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Efficient Asymmetric Synthesis of the Four Diastereomers of Diphenacoum and Brodifacoum

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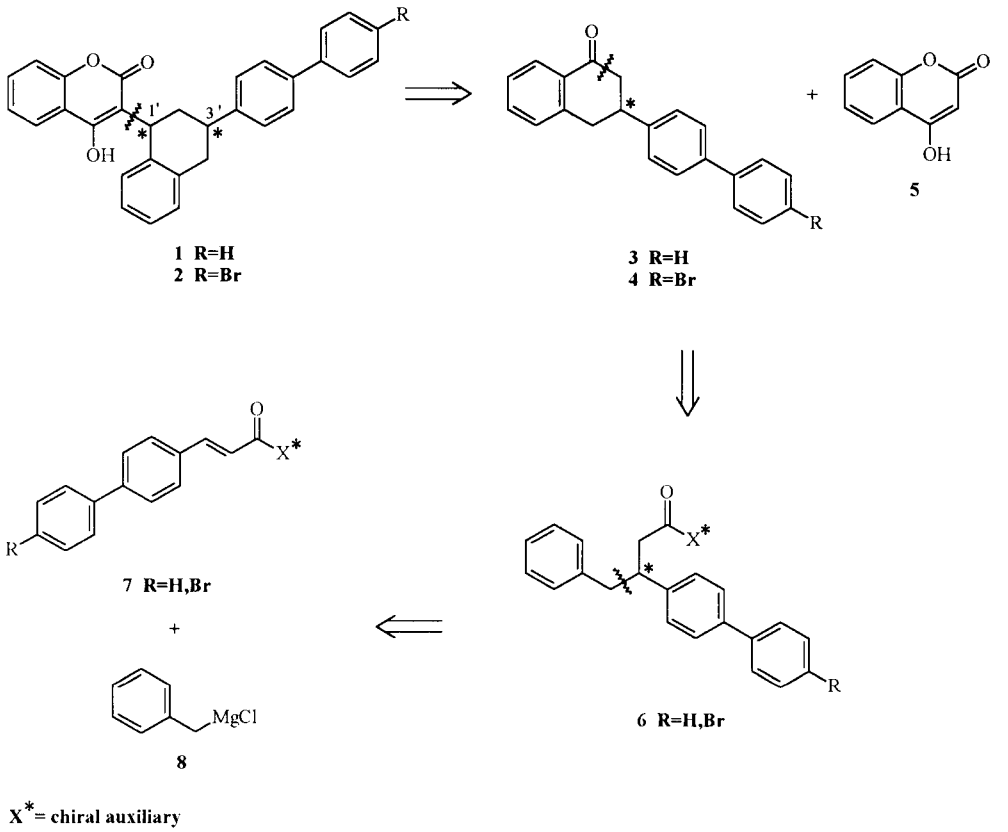
Abstract: A highly stereo- and enantio-selective approach to the four stereoisomers of the rodenticides, diphenacoum and brodifacoum, is described. The key step involves the stereospecific formation of one of the crucial bonds in the molecular backbone, and is based on asymmetric organocopper 1,4-addition to chiral imides. Intramolecular cyclization of the resulting butanoate and coupling with 4-hydroxycoumarin, afford the title compounds.

The 3-[4-(*p*-substituted phenyl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxycoumarins, diphenacoum **1** and brodifacoum **2**, have attracted considerable interest over the last few years on account of their anticoagulant properties, which render them useful as rodenticides or for the treatment of circulatory diseases in humans. Among the plethora of synthetic routes[1-5] to these compounds, none has addressed the issue of stereocontrol at any of the stereogenic centres, hence limiting the utilization of **1** and **2** as mixtures of four racemates. Owing to environmental factors there is a growing opposition against the marketing of racemates. The re-examination of older drugs may thus lead to the introduction of a single enantiomer in cases where a racemate had been marketed previously.[6,7] Recently, we have developed a novel and improved synthetic route[8,9] to **1** and **2** which possesses the potential to address the issue of stereocontrol in the synthesis of these anticoagulants. Herein, we thus report on the first stereoselective synthesis of diphenacoum **1** and brodifacoum **2**, utilizing asymmetric organocopper chemistry[10] to form one of the crucial bonds in their carbon backbones.

The retro-synthetic sequence, **1/2** $\Rightarrow$ **3/4** + **5** $\Rightarrow$ **6** $\Rightarrow$ **7** + **8**, indicates that the protocol for constructing the 1,3-disubstituted tetrahydronaphthyl framework is to involve the synthesis of chiral imides of type **7**, stereoselective 1,4-addition of a benzyl ligand **8** to give 3,4-diarylbutanoates of type **6**, and subsequent cyclization, reduction and condensation with coumarin **5** to give diphenacoum **1** and brodifacoum **2** (Scheme 1).

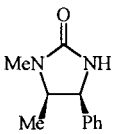


Scheme 1

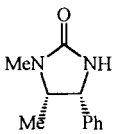
The successful asymmetric 1,4-addition of benzyl based organocuprates to chiral α,β-unsaturated imides,[10] prompted the utilization of the readily accessible (4*S*,5*R*)-(+)- **9** and (4*R*,5*S*)-(-)-1,5-dimethyl-4-phenyl-2-imidazolidinone **10**[11] as chiral auxiliaries for stereocontrol at the β-acyl position in intermediate of type 7. Since the requisite conjugated biphenyl imides **13a,b** and **14a,b** are easily obtainable from their corresponding achiral analogs, compounds **11** and **12** were first prepared in good yield *via* Wittig condensation of ethyl chloroacetate with biphenyl- and 4'-bromobiphenylcarboxaldehyde, respectively, as previously described.[8,9] Thus, the esters **11** and **12** were transformed *via* consecutive hydrolysis and halo-de-hydroxylation into the corresponding acid chlorides which were subsequently reacted with the lithium anions of **9** and **10** to afford the chiral imides **13a,b** and **14a,b** in 70-74% overall yields (Scheme 2).

