Improved synthesis for the rodenticides, diphenacoum and brodifacoum

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An improved synthesis of the 3-[3-(*p*-substituted phenyl)-1,2,3,4-tetrahydro-1-napththyl]-4-hydroxycoumarins, diphenacoum and brodifacoum, is described. The process is primarily based on the formation of one of the crucial bonds in the carbon backbone using organocopper methodology, and on the coupling of the 4-hydroxycoumarin moiety to the 3-biphenyl tetralin unit under strongly acidic conditions.

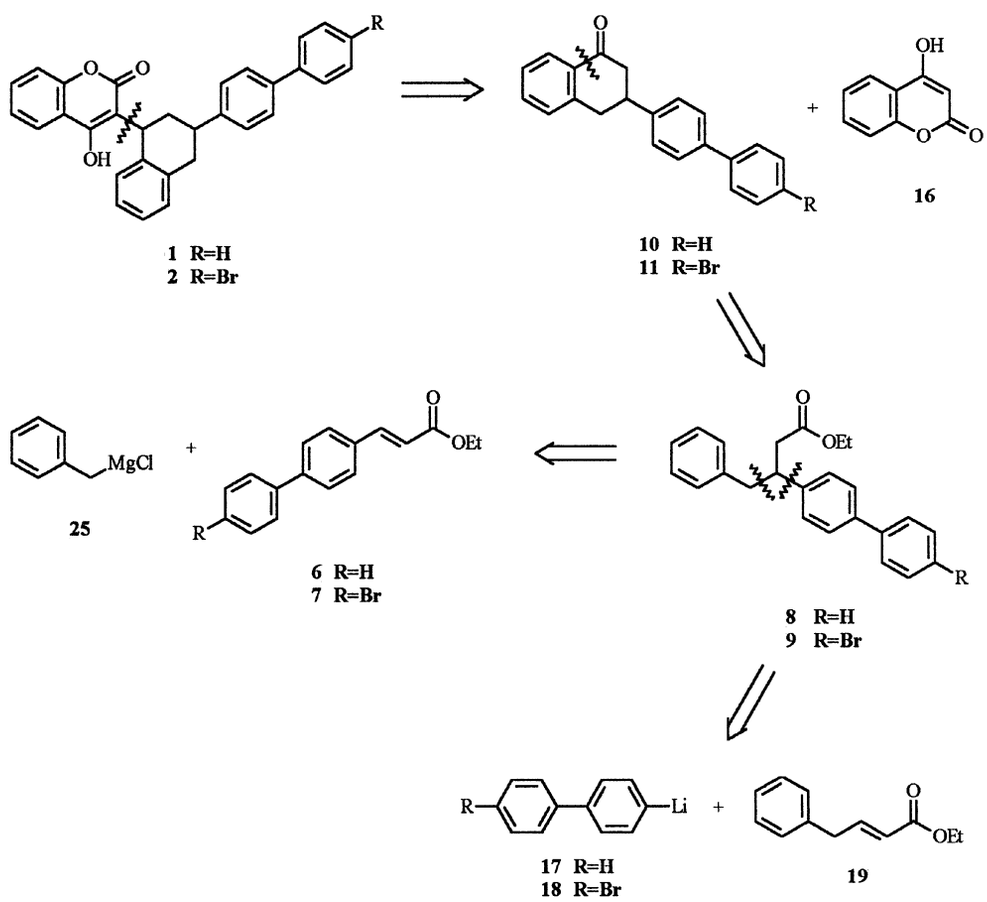
Introduction

The 3-[3-(*p*-substituted phenyl)-1,2,3,4-tetrahydro-1-naphthyl]-4-hydroxycoumarins, diphenacoum **1** and brodifacoum **2**, show outstanding activity against both Warfarin-sensitive and Warfarin-resistant rats, and are now used commercially as rodenticides. Owing to their anticoagulant properties these may also be used at extremely low concentrations in humans suffering from circulatory diseases. The total syntheses of these commercially important anticoagulants have been the topic of several reports over the last two decades.[1–5] Although some progress has been made to overcome the detrimental effect of stilbene formation in the Shadbolt and Woodward synthesis, the overall yields of both compounds are still very low (10–20%).[5]

Herein, we report on a new protocol for the synthesis of diphenacoum and brodifacoum from low-cost, commercially available starting materials and involving organocopper chemistry[6,7] to form one of the crucial bonds in their carbon frameworks. This method represents an improvement of existing processes leading to a two-fold increase in overall yield with a decrease in the number of steps from 8 and/or 9 to 5 and 6 respectively for diphenacoum and brodifacoum.

