in electrospray (ES) mode or a MicroMass Prospec operating in either electro impact (EI) or chemical ionisation (CI) mode. Chemical analyses were performed using a Perkin Elmer 2400 CHN elemental analyser. Optical rotations were measured on a Perkin Elmer 241 automatic polarimeter at λ 589 nm (Na, D-line) with a path length of 1 dm at the stated temperature and concentrations. The concentration is given in g per 100 ml and the optical rotations are quoted in 10^{-1} deg cm^2 g^{-1}. Infra-red spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer (υ_{max} in cm^{-1}) with KBr disks.

Thin layer chromatography (TLC) was performed on precoated plates (Merck aluminium sheets silica 60 F_{254}, art. no. 5554). Visualisation of compounds was achieved by illumination under ultraviolet light (254 nm) or using an appropriate staining reagent. Flash column chromatography was performed on silica gel 60 (Merck 9385).

General procedure 1: iodination of aromatic ethers using benzyltrimethylammonium dichloroiodate and zinc chloride

Following the method described by Kajigaeshi,[51] benzyltrimethylammonium dichloroiodate (2.2 eq.) and excess anhydrous $ZnCl_2$ was added to a stirred solution of the 1,1′-biarylphenol derivate (1 eq.) in acetic acid. The mixture was stirred at room temperature for 16 h. Water (20 ml) and aqueous $NaHSO_3$ (10% w/v solution, 20 ml) was added to the reaction mixture. The aqueous fraction was extracted with diethyl ether (3 × 50 ml), the organic fractions collected, dried over $MgSO_4$ and the solvent removed under reduced pressure to afford the crude product which was purified by silica gel column chromatography.

General procedure 2: zinc-activation and insertion into C–I bond using Me_3SiCl as the activating agent

Chlorotrimethylsilane (100–150 µl) was added to a rapidly stirred suspension of zinc powder (5–6 eq.) in dry DMF (2–3 ml) and the resulting mixture stirred for 15 min at room temperature under a nitrogen atmosphere. The suspension was allowed to settle, and the supernatant was removed by syringe and discarded. The zinc powder was washed with fresh dry DMF (3 × 1 ml) and the supernatant removed each time and discarded. Finally the powder was dried using a heating gun under reduced pressure. Once at room temperature, dry DMF (1 ml mmol^{-1} of iodo-alanine) was added to the zinc powder and the iodo-alanine derivative Boc–I–Ala–OMe (1.2 to 4 eq.) was added in one portion to the rapidly stirred suspension under nitrogen. An exotherm was typically observed during the zinc insertion process, which was controlled with the aid of a water bath at room temperature. The zinc insertion can be monitored by TLC (80% Et_2O–petroleum ether). Aryl iodide (1 eq.), $Pd_2(dba)_3$ (3 mol%) and P(*o*-Tol)$_3$ (12 mol%) were added to the stirred suspension at room temperature and the mixture stirred overnight. The suspension was filtered through silica gel, eluted with ethyl acetate and the solvent removed under reduced pressure to afford the crude reaction mixture which was purified by column chromatography.

General procedure 3: zinc-activation and insertion into C–I bond using Me_3SiCl as the activating agent

The general procedure 2 was followed, except that after zinc insertion, the stirred suspension was allowed to settle, and the solution transferred to a second flask which contained a stirred mixture of the aryl iodide (1 eq.), $Pd_2(dba)_3$ (3 mol%) and P(*o*-Tol)$_3$ (12 mol%) at room temperature under a nitrogen atmosphere, and was stirred overnight. The suspension was filtered through silica gel, eluted with ethyl acetate and the solvent removed under reduced pressure to afford the crude reaction mixture which was purified by column chromatography.

2′-Benzyloxybiphenyl-2-ol

Using the conditions originally reported for an analogous transformation by Oda,[47] a solution of benzyl bromide (1.91 ml, 16.2 mmol) in dry THF (75 ml) was added dropwise to a stirred suspension of 2,2′-biphenol (3.00 g, 16.1 mmol) and KO^{t}Bu (1.81 g, 16.2 mmol) in dry THF (300 ml) over a period of 10 min at room temperature, under an atmosphere of nitrogen. The suspension was heated at reflux for 14 h and the reaction was cooled to room temperature and concentrated under reduced pressure. The brown residue was partitioned between CH_2Cl_2 and a saturated aqueous solution of Na_2CO_3. The organic layer was separated, washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give a brown solid (4.44 g), which was purified by crystallization from methanol–water to give the benzyl monoprotected biphenol (4.22 g, 95%) as yellow crystals. Mp 97–98 °C (methanol–water). (Found: C, 82.7; H, 5.6. $C_{19}H_{16}O_2$ requires C, 82.6; H, 5.8%); υ_{max}(film)/cm^{-1} 3380, 3062, 1209; δ_H (400 MHz; $CDCl_3$) 5.12 (2 H, s, CH_2Ph), 6.33 (1 H, s, OH), 7.02 (2 H, br t, J 8.2, Ar), 7.11 (1 H, br d, J 9.0, Ar), 7.15 (1 H, br d, J 9.0, Ar) and 7.26–7.38 (9 H, m, Ar); δ_C (100 MHz; $CDCl_3$) 71.7, 114.3, 117.4, 120.9, 122.7, 126.3, 127.2, 128.0, 128.1, 128.5, 129.2 (×2), 131.2, 132.6, 135.9, 153.6 and 154.7; m/z (EI) 276 (M$^+$, 60%), 91 (100) (found M$^+$ 276.1149. $C_{19}H_{16}O_2$ requires 276.1150).