Organocopper chemistry was then successfully applied to the synthesis of biphenyl imides **15a,b** and **16a,b** by reacting the 1,4-Michael acceptors **13a,b** and **14a,b** separately with the BnCu-TMEDA complex in the presence of $^{n}Bu_2BOTf$,[10] resulting in good yields (85-88%), and regio- (only 1,4-addition) and diastereo-

selectivity (97-99% de) in all cases. The diastereoselectivity of these reactions was established by ^{1}H NMR spectroscopy as was previously described.[12,13] The absolute configuration of the N-acyl imidazolidinones **15a,b** and **16a,b** was tentatively assigned assuming that the stereochemistry of the course of these reactions is the same as for the conjugate addition of benzylcopper reagents to the analogous cinnamoyl imides.[10] Comparison of the CD spectra of imides **15a,b** and **16a,b** with that of **17** (Figure 1) unequivocally confirmed their absolute configurations, with the (-)-(3'*R*)- **15b,16b** and the (+)-(3'*S*)-biphenyl imides **15a** and **16a** exhibiting high-amplitude negative and positive Cotton effects respectively in the 215-225 nm region for the π,π^* transition. The n,π^* transition shows a weak positive extremum in the 240-260 region for the (-)-3'*R* analogues **15b** and **16b**, with the signs of these Cotton effects being reversed for the (+)-3'*S* isomers **15a** and **16a**.



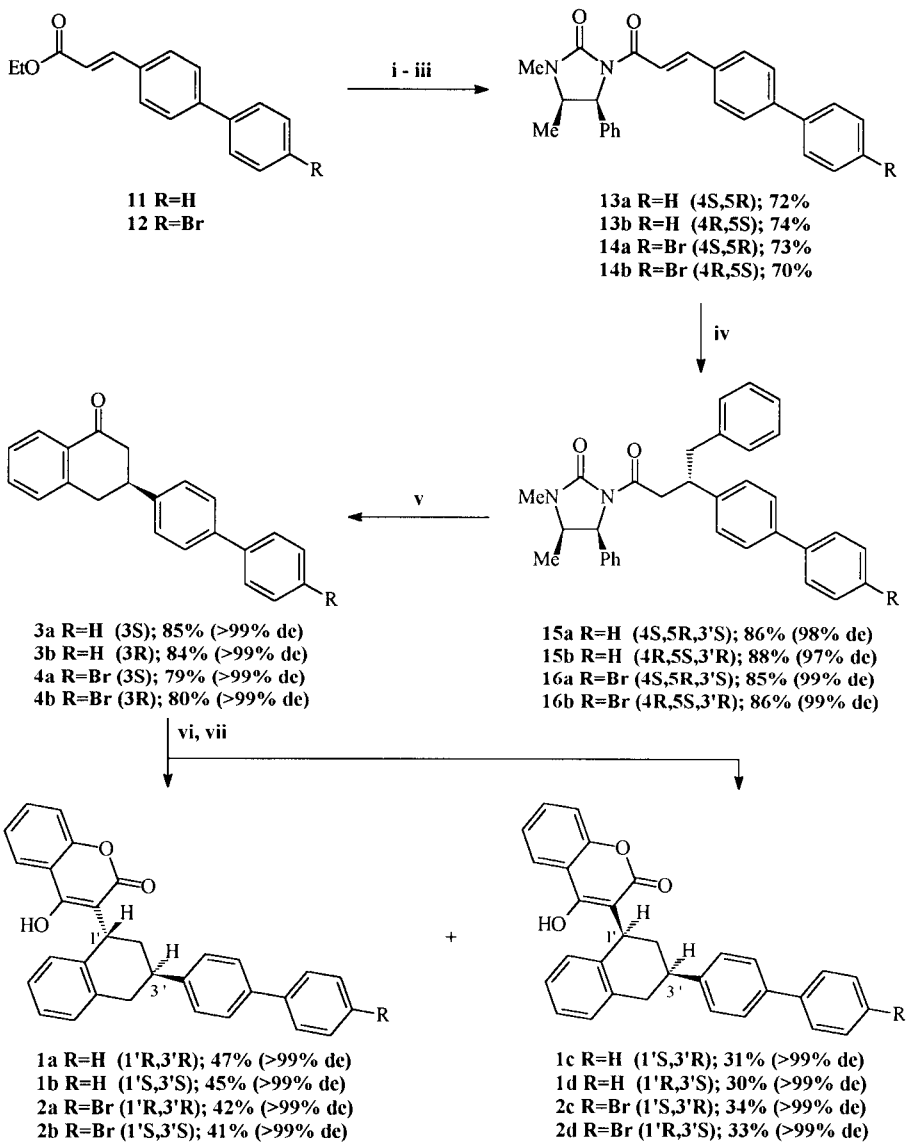
9 (4S,5R)



10 (4R,5S)