Results and discussion

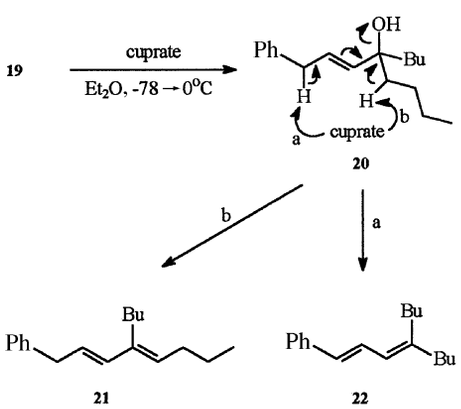
In order to establish an overall improvement of the existing syntheses of diphenacoum and brodifacoum, we have opted for the retrosynthetic sequence outlined in Scheme 1. Since 1,4-Michael additions can be accomplished in excellent yields *via*



Scheme 1

organocopper reagents, the butanoate esters **8** and **9** could either be synthesized through the organocopper-mediated 1,4-addition of biphenyl **17** and bromobiphenyl **18** units to ester **19**, or *via* transfer of a benzyl group **25** to α,β-enoates **6** and **7**. Acid-catalysed cyclization and subsequent condensation with 4-hydroxycoumarin **16**, would then give diphenacoum **1** and brodifacoum **2**. Owing to the successful conjugate addition of aryl based organocuprates to 1,4-Michael acceptors,[8,9] initial attempts to synthesize esters **8** and **9** were focused on the former approach. The unreported ethyl 4-phenylcrotonate **19** was prepared in good yield (81%) and selectivity (*E*:*Z* 7:1) by a standard Wittig reaction between (carbethoxy)triphenylphosphonium chloride and phenylacetaldehyde.

Conjugate addition of conventional Gilman reagents to α,β-unsaturated esters has met with limited success due to competitive reaction at the carbonyl centre. However, Yamamoto's Lewis acid-activated reagent[10] and Lipshutz's higher order cyanocuprate[8] represent viable alternatives for inducing 1,4-addition to enoates. In order to test the feasibility of our approach a variety of model conjugate addition reactions of cuprates [$Bu_2Cu(CN)Li_2$, BuCu–BF_3, Bu_2CuLi–BF_3] to enoate **19** was evaluated. Analysis of the ^{1}H NMR spectra of the reaction mixtures indicated in each case the exclusive formation of polyene-like material with no evidence of the formation of any addition product. Formation of these polyenes of types **21** and **22** presumably resulted from 1,2-addition followed by abstraction of the relatively acidic benzylic and homo-allylic protons in the adduct of type **20** by the cuprate (Scheme 2). Although



cuprate = $Bu_2Cu(CN)Li_2$, $BuCuBF_3$, $Bu_2CuLiBF_3$

Scheme 2

contrary to the usual mode of action of organocopper reagents, literature precedent[11] for cuprates acting as bases does exist.