2′-Benzyloxy-5-iodobiphenyl-2-ol

Following the procedure originally described by Edgar,[49] an aqueous solution of NaOCl (4% available chlorine, 6.4 g, 3.6 mmol) was slowly added over a period of 30 min to a stirred solution of 2′-benzyloxybiphenyl-2-ol (500 mg, 1.81 mmol), NaOH (72 mg, 1.8 mmol) and NaI (270 mg, 1.8 mmol) in methanol (5 ml) in an ice bath. When the reaction was judged complete by TLC, a saturated aqueous solution of $Na_2S_2O_3$ (5 ml) was added, followed by 1 M HCl until pH 6–7 was achieved. The mixture was extracted with EtOAc (3 × 20 ml) and the organic phases combined and washed with water, brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and purification by column chromatography (8% EtOAc–petroleum ether) gave 2′-benzyloxy-5-iodobiphenyl-2-ol (653 mg, 90%) as a pale yellow oil. ν(film)/cm^{-1} 3340, 2960, 2920 and 1215; δ_H (400 MHz; $CDCl_3$) 5.12 (2 H, s, CH_2Ph), 6.34 (1 H, s, OH), 6.79 (1 H, d, J 9.0, Ar), 7.09–7.16 (2 H, m, Ar), 7.24–7.28 (2 H, m, Ar), 7.29–7.34 (4 H, m, Ar), 7.35–7.40 (1 H, m, Ar) and 7.52–7.57 (2 H, m, Ar); δ_C (100 MHz; $CDCl_3$) 71.8, 82.9, 114.3, 119.7, 122.8, 126.5, 127.3, 128.4, 128.6, 128.8, 129.8, 132.3, 135.6, 137.8, 139.5, 153.7 and 154.5; m/z (ES) 401 ((M–H)$^-$, 30%) (found (M–H)$^-$ 401.0029. $C_{19}H_{14}O_2I$ requires 401.0039).

2-Acetoxy-2′-benzyloxy-5-iodobiphenyl (3a)

An excess of Ac_2O (2 ml) was added dropwise to a stirred solution of 2′-benzyloxy-5-iodobiphenyl-2-ol (500 mg, 1.24 mmol) in pyridine (3 ml) and was left to stir overnight. EtOAc (20 ml) and water (30 ml) were added and the mixture separated. The aqueous phase was extracted with EtOAc (20 ml) and the combined organic phases were washed with 1 M HCl (30 ml), saturated aqueous $NaHCO_3$ (30 ml), water and brine. The organic layer was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. Purification by column chromatography (30% Et_2O–petroleum ether) gave the iodophenol derivative **3a** (540 mg, 98%) as a viscous yellow oil υ_{max}(film)/cm^{-1} 3050, 2995, 1761 and 1182; δ_H (400 MHz; $CDCl_3$) 1.99 (3 H, s, OAc), 5.06 (2 H, s, CH_2Ph), 6.93 (1 H, d, J 8.5, Ar), 6.98–7.03 (2 H, m, Ar), 7.20 (1 H, dd, J 7.5 and 2.0, Ar), 7.27–7.34 (6 H, m, Ar), 7.68 (1 H, dd, J 8.5, J 2.0, Ar) and 7.74 (1 H, d, J 2.0, Ar); δ_C (100 MHz; $CDCl_3$) 20.7, 70.5, 89.7, 113.2, 120.9, 124.4, 125.7, 126.9, 127.6, 128.4, 129.5, 130.9, 134.0, 136.9, 137.2, 140.3, 148.4, 155.5 and 168.9; m/z (EI) 444 (M$^+$, 12%), 402 (M$^+$–Ac, 12) and 91 (100) (found M$^+$ 444.0205. $C_{21}H_{17}O_3I$ requires 444.0222).

(2*S*)-*tert*-Butoxycarbonylamino-3-(2-acetoxy-2′-benzyloxybiphenyl-5-yl)propionic acid methyl ester (1a)