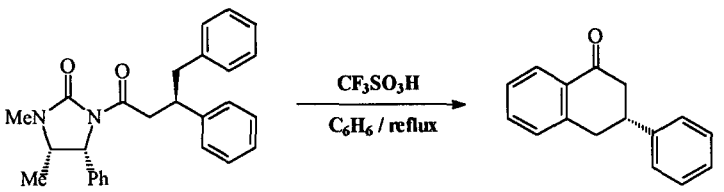
Direct transformation of imides **15a,b** and **16a,b** into the tetralones **3a,b** and **4a,b** was initially approached *via* a Friedel-Crafts type cyclization[8,9] involving treatment with $AlCl_3$ in toluene. These reactions, however, were hampered by low yields (5-10%), presumably due to the poor nucleofugic properties of the imidazolidinone moiety. However, trifluoromethanesulfonic acid[14] in dry benzene at 80°C effectively catalyzed the cyclization of N-acyl imidazolidinones **15a,b** and **16a,b** into tetralones **3a,b** and **4a,b** in good yields (79-85%). This method also led to an excellent recovery (87-90%) of the chiral auxiliaries, a major advantage from an economical perspective. The absolute configuration of the tetralones **3a,b** and **4a,b** was again confirmed by comparison of CD data (Figure 2) with those of (3*R*)-3-phenyl-1-tetralone **18**, obtained *via* cyclization of the correponding N-acyl imidazolidinone **17** (Scheme 3). The high-amplitude Cotton effects resulting from π,π^* transitions (215-225 nm) reflected *R* absolute configurations for **3b** and **4b**, and *S* absolute configurations for **3a** and **4a**. Despite the weaker Cotton effects arising from n,π^* (240-250 nm *vs* 230-240 nm for **18**), ^1L_a (250-265 nm *vs* 245-255 nm for **18**) and ^1L_b (285-305 nm *vs* 280-300 nm for **18**) transitions being shifted to longer wave-lengths due to the increased number of benzene chromophores in the biphenyl tetralones, the absolute configuration of the single chiral centre nevertheless remains evident.

The tetralone derivatives **3a,b** and **4a,b** were subsequently reduced with sodium borohydride hence affording the corresponding *cis* benzyl alcohols in high yields (97-98%) as was previously described.[8,9] Analogous to the racemic synthesis, these were smoothly converted into *trans/cis* mixtures of tetrahydro-



Scheme 2 *Reagents and Conditions*: i, KOH, EtOH, 40°C; ii, $SOCl_2$, rt; iii, (+)- or (-)-1,5-dimethyl-4-phenyl-2-imidazolidinone, ^{n}BuLi, Ph_3CH, THF, 0°C; iv, BnCu-TMEDA-$^n Bu_2BOTf$, THF, -78→30°C; v, CF_3SO_3H, C_6H_6, reflux; vi, $NaBH_4$, EtOH:THF 1:1 ($^V/_V$); vii, 4-hydroxycoumarin, HCl(g), 160°C.

naphthylcoumarins **1a-d** (75-78 %, *trans:cis* 3:2) and **2a-d** (74-76 %, *trans:cis* 5:4) by condensation with 4-hydroxycoumarin **5** under an HCl atmosphere at 160°C (Scheme 2). The mixture of isomers was readily separated by flash column chromatography yielding the four diastereomers of diphenacoum **1a-d** and



17 (4R,5S,3'R) **18 (3R)**

Scheme 3

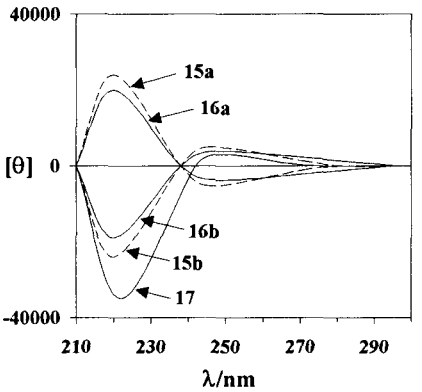


Fig 1 CD spectra of the imides **15a/b,16a/b** and **17**.

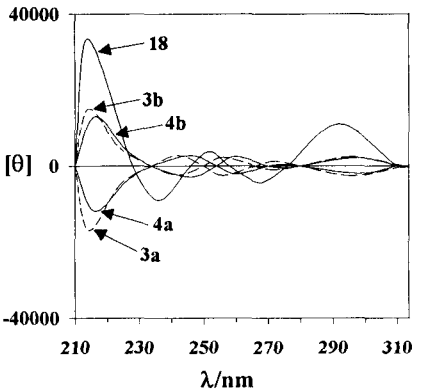


Fig 2 CD spectra of tetralones **3a/b,4a/b** and **18**.

brodifacoum **2a-d** in high optical purity (>99%). Assignment of the stereochemistry then follows from the already established configuration of the 3' stereocentre in the tetralin unit and a series of NOE experiments to assign the *cis/trans* stereochemistry as was previously reported.[8] The nature of the C-1' stereocentre in both the diphenacoum and brodifacoum diastereomers offered the opportunity to confirm the absolute configurations by application of the aromatic quadrant rule.[15] The CD curves of the anticoagulants **1a-d** and **2a-d** exhibit intense sequential positive Cotton effects for the (1'*R*)-isomers **1a,d/2a,d** (α-orientated 4-hydroxycoumarin moiety) and negative Cotton effects for the (1'*S*)-isomers **1b,c/2b,c** (β-orientated 4-hydroxycoumarin moiety) in the 225 nm and 250-290 nm regions (Figures 3 and 4). The absolute configuration of the C-3' stereogenic centres then follows unambiguously from the 1',3'-*cis* or -*trans* relationships established above.