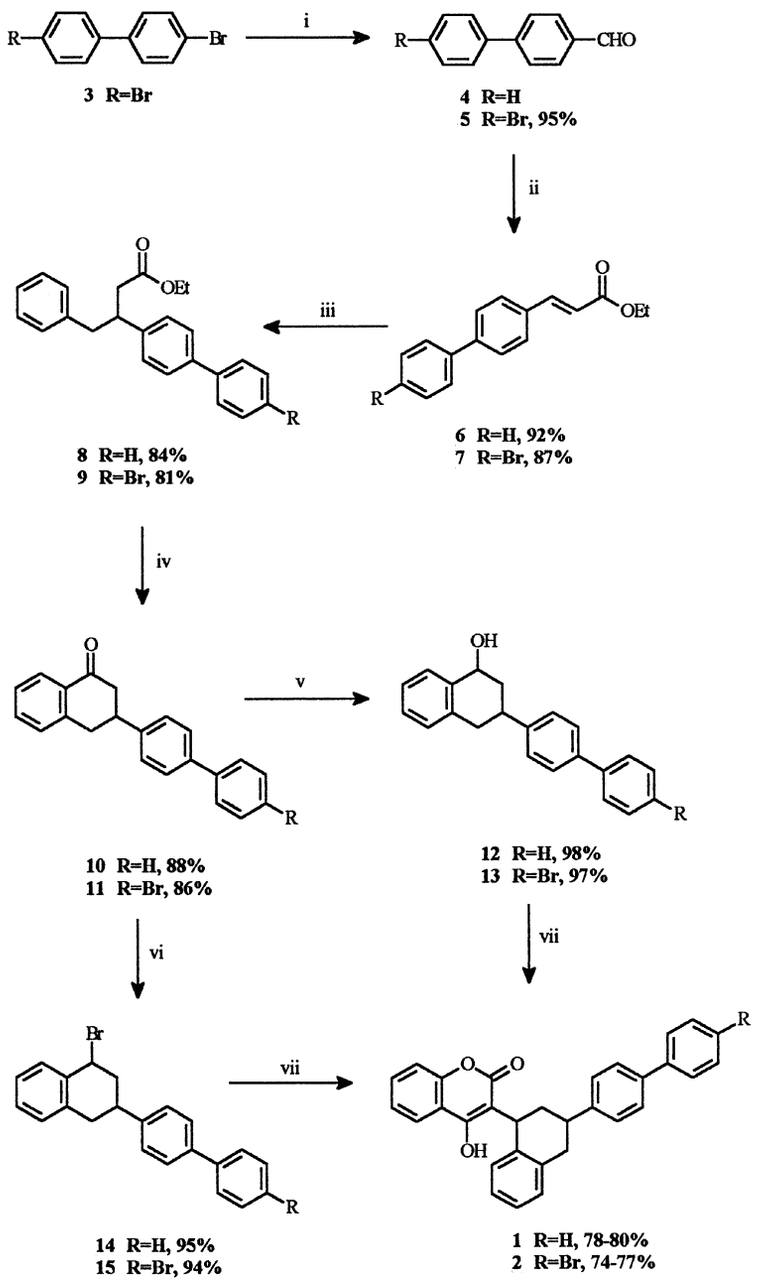
These complications prompted recourse to the alternative approach which required the introduction of a benzyl group to the β-position of the biphenyl esters **6** and **7**. Our recent demonstration of the highly successful conjugate addition[6,7] of the benzyl copper reagent, BnCu–TMEDA, to cinnamic esters, indicated that the corresponding additions of the biphenyl unsaturated esters **6** and **7** would proceed in an analogous fashion to give rise to butanoates **8** and **9**.

Initial attempts to synthesize the commercially unavailable carbaldehyde **5** *via* bromination [thallium(III) acetate–Br_2][12] of biphenylcarbaldehyde **4** and formylation [*N*-phenyl-*N*-methylformamide–$POCl_3$][13] of bromobiphenyl were unsuccessful, presumably due to low reactivity of the substrates. Careful lithiation of dibromobiphenyl **3** at low temperature, followed by treatment of the intermediate anion with *N*,*N*-dimethylformamide (DMF)[14] afforded 4′-bromobiphenylcarbaldehyde **5** (95%) (Scheme 3). With both precursors **4** and **5** available, separate Wittig condensation with (carbethoxy)triphenylphosphonium chloride in DMF and sodium methoxide at room temperature, gave the biphenyl esters **6** and **7** in 92 and 87% yields, respectively. Our organocopper methodology was then successfully applied to the synthesis of butanoates **8** and **9** by treating enoates **6** and **7** with the BnCu–TMEDA complex in the presence of TMSCl leading to good yields (81–84%) and regioselectivities (only 1,4-addition) in both cases. Transformation of butanoates **8** and **9** into the tetralones **10** and **11** was initially approached *via* the Kim–Lee protocol[5] involving cyclization of the butanoic acid analogue of **9** with polyphosphoric acid in toluene. Although the desired conversions were achieved in both cases, these reactions were not sufficiently high yielding (68–71%) and alternative methods were investigated. The use of $AlCl_3$ in dry toluene at 90 °C effectively catalysed the Friedel–Crafts type cyclization of butanoates **8** and **9** into the tetralones **10** and **11** in good yields (88 and 86%, respectively). Although this cyclization could give rise to either 3-(*p*-substituted phenyl)-3,4-dihydronapthalen-1(2*H*)-ones, *e.g.* **10**, or 6-(*p*-substituted phenyl)-3-benzylindan-1-ones, it has been shown that six-membered rings are formed in preference to five-membered rings.[15] Such a formation of a six-membered ring was confirmed by the carbonyl stretching bands at *ca.* 1680 cm^{-1} in the IR spectra of tetralones **10** and **11** in contrast to the expected absorption for substituted indanones at *ca.* 1720 cm^{-1}.[16] Thus, we have efficiently synthesized the tetralone derivatives **10** and **11** which are the key intermediates in the synthesis of diphenacoum **1** and brodifacoum **2**.