Using general procedure 2, compound **3a** (1.0 g, 2.25 mmol), Zn (0.88 g, 13.5 mmol), Boc–I–Ala–OMe (0.89 g, 2.70 mmol), $Pd_2(dba)_3$ (62 mg, 0.067 mmol) and P(o-Tol)$_3$ (82 mg, 0.27 mmol) in dry DMF (2.70 ml) gave, after purification by column chromatography (20% EtOAc–petroleum ether), the biaryl amino acid **1a** (726 mg, 62%) as an oil. $[\alpha]_D^{22}$ +32.7 (c 1.2 in $CHCl_3$); υ_{max}(film)/cm^{-1} 3372, 2964, 2924, 1759, 1744, 1713, 1500, 1444, 1362, 1220, 1189, 1011 and 751; δ_H (500 MHz; $CDCl_3$) 1.39 (9 H, s, $(CH_3)_3$C), 1.97 (3 H, s, OAc), 3.08–3.11 (2 H, m, β), 3.64 (3 H, s, OMe), 4.58 (1 H, dd, J 13.9 and 6.2, α), 5.00 (1 H, br s, NH), 5.03 (2 H, s, CH_2Ph), 6.95 (1 H, d J 8.2, Ar), 6.98 (1 H, td, J 7.5 and 0.9, Ar), 7.09 (1 H, d, J 9.0, Ar), 7.11–7.16 (2 H, m, Ar), 7.17 (1 H, dd J 7.5 and 1.8, Ar) and 7.23–7.30 (6 H, m, Ar); δ_C (125 MHz; $CDCl_3$) 20.7, 28.2(×3), 37.6, 52.2, 54.3, 70.5, 79.9, 113.3, 120.9, 122.4, 126.8(×2), 127.0, 127.5, 128.3(×2), 129.1(×2), 131.2, 131.8, 132.5, 133.4, 137.2, 147.5, 155.1, 155.7, 169.2 and 172.2; m/z (ES) 542 (MNa$^+$, 50%) and 420 (100) (found MNa$^+$ 542.2162. $C_{30}H_{33}NO_7Na$ requires 542.2155).

(2*S*)-*tert*-Butoxycarbonylamino-3-(2-acetoxybiphen-2′-ol-5-yl)-propionic acid methyl ester (1b) and (2*S*)-*tert*-butoxycarbonylamino-3-(2′-acetoxybiphen-2-ol-5-yl)propionic acid methyl ester (1c)

A degassed suspension of the amino acid **1a** (0.5 g, 0.96 mmol) in ethyl acetate (30 ml), Pd/C (10% on carbon, 50 mg) and 3 drops of acetic acid, under an atmosphere of hydrogen gas (balloon), was vigorously stirred until the reaction was judged complete by TLC analysis. The reaction mixture was filtered through Celite® and concentrated under reduced pressure. The crude mixture was purified by column chromatography (20% EtOAc–petroleum ether) to give isomeric phenols **1b** and **1c** (314 mg, 76% yield) as a mixture. υ_{max}(film)/cm^{-1} 3361, 2954, 2924, 1749, 1708, 1505, 1362, 1260, 1194, 1164, 1021 and 802; δ_H (500 MHz; $CDCl_3$) (X : Y ratio 40 : 60) 1.34 (9 H, s, $(CH_3)_3$C, Y), 1.39 (9 H, s, $(CH_3)_3$C, X), 1.98 (3 H, s, OAc, Y), 2.02 (3 H, s, OAc, X), 2.91 (1 H, dd, J 13.7 and 7.5, β, Y), 2.95 (1 H, dd, J 13.9 and 5.6, β, X), 3.03 (1 H, dd, J 13.9 and 5.7, β, X), 3.16 (1 H, dd, J 13.7 and 4.2, β, Y), 3.65 (3 H, s, OMe, X), 3.67 (3 H, s, OMe, Y), 4.48–4.53 (1 H, m, α, X), 4.56–4.64 (1 H, m, α, Y), 5.06 (1 H, br s, NH, X), 5.19 (1 H, br s, NH, Y), 6.83–6.67 (1 H, m, Ar, Y), 6.89 (1 H, t, J 7.5, Ar, Y), 6.92–6.99 (1 H, m, Ar, X and Y), 7.05–7.09 (1 H, m, Ar, X and Y), 7.11–7.24 (2 H, m, Ar, Y), 7.11–7.24 (3 H, m, Ar, X), 7.26–7.33 (1 H, m, Ar, X and Y) and 7.38 (1 H, t, J 7.8, Ar, X); δ_C (125 MHz; $CDCl_3$) (ratio 40 : 60) 20.5, 28.1, 37.1, 38.1, 52.1, 52.4, 54.3, 54.5, 79.8, 80.0, 116.2, 116.3, 119.6,

122.7, 122.8, 123.4, 124.0, 126.4, 127.4, 129.2, 129.4, 130.1, 130.2, 131.5, 131.6, 132.7, 134.3, 147.5, 148.5, 152.2, 153.3, 155.0, 169.7, 172.1 and 172.2; *m/z* (ES) 881 (M_2Na^+, 30%) and 452 (MNa^+, 100) (found MNa^+ 452.1692. $C_{23}H_{27}NO_7Na$ requires 452.1685).