With the optical pure diphenacoum and brodifacoum diastereomers in hand, the relevance of chirality to physiological activity (LD_{50}-values) was evaluated. Toxicity tests on mice showed the brodifacoum isomers **2a-d** to exhibit similar LD_{50}-values. Interestingly, these studies indicated LD_{50}-values comparable to those of brodifacoum for the evironmental friendly diphenacoum isomers **1b** and **1d**, obtained through utilization of the cheaper (-)-imidazolidinone **10** chiral auxiliary (Table 1).

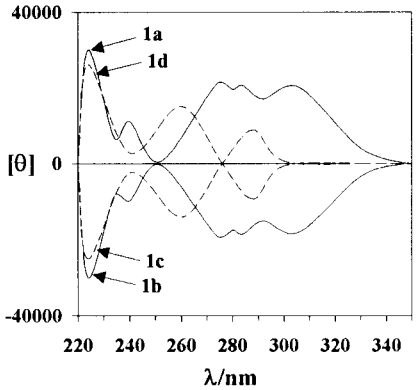


Fig 3 CD spectra of the Diphenacoum diastereomers **1a-d**.

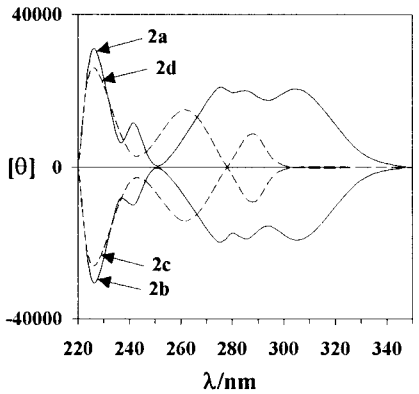


Fig 4 CD spectra of the Brodifacoum diastereomers **2a-d**.

Diphenacoum isomers	LD_{50}-value	Brodifacoum isomers	LD_{50}-value
1a	2.5-5.0 mg/kg	**2a**	0.5-0.8 mg/kg
1b	0.8-1.5 mg/kg	**2b**	0.4-0.9 mg/kg
1c	2.5-5.0 mg/kg	**2c**	0.4-0.9 mg/kg
1d	0.3-0.9 mg/kg	**2d**	0.5-0.8 mg/kg

Table 1 LD_{50}-values of the diphenacoum and brodifacoum diastereomers.

In summary, the highly stereoselective organocopper conjugate addition of a benzyl ligand to chiral biphenylimides afforded the four stereoisomers of the rodenticides diphenacoum and brodifacoum in high enantiomeric excess. The four diastereomers of each of diphenacoum and brodifacoum for the first time permitted biological evaluation of these anticoaculants.

EXPERIMENTAL

^{1}H NMR spectra were recorded at ambient temperatures on a Bruker AM-300 spectrometer for solutions in $CDCl_3$ or C_6D_6 with Me_4Si as internal standard. IR spectra were recorded on a Unicam SP 100 spectrophotometer, using 0.1 cm sodium chloride solution cells. High and low resolution mass spectra were obtained on a Kratos MS-80 mass spectrometer. Melting points were measured on a Reichert hot-stage apparatus and are uncorrected. CD measurements were obtained for solutions in MeOH on a Jasco J-710 spectropolarimeter and optical rotations measured with a Bendix-NPL automatic polarimeter for solutions in

$CHCl_3$. Flash column chromatography was on Merck Kieselgel 60 (230-400mesh) under a positive pressure by means of compressed nitrogen. Thin layer chromatography (TLC) was carried out on Merch Kieselgel 60 F_{254} plates with visualisation by ultraviolet light and/or formaldehyde-sulphuric acid spray. Reagents and solvents were purified by standard procedures.[16] CuI was freshly prepared[17] and purified[18] under an argon atmosphere. The (+)- **9** and (-)-1,5-dimethyl-4-phenyl-2-imidazolidinone **10** chiral auxiliaries were prepared according to the Close fusion method.[11] All other chemicals were used as purchased. Experiments were performed under anhydrous conditions in an Ar atmosphere, unless specified to the contrary, using oven-dried apparatus and employing standard techniques for handling air-sensitive materials.

General procedure for preparation of the biphenyl imides 13a,b and 14a,b

A suspension of the ester **11/12** (3.54 mmol) in a solution of potassium hydroxide (1.5g) in water (5 cm^3) was stirred at 60°C. After 6 hours the solution was acidified (HCl) and extracted with EtOAc (3 x 50 cm^3), washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to afford the corresponding acid in nearly quantitative yield. Thionyl chloride (0.85 cm^3, 7.08 mmol, 2 eq) was added and the mixture was stirred at room temperature for 12 hours. After removal of the excess of $SOCl_2$, dry hexane (10 cm^3) was added and the solution was concentrated *in vacuo* to give the corresponding acid chloride. To a stirred, precooled solution (-78°C) of (4*S*,5*R*)- **9** or (4*R*,5*S*)-1,5-dimethyl-4-phenyl-2-imidazolidinone **10** (0.575g, 3 mmol, 1 eq) in dry THF (10 cm^3) was added *n*-BuLi (1.6 M in hexanes; 1.9 cm^3, 3 mmol, 1 eq) by syringe. The resulting solution was stirred at this temperature for 20 min, and a solution of the α,β-unsaturated acyl chloride (3.3 mmol, 1.1 eq) in dry THF (5 cm^3) was added to the resulting slurry. The mixture was stirred at -78°C for 30 min and at 0°C for 1 hour when a saturated solution of NH_4Cl (50 cm^3) was added. EtOAc (50 cm^3) was added, and the organic layer separated and washed with a saturated solution of $NaHCO_3$ (2 x 25 cm^3) and brine (25 cm^3). The organic solution was dried over Na_2SO_4, filtered, and evaporated and the resulting crude mixture was purified by PLC as is indicated below.