In the Shadbolt–Woodward synthesis, access to **1** and **2** is feasible by condensation of 4-hydroxycoumarin **16** and the corresponding 1-bromotetralin derivatives **14** and **15**. Owing to steric hindrance, forcing conditions (140 °C) were required to establish coupling. In our hands this procedure, however, led to preferential dehydrohalogenation of **14** and **15**, giving only poor yields (~20–30%) of diphenacoum **1** and broadifacoum **2** (Scheme 4).

Upon reduction of tetralones **10** and **11** with either sodium boranuide or aluminium isopropoxide, Shadbolt and Woodward reported products with *cis* and *trans* relative stereochemistry respectively.[1] Since a 1,3-*cis* orientation would facilitate a possible S_N2 coupling mechanism through minimization of the steric effect caused by the bulky biphenyl substituents, ketones **10** and **11** were thus treated with $NaBH_4$–EtOH–THF yielding the corresponding *cis* benzyl alcohols **12** (98%, 90% de) and **13** (97%, 90% de). The relative stereochemistry of **12** and **13** was established by ^{1}H NMR spectroscopy. Following previous suggestions,[17,18] the observed NOE (2.69 and 2.48%, respectively for **12** and **13**) between H-1 and H-3 in both 1,2,3,4-tetrahydro-3-biphenyl-4-yl-1-naphthols for the first time confirmed the 1,3-*cis* relationship of the hydroxy and biphenyl groups. The alicyclic rings are held in half-chair conformations with both substituents occupying pseudo-equatorial orientations (Fig. 1). Owing to the bulkiness of the biphenyl substituents, the observed diastereoselectivity presumably resulted by attack of the sodium boranuide from the less hindered face of the carbonyl functionality.

Subsequent *in situ* bromination (PBr_3) of alcohols **12** and **13** afforded tetrahydronapththyl halides **14** and **15** in good yields. In principle, deprotonation of 4-hydroxycoumarin **16** followed by addition of the corresponding bromotetralin electrophile, *e.g.* **14**, should lead to the target α-alkylated products **1** and **2**. These base-catalysed couplings would require lower temperatures, hence inhibiting dehydrotetralin formation and leading to increased yields. However, even the mild deprotonation (lutidine–THF or K_2CO_3–acetone) of coumarin **16** at room temperature and subsequent treatment with either **14** or **15**, resulted in the preferential formation of the unwanted products of dehydrohalogenation. Such a propensity of the bromotetralins to dehydrohalogenation under basic conditions prompted investigation of alternative acid-catalysed couplings. The following variation of the Shadbolt–Woodward procedure was found to be superior in terms of product yield and reproducibility of the reaction. Separate treatment of a

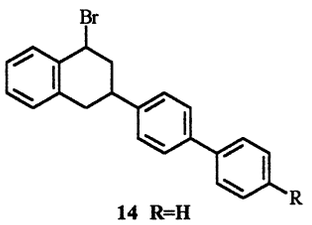


Scheme 3 *Reagents and conditions:* i, BuLi, THF, −78 °C, then DMF, −78→0 °C; ii, $Ph_3P^+CH_2CO_2EtCl^-$, NaOMe, DMF; iii, $PhCH_2Cu$–TMEDA, TMSCl, THF, −78→−30 °C; iv, $AlCl_3$, toluene, 90 °C; v, $NaBH_4$, EtOH–THF, RT; vi, $NaBH_4$, EtOH–THF, RT, then PBr_3, DCM, 0 °C; vii, 4-hydroxycoumarin, HCl(g), 160 °C