(2*S*)-*tert*-Butoxycarbonylamino-3-(2,2′-biphenol-5-yl)propionic acid methyl ester (1d)

K_2CO_3 (0.50 g, 3.62 mmol) was added to a stirred solution of the mixture of phenols **1b** and **1c** (0.53 g, 1.23 mmol) in methanol (20 ml) at room temperature. The reaction was stirred overnight at this temperature and quenched by the addition of EtOAc (20 ml) and water (30 ml). The layers were separated and the aqueous phase extracted with EtOAc (20 ml). The organic phases were combined and washed with 1 M HCl (30 ml), saturated aqueous $NaHCO_3$ (30 ml), water and brine. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography (40% EtOAc–petroleum ether) gave the biphenol **1d** (433 mg, 91% yield) as a viscous oil. $[\alpha]_D^{22}$ +34.6 (*c* 1.0 in $CHCl_3$); υ_{max}(film)/cm^{-1} 3343, 2972, 2918, 1738, 1679, 1503, 1489, 1362, 1226 and 1163; δ_H (500 MHz; $CDCl_3$) 1.37 (9 H, s, $(CH_3)_3C$), 2.93 (1 H, dd, *J* 13.9 and 6.7, β), 3.07 (1 H, dd, *J* 13.9 and 5.3, β), 3.79 (3 H, s, OMe), 4.51–4.58 (1 H, m, α), 5.19 (1 H, d, *J* 8.2, NH) and 6.96–7.27 (9 H, m, Ar and ArOH); δ_C (125 MHz; $CDCl_3$) 28.2(×3), 37.5, 52.4, 54.6, 80.5, 116.9(×2), 121.1, 124.8, 125.2, 128.3, 129.3, 130.0, 131.3, 132.4, 152.1, 153.0, 155.4 and 172.6; *m/z* (ES) 410 (MNa^+, 50%) and 288 (100) (found MNa^+ 410.1566. $C_{21}H_{25}NO_6Na$ requires 410.1580).

(2*S*)-*tert*-Butoxycarbonylamino-3-(2,2′-diacetoxybiphenyl-5-yl)-propionic acid methyl ester (1e)

An excess of Ac_2O (2 ml) was added dropwise to a stirred solution of the mixture of phenols **1b** and **1c** (0.5 g, 1.16 mmol) in pyridine (3 ml) at room temperature. The reaction was stirred overnight at this temperature and quenched by the addition of EtOAc (20 ml) and water (30 ml). The layers were separated and the aqueous phase extracted with EtOAc (20 ml). The organic phases were combined and washed with 1 M HCl (30 ml), saturated aqueous $NaHCO_3$ (30 ml), water and brine. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography (20% EtOAc–petroleum ether) gave the diacetate **1e** (519 mg, 95%) $[\alpha]_D^{22}$ +33.6 (*c* 0.5 in $CHCl_3$); υ_{max}(film)/cm^{-1} 3372, 2964, 2913, 1764, 1708, 1499, 1367, 1194, 1011, 914 and 756; δ_H (400 MHz; $CDCl_3$) 1.41 (9 H, s, $(CH_3)_3C$), 2.03 (3 H, s, OAc), 2.05 (3 H, s, OAc), 3.06 (1 H, dd, *J* 13.9 and 5.9, β), 3.14 (1 H, dd, *J* 13.9 and 5.8, β), 3.71 (3 H, s, OMe), 4.55–4.63 (1 H, m, α), 5.05 (1 H, d, *J* 7.9, NH), 7.04 (1 H, br s, Ar), 7.08 (1 H, d, *J* 8.2, Ar), 7.13 (1 H, d, *J* 7.6, Ar), 7.14–7.17 (1 H, m, Ar), 7.24–7.30 (2 H, m, Ar) and 7.39 (1 H, ddd, *J* 7.9, 6.7 and 2.3, Ar); δ_C (125 MHz; $CDCl_3$) 20.7(×2), 28.3(×3), 37.6, 52.3, 54.3, 80.0, 122.5, 122.6, 125.9, 129.0, 129.7, 130.3, 130.5, 131.1, 132.2, 133.7, 147.1, 148.0, 155.0, 169.3(×2) and 172.1; *m/z* (ES) 494 (MNa^+, 100%) and 372 (30) (found MNa^+ 494.1782. $C_{25}H_{29}NO_8Na$ requires 494.1791).

2,2′-Dibenzyloxybiphenyl (5)

Modifying the conditions originally reported by Oda for mono-benzylation of a binaphthol derivative,[47] benzyl bromide (0.96 ml, 8.03 mmol) was added dropwise to a stirred solution of 2,2′-biphenol (0.50 g, 2.68 mmol) and KO′Bu (0.66 g, 5.90 mmol) in THF (30 ml) at room temperature, under an atmosphere of nitrogen. The stirred suspension was heated at reflux for 14 h and the reaction was then cooled to room temperature and concentrated under reduced pressure. The brown residue was partitioned between CH_2Cl_2 and a saturated aqueous solution of Na_2CO_3. The organic layer was separated, washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give, without the need for further purification, the dibenzyl protected biphenol[58] **5** (0.90 g, 92%) as a white solid. Mp 100–102 °C; υ_{max}(film)/cm^{-1} 3065, 3016, 2919, 2852, 1592, 1500, 1481, 1442, 1263, 1224, 1021, 749 and 696; δ_H (250 MHz; $CDCl_3$) 5.07 (4 H, s, CH_2Ph), 7.03 (2 H, dd, *J* 8.2 and 0.9, Ar), 7.11 (2 H, td, *J* 7.3 and 0.9, Ar), 7.26 (8 H, br s, Ar) and 7.32–7.44 (6 H, m, Ar); δ_C (62.5 MHz; $CDCl_3$) 70.2, 113.0, 120.8, 126.6, 127.4, 128.3, 128.5, 128.6, 131.7, 137.6 and 156.3; *m/z* (CI) 384 ($M + NH_4^+$, 8%), 367 (MH^+, 10), 289, 275, 216, 199, 108 and 91 (100).