(4S,5R)-1,5-Dimethyl-4-phenyl-1-[3'-(4''-biphenyl)-2'(E)-propenoyl]-2-imidazolidinone **13a**. mp 170°C; R_f 0.22 (hexane-benzene-acetone 6:3:1); ν_{max} (liquid film)/cm^{-1} 1734 (C=O), 3022, 1428 and 1041; ^1H NMR δ 8.24 (1H, d, J 15.5, H-2'), 7.75 (1H, d, J 15.5, H-3'), 7.66 (2H, d, J 8.5, Ph), 7.62-7.17 (12H, m, Ph), 5.43 (1H, d, J 8.5, H-4), 3.93 (1H, dq, J 8.5 and 6.5, H-5), 2.86 (3H, s, NCH_3), 0.82 (3H, d, J 6.5, 5-CH_3); *m/z* 396 (M^+, 8%), 307(10), 207(18), 189(14), 178(16), 149(29), 131(100), 117(13), 103(26), 91(14), 77(20), 57(25), 43(24) (Found M^+, 396.1819. $C_{26}H_{24}O_2N_2$ requires M^+, 396.1837); $[\alpha]_D^{25}$ = -34.8 (*c* 1.00); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = +21.0x10^3 (228), +15.0x10^3 (240), +22.0x10^3 (257), -2.7x10^3 (300), -6.7x10^3 (328).

(4R,5S)-1,5-Dimethyl-4-phenyl-1-[3'-(4''-biphenyl)-2'(E)-propenoyl]-2-imidazolidinone **13b**. mp 170°C; R_f 0.22 (hexane-benzene-acetone 6:3:1); $[\alpha]_D^{25}$ = +31.6 (*c* 1.00); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = -18.0x10^3 (228), -13.0x10^3

(240), -24.0x10^3 (257), -2.8x10^3 (300), +3.8x10^3 (333); The IR, ^{1}H NMR and MS data corresponded to those reported for **13a**.

(4S,5R)-1,5-Dimethyl-4-phenyl-1-[3'-(4'',4'''-bromobiphenyl)-2'(E)-propenoyl]-2-imidazolidinone **14a**. mp 175-180°C; R_f 0.25 (hexane-benzene-acetone 6:3:1); ν_{max} (liquid film)/cm^{-1} 1728 (C=O), 3022, 1362 and 1044; ^{1}H NMR δ 8.21 (1H, d, J 15.5, H-2'), 7.72 (1H, d, J 15.5, H-3'), 7.64 (2H, d, J 8.5, H-3''',5'''), 7.55 (2H, d, J 8.5, H-2''',6'''), 7.53 (2H, d, J 8.5, H-3'',5''), 7.45 (2H, d, J 8.5, H-2'',6''), 7.35-7.15 (5H, m, Ph), 5.42 (1H, d, J 8.5, H-4), 3.95 (1H, dq, J 8.5 and 6.5, H-5), 2.87 (3H, s, NCH_3), 0.83 (3H, d, J 6.5, 5-CH_3); *m/z* 476 (M^+, 10%), 446(8), 285(16), 189(48), 178(41), 132(53), 105(25), 97(30), 91(30), 83(38), 69(57), 57(85), 43(100) (Found M^+, 474.0940 and 476.0922. $C_{26}H_{23}O_2N_2Br$ requires M^+, 474.0943 and 476.0924); $[\alpha]_D^{25}$ = -35.7 (*c* 0.96); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = +6.0x10^3 (227), +4.3x10^3 (241), +7.7x10^3 (257), -2.2x10^3 (332).

(4R,5S)-1,5-Dimethyl-4-phenyl-1-[3'-(4'',4'''-bromobiphenyl)-2'(E)-propenoyl]-2-imidazolidinone **14b**. mp 175-180°C; R_f 0.25 (hexane-benzene-acetone 6:3:1); $[\alpha]_D^{25}$ = +34.8 (*c* 1.03); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = -5.9x10^3 (226), -3.6x10^3 (241), -7.2x10^3 (257), +2.1x10^3 (331); The IR, ^{1}H NMR and MS data corresponded to those reported for **14a**.

General procedure for the organocopper benzyl transfer to imides 13a,b and 14a,b

A mixture of CuI (420 mg, 0.00221 mol, 2 eq) and dry THF (8 cm^3) in a round bottom flask was sealed with a rubber septum, flushed with argon and dry TMEDA (0.4 cm^3, 0.00243 mol, 2.2 eq) was added. After the mixture was stirred at room temperature for 10 minutes the flask was cooled to -78°C and the benzyl Grignard reagent (1.9 cm^3 of a 1.17 M solution in THF, 0.00221 mol, 2 eq) was added followed by stirring at -78°C for 15 minutes. A solution of dibutylborontriflate (1.33 cm^3, 0.00133 mol, 1.2 eq) and the imide **13a,b/14a,b** (0.0011 mol), in dry THF (5 cm^3), was injected with stirring *via* syringe, and the temperature of the mixture was allowed to rise to -30°C. After 12 hours the cold reaction mixture was poured into a separatory funnel containing a saturated NH_4Cl-NH_4OH solution (3:2, 5 cm^3) and extracted twice with ether (40 cm^3). The combined ether extract was then washed with H_2O (40 cm^3), dried (Na_2SO_4) and evaporated to dryness. Flash chromatography (hexanes:acetone 9:1) gave the product.