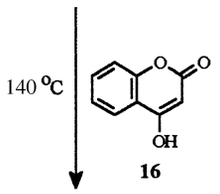
mixture of **14** or **15** and **16** under an HCl atmosphere at 160 °C for 30 min gave approximately equal quantities of the *cis* and *trans* isomers [R_F 0.13 and 0.26 on silica in hexane–benzene–acetone (6:3:1)] of anticoagulants **1** (80%) and **2** (77%), together with minor quantities of the elimination artefacts **23** and **24**. Owing to the success of this condensation, it was expected that coupling between 4-hydroxycoumarin **16** and alcohols **12** and **13** would also be feasible under strongly acidic conditions at elevated temperatures. Such an approach would reduce the number of steps and result in an economically more favourable process. Thus by analogy, condensation of **16** and alcohols **12** and **13** provided a *trans/cis* mixture of tetrahydronaphthylcoumarins **1** (*trans*:*cis* 3:2) and **2** (*trans*:*cis* 5:4) in 78 and 74% yields, respectively (Scheme 3). The relative stereochemistry of the *trans/cis* isomers of diphenacoum **1** and brodifacoum **2** was again assigned by a series of NOE experiments (Scheme 5). Irradiation of the C-1 benzylic protons in the corresponding *cis*-isomers caused a substantial NOE enhancement (2.13 and 2.30%, respectively) of the C-3 benzylic signals at δ 3.04. Similar NOE enhancement was conspicuously absent when H-1 of the corresponding *trans*-isomers was irradiated.

The coupling reaction presumably occurs according to the sequence outlined in Scheme 5. Since an almost 1:1 ratio of diastereoisomeric compounds **1** and **2** was obtained, it appears that initial dehydration is followed by random S_N1-attack on carbocation **26** by 4-hydroxycoumarin **16**. In addition, the coupling is driven to completion by the reversible regeneration of carbocation **26** from the elimination by-products **23** and **24**. The slight selectivity may be attributed to the steric effect caused by the biphenyl unit, leading to predominant formation of the *trans*-isomers (Scheme 5).

We have thus developed a viable total synthesis of the anticoagulants diphenacoum **1** and brodifacoum **2** with a marked increase in overall yield to 54 and 43% compared to those of existing processes. Besides limiting the number of steps to five and six this protocol also has the potential to address the stereoselective synthesis of these compounds, a process which is currently being pursued and will be the subject of an impending publication.



14 R=H
15 R=Br



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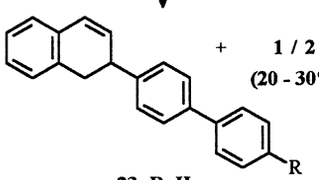
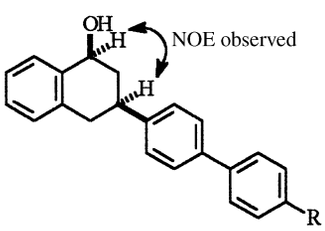


1 / 2
(20 - 30%)

23 R=H
24 R=Br

Scheme 4



(±)-12 R=H
(±)-13 R=Br

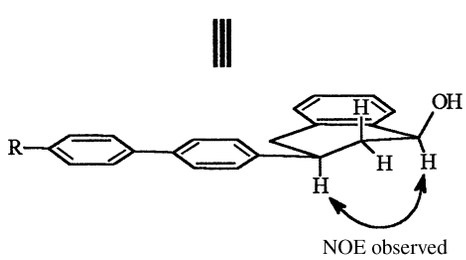
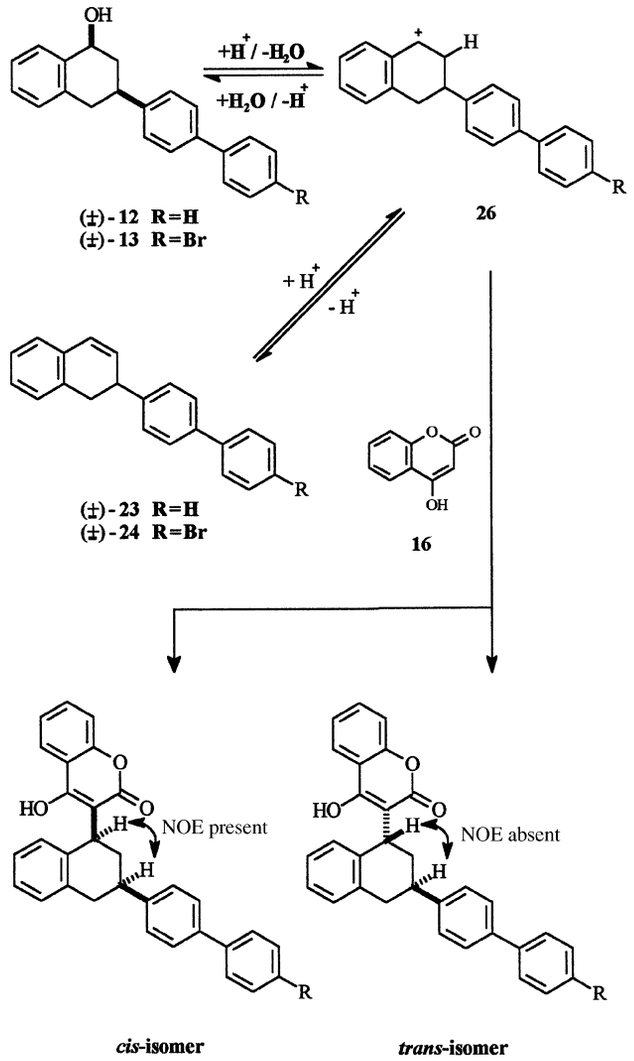