2,2′-Dibenzyloxy-5,5′-diiodobiphenyl (3b)

Following general procedure 1, dibenzyl protected biphenol **5** (0.40 g, 1.09 mmol), benzyltrimethylammonium dichloroiodate (0.836 g, 2.40 mmol) and $ZnCl_2$ (1.6 g, 11.7 mmol) in acetic acid (24 ml) gave, after purification by column chromatography (10% EtOAc–petroleum ether), the diiodo dibenzyl biphenol derivative **3b** (506 mg, 75%) as a white solid. Mp 144–146 °C; υ_{max}(film)/cm^{-1} 3025, 2916, 2847, 1494, 1450, 1252, 1242, 1144, 1005, 798, 733 and 694; δ_H (250 MHz; $CDCl_3$) 4.98 (4 H, s, CH_2Ph), 6.73 (2 H, d, *J* 8.2, Ar), 7.16–7.30 (10 H, m, Ar), 7.55 (2 H, dd, *J* 8.2 and 2.1, Ar) and 7.58 (2 H, s, Ar); δ_C (62.5 MHz; $CDCl_3$) 70.3, 82.9, 115.0, 126.6, 127.7, 128.5, 129.3, 136.7, 137.6, 139.8 and 156.0; *m/z* (ES) 641 (MNa^+, 100%) and 515 (34) (found MNa^+ 640.9457. $C_{26}H_{20}O_2I_2Na$ requires 640.9451).

5,5′-Diiodo-2,2′-biphenol (3c) with ~10% 5-chloro-5′-iodo-2,2′-biphenol (3c′)

Following general procedure 1, 2,2′-biphenol (0.40 g, 2.15 mmol), benzyltrimethylammonium dichloroiodate (1.64 g, 4.71 mmol) and $ZnCl_2$ (1.6 g, 11.7 mmol) in acetic acid (24 ml) gave, after purification by column chromatography (20% EtOAc–petroleum ether), diiodo biphenol **3c** (0.772 g, 82%), contaminated with ~10% 5-chloro-5′-iodo-2,2′-biphenol **3c′**. υ_{max}(film)/cm^{-1} 3155 (br), 1474, 1382, 1222, 1180, 1111, 1015 and 877; δ_H (250 MHz; CD_3OD) 5.12 (2 H, br s, OH), 6.73 (2 H, d, *J* 8.5, Ar) and 7.45–7.57 (4 H, m, Ar); δ_C (62.5 MHz; CD_3OD) 80.6, 117.9, 127.1, 137.2, 139.3 and 153.9; *m/z* (EI) 438 (M^+(**3c**), 100%) and 346 (M^+(**3c′**), 10%) (found M^+ 437.862264. $C_{12}H_8O_2I_2$ requires 437.861384).

2,2′-Acetoxy-5,5′-diiodobiphenyl (3d) with ~10% 2,2′-acetoxy-5-chloro-5′-iodobiphenyl (3d′)

Acetic anhydride (2.0 ml, 21 mmol) was added dropwise to a stirred solution of the diiodo biphenol **3c** (0.50 g, 1.14 mmol) in pyridine (3 ml), and the solution allowed to stir for 16 h. EtOAc (20 ml) and water (30 ml) were added to the reaction mixture. The layers were partitioned, separated and the aqueous phase washed with EtOAc (20 ml). The combined organic fractions were washed with 1 M HCl (30 ml), saturated aqueous $NaHCO_3$

(30 ml), water and brine. The organic fraction was dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give, after purification by column chromatography (30% EtOAc–petroleum ether), the diacetate protected biphenol derivative **3d** (566 mg, 95%), contaminated with ~10% 2,2′-acetoxy-5-chloro-5′-iodobiphenyl (**3d′**) as a white solid. Mp 119–123 °C; υ_{max}(film)/cm^{-1} 3508, 3327, 3064, 2919, 2847, 1762, 1490, 1468, 1368, 1205, 1182, 1114, 1019 and 906; δ_H (250 MHz; $CDCl_3$) 2.06 (6 H, s, OAc), 6.92 (2 H, d, *J* 8.5, Ar), 7.62 (2 H, d, *J* 2.1, Ar) and 7.70 (2 H, dd, *J* 8.5 and 2.1, Ar); δ_C (62.5 MHz; $CDCl_3$) 20.7, 89.9, 124.7, 131.2, 138.3, 139.6, 147.9 and 168.8; *m*/*z* (EI) 522 (M$^+$(**3d**), 21%), 430 (M$^+$(**3d′**), 2); *m*/*z* (ES) 545 (MNa$^+$(**3d**), 100%) (found MNa$^+$ 544.8714. $C_{16}H_{12}O_4I_2Na$ requires 544.8723).