(3'S,4S,5R)-1-[3'-(4''-Biphenyl)-4'-phenylbutanoyl]-1,5-dimethyl-4-phenyl-2-imidazolidinone **15a**. mp 132-135°C; R_f 0.30 (hexane-benzene-acetone 6:3:1); ν_{max} (liquid film)/cm^{-1} 1728 (C=O), 3022, 1428 and 1044; ^{1}H NMR δ 7.55 (2H, m, Ph), 7.47-7.02 (17H, m, Ph), 5.09 (1H, d, J 8.5, H-4), 3.74 (1H, dd, J 16 and 9.5, 2'-CH), 3.66 (1H, dq, J 8.5 and 6.5, H-5), 3.60-3.50 (1H, m, H-3'), 3.16 (1H, dd, J 16 and 5, 2'-CH), 2.95 (1H, dd, J 14 and 8) and 2.90 (1H, dd, J 14 and 7.5)(4'-CH_2), 2.76 (3H, s, NCH_3), 0.71 (3H, d, J 6.5, 5-CH_3); *m/z* 476 (M^+, 6%), 397(76), 355(10), 256(22), 232(50), 207(100), 191(27), 178(24), 165(21), 113(14), 91(15), 58(13); $[\alpha]_D^{25}$ = +23.8 (*c* 1.00); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = +24.0x10^3 (220), -5.3x10^3 (246), -1.0x10^3 (272).

(3'R,4R,5S)-1-[3'-(4''-Biphenyl)-4'-phenylbutanoyl]-1,5-dimethyl-4-phenyl-2-imidazolidinone **15b**. mp 132-135°C; R_f 0.30 (hexane-benzene-acetone 6:3:1); $[\alpha]_D^{25}$ = -21.1 (*c* 1.03); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = -24.0x10^3 (220), +5.0x10^3 (246), +1.05x10^3 (272); The IR, ^{1}H NMR and MS data corresponded to those reported for **15a**.

(3'S,4S,5R)-1-[3'-(4'',4'''-Bromobiphenyl)-4'-phenylbutanoyl]-1,5-dimethyl-4-phenyl-2-imidazolidinone **16a**. mp 153-156°C; R_f 0.33 (hexane-benzene-acetone 6:3:1); ν_{max} (liquid film)/cm^{-1} 1731 (C=O), 3022, 1428 and 1206; ^{1}H NMR δ 7.53 (2H, d, J 8.5, H-3''',5'''), 7.41 (2H, d, J 8.5, H-2''',6'''), 7.40 (2H, d, J 8.5, H-3'',5''), 7.31-7.01 (12H, m, Ph), 5.12 (1H, d, J 8.0, H-4), 3.76-3.66 (2H, m, 2'-CH, H-5), 3.60-3.50 (1H, m, H-3'), 3.18 (1H, dd, J 16.5 and 5, 2'-CH), 2.92 (2H, d, J 7.5, 4'-CH_2), 2.78 (3H, s, NCH_3), 0.73 (3H, d, J 6.5, 5-CH_3); *m/z* 567 (M^+, 3%), 391(30), 232(10), 191(21), 167(10), 149(100), 137(22), 113(53); $[\alpha]_D^{25}$ = +16.9 (*c* 1.03); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = +20.0x10^3 (220), -3.8x10^3 (248), -0.8x10^3 (286).

(3'R,4R,5S)-1-[3'-(4'',4'''-Bromobiphenyl)-4'-phenylbutanoyl]-1,5-dimethyl-4-phenyl-2-imidazolidinone **16b**. mp 153-156°C; R_f 0.33 (hexane-benzene-acetone 6:3:1); $[\alpha]_D^{25}$ = -17.2 (*c* 0.96); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = -19.0x10^3 (220), +3.9x10^3 (248), +0.8x10^3 (286); The IR, ^{1}H NMR and MS data corresponded to those reported for **16a**.

General procedure for the cyclization of imides 15a,b and 16a,b

A solution of the imide **15a,b/16a,b** (0.54 mmol) and trifluoromethanesulfonic acid (0.5 cm^3, 0.0055 mol, 10 eq) in dry benzene (1 cm^3) was refluxed at 80°C until complete conversion of the starting material. The reaction mixture was neutralized with 4N NaOH, extracted with CH_2Cl_2 (3 x 30 cm^3), the organic phase dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by flash column chromatography afforded the corresponding tetralone derivative.

(3S)-3-(4'-Biphenyl)-tetralin-1-one **3a**. mp 95°C (lit.[1] 92-94°C, racemate); R_f 0.3 (hexane-acetone 9:1); ν_{max} (liquid film)/cm^{-1} 1683 (C=O), 2260, 1386 and 897; ^{1}H NMR δ 8.09 (1H, dd, J 8 and 1.5, H-8), 7.62-7.28 (12H, m, Ph), 3.57-3.46 (1H, m, H-3), 3.31-3.18 (2H, m, 4-CH_2), 3.02 ([1H, ddd, J 14, 4 and 2, H-2(eq)] and 2.87 [1H, dd, J 16.5 and 12.5, H-2(ax)]; $[\alpha]_D^{25}$ = -6.9 (*c* 1.00); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = -17.0x10^3 (214), -5.0x10^3 (224), +2.8x10^3 (242), -2.5x10^3 (256), +1.2x10^3 (272), -2.7x10^3 (296).

(3R)-3-(4'-Biphenyl)-tetralin-1-one **3b**. mp 95°C (lit.[1] 92-94°C, racemate); R_f 0.3 (hexane-acetone 9:1); $[\alpha]_D^{25}$ = +26.9 (*c* 0.95); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = +15.0x10^3 (214), +4.8x10^3 (224), -2.4x10^3 (242), +2.3x10^3 (256), -1.0x10^3 (272), +2.4x10^3 (296); The IR and ^{1}H NMR data corresponded to those reported for **3a**.