Fig. 1

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. 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. Flash column chromatography was on Merck Kieselgel 60 (230–400 mesh) under a positive pressure by means of compressed nitrogen. Thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates with visualization by UV light and/or formaldehyde–sulfuric acid spray. Reagents and solvents were purified by standard procedures.[19] CuI was freshly prepared[20] and purified[21] under an argon atmosphere. 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. Ether refers to diethyl ether.



(±)-1 R=H, 78%,*trans:cis* 3:2
(±)-2 R=Br, 74%,*trans:cis* 5:4

Scheme 5

4′-Bromobiphenyl-4-carbaldehyde 5

To a solution of 4,4′-dibromobiphenyl **3** (2 g, 6.41 mmol) in dry THF (20 ml) under argon at −78 °C butyllithium (1.63 M solution in hexanes; 3.93 ml, 6.41 mmol, 1 equiv.) was added dropwise with stirring. After 15 min DMF (20 ml) was added to the mixture, the temperature of which was allowed to rise to room temperature, while stirring was continued for 2 h. The mixture was diluted with water (50 ml) and extracted with ether (3 × 50 ml). The combined extracts were dried (Na_2SO_4) and evaporated and flash chromatography (hexane–acetone 9:1) of the residue gave the carbaldehyde **5** as a *white powder* (1.6 g, 95%); mp 158 °C; R_F 0.26 (hexane–acetone 9:1); *m/z* 260 and 262 (M^+, 77%), 262 (74), 261 (55), 259 (46), 153 (16), 152 (100), 151 (23), 150 (12), 126 (10), 76 (23) and 75 (12) (Found: M^+, 259.9838 and 261.9816. $C_{13}H_9OBr$ requires M^+, 259.9837 and 261.9817); ν_{max}(liquid film)/cm^{-1} 1707 (C=O), 3022, 1428 and 750; δ_H($CDCl_3$) 10.06 (1 H, s, CHO), 7.96 (2 H, d, *J* 8.5, H-2,6), 7.72 (2 H, d, *J* 8.5, H-3,5), 7.62 (2 H, d, *J* 8.5, H-3′,5′) and 7.50 (2 H, d, *J* 8.5, H-2′,6′).

(*E*)-Ethyl 4′-phenylcinnamate 6

A suspension of sodium methoxide (1.3 g, 23.85 mmol, 2.3 equiv.) in dry DMF (100 ml) was added to (carboxyethyl)triphenylphosphonium chloride (4.6 g, 12.14 mmol, 1.1 equiv.) [prepared by stirring triphenylphosphine (21.67 g, 82.6 mmol) and ethyl chloroacetate (10 g, 81.6 mmol) in dry benzene (50 ml) at room temperature] and the mixture

was stirred at room temperature for 12 h. It was then treated with a solution of carbaldehyde **4** (2 g, 10.99 mmol) in dry DMF (50 ml), added dropwise over a period of 1 h. Stirring was continued for 48 h, after which the mixture was diluted with water (150 ml) and extracted with ether (3 × 150 ml). The combined extracts were successively washed with water (50 ml), 0.1 M hydrochloric acid (2 × 100 ml), water (50 ml), dried (Na_2SO_4) and evaporated. Flash chromatography (hexane–acetone, 9:1) of the residue gave the cinnamate **6** as a white solid (2.6 g, 92%); mp 89 °C (lit.,[22] 87 °C); R_F 0.34 (hexane–acetone, 9:1); *m/z* 252 (M^+, 100%), 224 (10), 208 (11), 207 (61), 182 (49), 181 (56), 180 (39), 179 (27), 178 (65), 165 (20), 154 (13), 153 (25), 152 (58) and 151 (20); ν_{max}(liquid film)/cm^{-1} 1713 (C=O), 2938, 1314 and 1035; δ_H($CDCl_3$) 7.72 (1 H, d, *J* 15.5, H-3), 7.64–7.56 (6 H, m, Ph), 7.48–7.35 (3 H, m, Ph), 6.48 (1 H, d, *J* 15.5, H-2), 4.28 (2 H, q, *J* 7, OCH_2CH_3) and 1.35 (3 H, t, *J* 7, OCH_2CH_3).