Table 1, entry 1

Following general procedure 2, 2,2′-dibenzyloxy-5,5′-diiodobiphenyl **3b** (250 mg, 0.40 mmol), Zn (320 mg, 4.89 mmol), Boc–I–Ala–OMe (320 mg, 0.97 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol) and P(*o*-Tol)$_3$ (15 mg, 0.048 mmol) in dry DMF (0.97 ml) gave, after purification by column chromatography (gradient 10–20% EtOAc–petroleum ether), the mono-coupled products **6a**, **6b** and **6c** as a mixture, and the bis- and homo-coupled products **2a** and **8** also as a mixture. Compounds **6a** and **6b** were separated from **6c** by column chromatography (2% Et_2O–petroleum ether) to give (2*S*)-*tert*-butoxycarbonylamino-3-(2,2′-dibenzyloxy-5′-iodobiphenyl-5-yl)propionic acid methyl ester (**6a**) and (2*S*)-*tert*-butoxycarbonylamino-3-(2,2′-dibenzyloxy-5′-chloro-biphenyl-5-yl)propionic acid methyl ester (**6b**) as a 80 : 20 mixture (37 mg, 14%) as an oil δ_H (500 MHz; $CDCl_3$) 1.40 (9 H, s, $(CH_3)_3C$), 3.00–3.10 (2 H, m, β), 3.66 (3 H, s, OMe), 4.51–4.58 (1 H, m, α), 4.95 (2 H, s, CH_2Ph), 4.97 (2 H, s, CH_2Ph), 4.99 (1 H, br s, NH), 6.69 (1 H, d, *J* 8.6, Ar), 6.88 (1 H, d, *J* 8.5, Ar), 7.00–7.07 (3 H, m, Ar), 7.12–7.26 (9 H, m, Ar), 7.53 (1 H, dd, *J* 8.6 and 2.3, Ar) and 7.56 (1 H, d, *J* 2.3, Ar); δ_C (125 MHz; $CDCl_3$) 28.3, 37.4, 52.1, 54.5, 70.2, 70.3, 79.9, 82.9, 112.8, 115.1, 126.5, 126.6, 127.0, 127.4, 127.5, 128.0(×2), 128.3(×2), 126.6, 130.9, 132.3, 136.9(×2), 137.2, 139.8, 155.2, 156.1 and 172.4; *m*/*z* (ES) 716 (MNa$^+$ (**6a**), 100%) and 624 (MNa$^+$ (**6b**), 30%) (found MNa$^+$ (**6a**) 716.1461. $C_{35}H_{36}NIO_6Na$ requires 716.1485) and (found MNa$^+$ (**6b**) 624.2133. $C_{35}H_{36}NClO_6Na$ requires 624.2129), and (2*S*)-*tert*-butoxycarbonylamino-3-(2,2′-dibenzyloxybiphenyl-5-yl)propionic acid methyl ester (**6c**) (43.5 mg, 19%) as an oil. $[\alpha]_D^{22}$ +46.5 (*c* 0.4 in $CHCl_3$); υ_{max}(film)/cm^{-1} 3423, 2915, 2849, 1739, 1711, 1495, 1448, 1363, 1222, 1161, 1016 and 734; δ_H (500 MHz; $CDCl_3$) 1.40 (9 H, s, $(CH_3)_3C$), 3.02–3.11 (2 H, m, β), 3.66 (3 H, s, OMe), 4.54–4.58 (1 H, m, α), 4.97 (1 H, br s, NH), 4.98 (2 H, s, CH_2Ph), 5.00 (2 H, s, CH_2Ph), 6.89 (1 H, d, *J* 8.2, Ar), 6.96 (1 H, br d, *J* 7.8, Ar), 7.00–7.08 (4 H, m, Ar), 7.14–7.19 (3 H, m, Ar), 7.19–7.23 (5 H, m, Ar) and 7.28–7.30 (3 H, m, Ar); δ_C (125 MHz; $CDCl_3$) 28.3(×3), 37.4, 52.1, 54.5, 70.2(×2), 79.8, 112.9, 120.7, 126.5(×3), 126.6(×3), 127.3, 127.8(×2), 128.4(×4), 128.6, 128.7, 128.8, 129.1, 131.4, 132.5, 137.5, 155.4(×2), 156.2 and 172.5; *m*/*z* (ES) 590 (MNa$^+$, 50%) and 534 (100) (found MNa$^+$ 590.2545. $C_{35}H_{37}NO_6Na$ requires 590.2519).