(3S)-3-(4',4''-Bromobiphenyl)-tetralin-1-one **4a**. mp 153°C (lit.[1] 156-158°C, racemate); R_f 0.29 (hexane: acetone 9:1); ν_{max} (liquid film)/cm^{-1} 1689 (C=O), 1605, 1488 and 906; ^{1}H NMR δ 8.09 (1H, dd, J 8 and 1.5, H-8), 7.62-7.28 (11H, m, Ph), 3.57-3.46 (1H, m, H-3), 3.31-3.18 (2H, m, 4-CH_2), 3.02 [1H, ddd, J 16.5, 4 and 2,

H-2(eq)] and 2.86 [1H, dd, J 16.5 and 12.5, H-2(ax)]; $[\alpha]_D^{25}$ = -11.8 (*c* 1.05); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = -12.0x10^3 (216), -4.0x10^3 (226), +2.8x10^3 (246), -2.2x10^3 (260), +0.4x10^3 (276), -2.0x10^3 (298).

(3R)-3-(4',4''-Bromobiphenyl)-tetralin-1-one **4b**. mp 153°C (lit.[1] 156-158°C, racemate); R_f 0.29 (hexane: acetone 9:1); $[\alpha]_D^{25}$ = +37.8 (*c* 0.95); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = +13.0x10^3 (216), +4.1x10^3 (226), -2.9x10^3 (246), +2.5x10^3 (260), -0.45x10^3 (276), +2.2x10^3 (298); The IR and ^{1}H NMR data corresponded to those reported for **4a**.

General procedure for the condensation of tetralones 3a,b/4a,b with 4-hydroxycoumarin

Sodium borohydride (50 mg, 1.342 mmol, 4eq) was added to a solution of the tetralin-1-one **3a,b/4a,b** (0.3355 mmol) in EtOH-THF (5 cm^3, 1:1) and the mixture was stirred at room temperature for 4 hours. The excess borohydride was destroyed by the addition of acetone prior to removal of the solvent *in vacuo* and the addition of water (5 cm^3). The benzyl alcohol was extracted into ether (3 x 10 cm^3), dried (Na_2SO_4), and isolated by evaporation of the ether. A mixture of 4-hydroxycoumarin **5** (106 mg, 0.6532 mmol, 2 eq) and the corresponding tetralol (0.3266 mmol) was heated at 160°C for 30 minutes under an HCl(g) atmosphere. Flash chromatography (hexane:benzene:acetone 6:3:1) afforded the corresponding *trans* and *cis* isomers **1a-d/2a-d**.

(1'R,3'R)-4-Hydroxy-3-[3'(4''-biphenyl)-1',2',3',4'-tetrahydro-1'-naphtyl]-coumarin **1a**. mp 213°C (lit.[1] 215-217°C, mixture of isomers); R_f 0.26 (hexane:benzene: acetone 6:3:1); ν_{max} (liquid film)/cm^{-1} 1698 (C=O), 3022, 1425 and 1035; ^{1}H NMR δ 7.63 (1H, dd, J 8 and 1.5, H-5), 7.52-7.48 (2H, m, Ph), 7.4 (2H, d, J 8, Ph), 7.26-6.72 (12H, m, Ph), 6.17 (br. s, OH), 4.84 (1H, dd, J 6 and 2.5, H-1'), 3.10-2.99 (1H, m, H-3'), 2.88-2.79 (1H, m) and 2.68-2.58 (1H, m)(4'-CH_2), 2.53-2.45 (1H, m) and 2.18-2.06 (1H, m)(2'-CH_2);); (Found M^+, 444.1728. $C_{31}H_{24}O_3$ requires M^+, 444.1726); $[\alpha]_D^{25}$ = +193.8 (*c* 1.00); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = +30.0x10^3 (224), +6.7x10^3 (234), +11.0x10^3 (240), +0.5x10^3 (252), +21.0x10^3 (274), +19.5x10^3 (280), +20.5x10^3 (284), +17.0x10^3 (292), +20.0x10^3 (306), +4.0x10^3 (330).

(1'S,3'S)-4-Hydroxy-3-[3'(4''-biphenyl)-1',2',3',4'-tetrahydro-1'-naphtyl]-coumarin **1b**. mp 213°C (lit.[1] 215-217°C, mixture of isomers); R_f 0.26 (hexane-benzene-acetone 6:3:1); $[\alpha]_D^{25}$ = -154.3 (*c* 1.03); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = -30.0x10^3 (224), -8.5x10^3 (234), -9.8x10^3 (240), -0.45x10^3 (252), -19.0x10^3 (274), -17.5x10^3 (280), -18.5x10^3 (284), -15.0x10^3 (292), -18.0x10^3 (306), -3.5x10^3 (330); The IR, MS and ^{1}H NMR data corresponded to those reported for **1a**.

(1'S,3'R)-4-Hydroxy-3-[3'(4''-biphenyl)-1',2',3',4'-tetrahydro-1'-naphtyl]-coumarin **1c**. mp 216°C (lit.[1] 215-217°C, mixture of isomers); R_f 0.13 (hexane-benzene-acetone 6:3:1); ν_{max} (liquid film)/cm^{-1} 1698 (C=O), 3022, 1425 and 1035; ^{1}H NMR δ 7.72-7.62 (br. s, OH), 7.54 (2H, dd, J 8 and 1.5, H-5), 7.47 (2H, d, J 8, Ph), 7.29-6.77 (13H, m, Ph), 5.02-4.92 (1H, br. s, H-1'), 2.85-2.65 (4H, br. s) and 2.4-2.3 (1H, br. s)(2'-CH_2, H-3', 4'-

CH_2); (Found M^+, 444.1725. $C_{31}H_{24}O_3$ requires M^+, 444.1726); $[\alpha]_D^{25}$ = -81.3 (*c* 1.00); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = -25.0x10^3 (224), -2.5x10^3 (240), -14.0x10^3 (260), +8.7x10^3 (288), +0.6x10^3 (300).

(1'R,3'S)-4-Hydroxy-3-[3'(4''-biphenyl)-1',2',3',4'-tetrahydro-1'-naphtyl]-coumarin **1d**. mp 216°C (lit.[1] 215-217°C, mixture of isomers); R_f 0.13 (hexane-benzene-acetone 6:3:1); $[\alpha]_D^{25}$ = +72.9 (*c* 1.02); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = +26.0x10^3 (224), +2.7x10^3 (240), +15.0x10^3 (260), -9.3x10^3 (288), -0.7x10^3 (300); The IR, MS and ^{1}H NMR data corresponded to those reported for **1c**.

(1'R,3'R)-4-Hydroxy-3-[3'(4'',4'''-bromobiphenyl)-1',2',3',4'-tetrahydro-1'-naphtyl]-coumarin **2a**. mp 224°C (lit.[1] 228-230°C, mixture of isomers); R_f 0.26 (hexane-benzene-acetone 6:3:1); ν_{max} (liquid film)/cm^{-1} 1695 (C=O), 3016, 1422 and 1035; ^{1}H NMR δ 7.63 (1H, dd, J 8 and 1.5, H-5'), 7.49 (1H, dd, J 8 and 1.5, Ph), 7.39 (1H, d, J 8, Ph), 7.32 (1H, d, J 8, H-3''',5'''), 7.26-6.70 (11H, m, Ph), 4.86-4.81 (1H, br. s, H-1'), 3.10-2.99 (1H, m, H-3'), 2.88-2.79 (1H, m) and 2.68-2.58 (1H, m)(4'-CH_2), 2.53-2.45 (1H, m) and 2.18-2.06 (1H, m)(2'-CH_2); (Found M^+, 522.0830 and 524.0811. $C_{31}H_{23}O_3Br$ requires M^+, 522.0831 and 524.0811); $[\alpha]_D^{25}$ = +155.0 (*c* 1.00); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = +31.0x10^3 (226), +6.9x10^3 (236), +11.5x10^3 (242), +0.5x10^3 (252), +20.5x10^3 (274), +19.5x10^3 (280), +20.0x10^3 (286), +17.4x10^3 (294), +19.8x10^3 (308), +3.9x10^3 (330).

(1'S,3'S)-4-Hydroxy-3-[3'(4'',4'''-bromobiphenyl)-1',2',3',4'-tetrahydro-1'-naphtyl]-coumarin **2b**. mp 224°C (lit.[1] 228-230°C, mixture of isomers); R_f 0.26 (hexane-benzene-acetone 6:3:1); $[\alpha]_D^{25}$ = -210.9 (*c* 1.00); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = -30.5x10^3 (226), -8.7x10^3 (236), -10.0x10^3 (242), -0.45x10^3 (252), -19.5x10^3 (274), -17.5x10^3 (280), -19.0x10^3 (286), -15.6x10^3 (294), -18.8x10^3 (308), -3.5x10^3 (330); The IR, MS and ^{1}H NMR data corresponded to those reported for **2a**.

(1'S,3'R)-4-Hydroxy-3-[3'(4'',4'''-bromobiphenyl)-1',2',3',4'-tetrahydro-1'-naphtyl]-coumarin **2c**. mp 227°C (lit.[1] 228-230°C, mixture of isomers); R_f 0.13 (hexane-benzene-acetone 6:3:1); ν_{max} (liquid film)/cm^{-1} 1695 (C=O), 3016, 1422 and 1035; ^{1}H NMR δ 7.66-7.63 (br. s, OH), 7.54 (2H, dd, *J* 8 and 1.5, H-5), 7.48 (1H, d, *J* 8, Ph), 7.37-6.76 (14H, m, Ph), 5.02-4.92 (1H, br. s, H-1'), 2.85-2.65 (4H, br. s) and 2.4-2.3 (1H, br. s)(2'-CH_2, H-3', 4'-CH_2); (Found M^+, 522.0829 and 524.0812. $C_{31}H_{23}O_3Br$ requires M^+, 522.0831 and 524.0811); $[\alpha]_D^{25}$ = -114.3 (*c* 1.03); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = -26.0x10^3 (226), -2.9x10^3 (242), -14.3x10^3 (262), +8.7x10^3 (288), +0.5x10^3 (300).

(1'R,3'S)-4-Hydroxy-3-[3'(4'',4'''-bromobiphenyl)-1',2',3',4'-tetrahydro-1'-naphtyl]-coumarin **2d**. mp 227°C (lit.[1] 228-230°C, mixture of isomers); R_f 0.13 (hexane-benzene-acetone 6:3:1); $[\alpha]_D^{25}$ = +92.0 (*c* 1.05); CD: $\Delta\varepsilon_{max}$ [λ(nm)] = +26.0x10^3 (226), +3.0x10^3 (242), +15.0x10^3 (262), -9.3x10^3 (288), -0.65x10^3 (300); The IR, MS and ^{1}H NMR data corresponded to those reported for **2c**.

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