The mixture of compounds **2a** and **8** was separated by a second chromatography column (8% Et_2O–petroleum ether), which gave the bis-coupled product (2*S*)-*tert*-butoxycarbonylamino-3-{2,2′-dibenzyloxy-5′-[(2*S*)-*tert*-butoxycarbonylamino-2-methoxycarbonyl-ethyl]biphenyl-5-yl}propionic acid methyl ester (**2a**) (68 mg, 22%) as an oil $[\alpha]_D^{22}$ +37.2 (*c* 2.0 in $CHCl_3$); υ_{max}(film)/cm^{-1} 3367, 2974, 2916, 1745, 1712, 1497, 1362, 1249, 1220, 1166 and 1016; δ_H (500 MHz; $CDCl_3$) 1.39 (18 H, s, $(CH_3)_3C$), 3.05 (4 H, d, *J* 5.8, β), 3.65 (6 H, s, OMe), 4.53–4.58 (2 H, m, α), 4.97 (4 H, s, CH_2Ph), 5.01 (2 H, br s, NH), 6.88 (2 H, d, *J* 8.2, Ar), 7.02–7.07 (4 H, m, Ar), 7.10–7.19 (4 H, m, Ar) and 7.20–7.28 (6 H, m, Ar); δ_C (125 MHz; $CDCl_3$) 28.2(×3), 37.5, 52.1, 54.5, 70.3, 79.8, 130.0, 126.5(×2), 127.3, 127.9, 128.3(×2), 128.5, 129.2, 132.3, 137.4, 155.1, 155.3 and 172.5; *m*/*z* (ES) 791.6 (MNa$^+$, 100%) and 769.6 (MH$^+$, 45) (found MH$^+$ 769.3699. $C_{44}H_{53}N_2O_{10}$ requires 769.3700), and the homo-coupled compound (2*S*,5*S*)-2,5-bis-*tert*-butoxycarbonylaminohexane-1,6-dioic acid dimethyl ester (**8**) (31 mg, 8%) as an oil υ_{max}(film)/cm^{-1} 3361, 2968, 2925, 1742, 1712, 1515, 1362, 1249, 1161 and 1057; δ_H (500 MHz; $CDCl_3$) 1.42 (18 H, s, $(CH_3)_3C$), 1.57–1.68 (2 H, m, β), 1.84–1.93 (2 H, m, β), 3.72 (6 H, s, OMe), 4.26–4.35 (2 H, m, α) and 5.03 (2 H, d, *J* 7.8, NH); δ_C (125 MHz; $CDCl_3$) 28.2, 28.8, 52.4, 52.9, 80.0, 155.3 and 172.8; *m*/*z* (ES) 427 (MNa$^+$, 100%) and 405 (MH$^+$, 40) (found MH$^+$ 405.2221. $C_{18}H_{33}N_2O_8$ requires 405.2237).

Table 1, entry 2

Following general procedure 2, diiodo diacetate biphenol derivative **3d** (250 mg, 0.48 mmol), Zn (187 mg, 2.86 mmol), Boc–I–Ala–OMe (188 mg, 0.57 mmol), $Pd_2(dba)_3$ (13 mg, 0.014 mmol) and P(*o*-Tol)$_3$ (17 mg, 0.057 mmol) in dry DMF (0.57 ml) gave, after purification by column chromatography (gradient 20–30% EtOAc–petroleum ether), the mono-coupled products **1e**, **7b** and the homo-coupled product **8** as a mixture, and the bis-coupled product (2*S*)-*tert*-butoxycarbonylamino-3-{2,2′-diacetoxy-5′-[(2*S*)-*tert*-butoxycarbonylamino-2-methoxycarbonylethyl]biphenyl-5-yl}propionic acid methyl ester (**2b**) (116 mg, 36%) as an oil $[\alpha]_D^{22}$ +46.5 (*c* 1.0 in $CHCl_3$); υ_{max} (film)/cm^{-1} 3370, 2979, 2928, 1760, 1749, 1708, 1500, 1365, 1195, 1165, 1055, 1012 and 910; δ_H (500 MHz; $CDCl_3$) 1.40 (18 H, s, $(CH_3)_3C$), 2.02 (6 H, s, OAc), 3.03 (2 H, dd, *J* 13.8 and 6.2, β), 3.11 (2 H, dd, *J* 13.8 and 5.5, β), 3.69 (6 H, s, OMe), 4.54–4.59 (2 H, m, α), 5.05 (2 H, br d, *J* 7.5, NH), 7.00 (2 H, br s, Ar), 7.05 (2 H, d, *J* 8.2, Ar) and 7.15 (2 H, br d, *J* 8.2, Ar); δ_C (125 MHz; $CDCl_3$) 14.1, 28.2(×3), 37.6, 52.3, 54.3, 80.0, 122.5, 129.8, 130.3, 132.0, 133.8, 147.1, 155.1, 169.3 and 172.1; *m*/*z* (ES) 695 (MNa$^+$, 1%), 673 (MH$^+$, 18) and 517 (100) (found MNa$^+$ 695.2761. $C_{34}H_{44}N_2O_{12}Na$ requires 695.2792).

The mixture of compounds **1e**, **7b** and **8** was separated by a second chromatography column (8% Et_2O–petroleum ether), which gave the mono-coupled product (2*S*)-*tert*-butoxycarbonylamino-3-(2,2′-diacetoxy-5′-chloro-biphenyl-5-yl)propionic acid methyl ester (**7b**) (9.5 mg, 4%) as an oil $[\alpha]_D^{22}$ +53.7 (*c* 0.9 in $CHCl_3$); υ_{max}(film)/cm^{-1} 3375, 2980, 2923, 1759, 1711, 1499, 1364, 1191, 1042, 1008, 907 and 734; δ_H (500 MHz; $CDCl_3$) 1.41 (9 H, s, $(CH_3)_3C$), 2.03 (3 H, s, OAc), 2.05 (3 H, s, OAc), 3.05 (1 H, dd, *J* 13.9 and 6.0, β), 3.14 (1 H, dd, *J* 13.9 and 6.0, β), 3.71 (3 H, s, OMe), 4.55–4.61 (1 H, m, α), 5.04 (1 H, d, *J* 7.8, NH), 7.02 (1 H, d, *J* 1.8, Ar), 7.07 (1 H, d, *J* 8.6, Ar), 7.08 (1 H, d, *J* 8.4, Ar), 7.16 (1 H, dd, *J* 8.4 and 1.8, Ar), 7.26 (1 H, d, *J* 2.6, Ar) and 7.34 (1 H, dd, *J* 8.6 and 2.6, Ar); δ_C (125 MHz; $CDCl_3$) 20.6, 20.7, 28.3(×3), 37.6, 52.4, 54.3, 80.1, 122.7, 123.8, 128.9, 129.1, 130.2, 130.9, 131.2, 131.9, 134.0(×2), 146.6, 146.9, 155.0, 169.1(×2) and 172.0; *m*/*z* (ES) 528 (MNa$^+$, 90%), 506 (MH$^+$, 34) and 406 (100)

(found MNa^+ 528.1388. $C_{25}H_{28}NO_8ClNa$ requires 528.1401), the mono-coupled product **1e** (34 mg, 15%) and the homo-coupled product **8** (9 mg, 4%) as oils, all spectroscopically consistent with the data already reported.

Table 1, entry 4

2*S*-*tert*-Butoxycarbonylamino-3-(2,2′-diacetoxy-5′-iodobiphenyl-5-yl)propionic acid methyl ester (7a). A pure sample of compound **7a** was obtained following general procedure 3, with diiodo diacetate biphenol derivative **3d** (250 mg, 0.48 mmol), Zn (187 mg, 2.86 mmol), Boc–I–Ala–OMe (188 mg, 0.57 mmol), $Pd_2(dba)_3$ (13 mg, 0.014 mmol) and P(*o*-Tol)$_3$ (17 mg, 0.057 mmol) in dry DMF (0.57 ml) which gave, after purification by column chromatography (gradient 20–30% EtOAc–petroleum ether), the mono-coupled product **7a** (72 mg, 25%) as an oil $[\alpha]_D^{22}$ +33.1 (*c* 0.7 in $CHCl_3$); υ_{max}(film)/cm^{-1} 3377, 2969, 2919, 1760, 1711, 1494, 1478, 1365, 1195, 1007 and 912; δ_H (500 MHz; $CDCl_3$) 1.41 (9 H, s, $(CH_3)_3C$), 2.03 (3 H, s, OAc), 2.06 (3 H, s, OAc), 3.05 (1 H, dd, *J* 13.9 and 6.0, β), 3.14 (1 H, dd, *J* 13.9 and 5.5, β), 3.71 (3 H, s, OMe), 4.55–4.61 (1 H, m, α), 5.04 (1 H, br d, *J* 8.1, NH), 6.89 (1 H, d, *J* 8.6, Ar), 7.01 (1 H, br s, Ar), 7.08 (1 H, d, *J* 8.2, Ar), 7.16 (1 H, br d, *J* 8.2, Ar), 7.59 (1 H, d, *J* 2.2, Ar) and 7.68 (1 H, dd, *J* 8.6 and 2.2, Ar); δ_C (125 MHz; $CDCl_3$) 20.6, 20.7, 28.3(×3), 37.6, 52.3, 54.3, 80.1, 89.8, 122.7, 124.5, 128.9, 130.2, 131.9, 132.7, 134.0, 137.9, 139.7, 146.9, 148.0, 155.0, 168.9, 169.1 and 172.0; *m*/*z* (ES) 620 (MNa^+, 100%) (found MNa^+ 620.0742. $C_{25}H_{28}NO_8INa$ requires 620.0757). The bis-coupled product **2b** (61 mg, 19%) and the homo-coupled product **8** (15 mg, 6%) were also obtained as oils and spectroscopically consistent with the data already reported.

Table 1, entry 5

Following general procedure 3, diiodo diacetate biphenol derivative **3d** (250 mg, 0.48 mmol), Zn (0.62 g, 9.48 mmol), Boc–I–Ala–OMe (0.62 g, 1.91 mmol), $Pd_2(dba)_3$ (13 mg, 0.014 mmol) and P(*o*-Tol)$_3$ (17 mg, 0.057 mmol) in dry DMF (1.91 ml) gave, after purification by column chromatography (gradient 20–30% EtOAc–petroleum ether), the bis-coupled product **2b** (210 mg, 65%), and after further purification by column chromatography (8% Et_2O–petroleum ether), the mono-coupled products **1e** (36 mg, 16%) and **7b** (12 mg, 5%), and the homo-coupled product **8** (46 mg, 6%), all obtained as oils and spectroscopically consistent with the data already reported.

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