(*E*)-Ethyl 4′-(4″-bromophenyl)cinnamate 7

The cinnamate **7** was prepared by treating a suspension of sodium methoxide (3.2 g, 59.63 mmol, 2.3 equiv.) and (carboxyethyl)triphenylphosphonium chloride (7.9 g, 21.1 mmol, 1.1 equiv.) in dry DMF (200 ml) with 4′-bromobiphenyl-4-carbaldehyde **5** (5.0 g, 19.2 mmol) in dry DMF (200 ml) as was described for compound **6**. Flash chromatography (hexane–acetone, 9:1) afforded the target molecule **7** as a white solid (5.5 g, 87%); mp 79 °C; R_F 0.54; *m/z* 330 and 302 (M^+, 100%), 332 (99), 304 (12), 302 (12), 287 (47), 286 (10), 285 (48), 260 (29), 259 (15), 258 (34), 206 (20), 179 (13), 178 (71), 177 (14), 176 (27), 152 (31), 151 (19), 89 (14), 88 (12) and 76 (21) (Found: M^+, 330.0254 and 332.0235. $C_{17}H_{15}O_2Br$ requires M^+, 330.0255 and 332.0233); ν_{max}(liquid film)/cm^{-1} 1713 (C=O), 3016, 1524 and 1245; δ_H($CDCl_3$) 7.76 (1 H, d, *J* 15.5, H-3), 7.62–7.56 (6 H, m, Ph), 7.47 (2 H, d, *J* 8.5, H-2′,6′), 6.48 (1 H, d, *J* 15.5, H-2), 4.28 (2 H, q, *J* 7, OCH_2CH_3), 1.35 (3 H, t, *J* 7, OCH_2CH_3).

Ethyl 3-(biphenyl-4′-yl)-4-phenylbutanoate 8

A mixture of CuI (8.4 g, 44.2 mmol, 2 equiv.) and dry THF (160 ml) in a round-bottom flask was sealed with a rubber septum, flushed with argon and dry TMEDA (8 ml, 48.6 mmol, 2.2 equiv.) was added. After the mixture had been stirred at room temperature for 10 min the flask was cooled to −78 °C and the benzyl Grignard reagent (1.17 M solution in THF; 38 ml, 44.2 mmol, 2 equiv.) was added to it. The mixture was then stirred at −78 °C for 15 min after which a solution of chlorotrimethylsilane (14.2 ml, 110.5 mmol, 5 equiv.) and the enoate **6** (5.6 g, 22.1 mmol), in dry THF (110 ml), was injected into it *via* a syringe with continued stirring; during this operation the temperature of the mixture was allowed to rise to −30 °C. After 24 h the cold reaction mixture was poured into a separatory funnel containing saturated aqueous NH_4Cl–NH_4OH (3:2; 100 ml) and extracted twice with ether (200 ml). The combined extracts were then washed with water (200 ml), dried (Na_2SO_4) and evaporated to dryness. Flash chromatography (hexane–acetone, 9:1) of the residue gave butanoate **8** as a *white solid* (6.3 g, 84%); mp 67 °C; R_F 0.34 (hexane–acetone, 9:1); *m/z* 344 (M^+, 27%), 299 (8), 256 (9), 254 (18), 253 (84), 252 (11), 212 (16), 211 (100), 183 (11), 181 (28), 180 (34), 179 (18), 178 (20), 167 (18), 166 (11), 165 (17), 149 (15), 91 (17) and 88 (10) (Found; M^+, 344.1762. $C_{24}H_{24}O_2$ requires M^+, 344.1776); ν_{max}(liquid film)/cm^{-1} 1731 (C=O), 2938, 1491 and 1146; δ_H($CDCl_3$) 7.59–7.04 (14 H, m, Ph), 3.99 (2 H, q, *J* 7, OCH_2CH_3), 3.51–3.41 (1 H, m, H-3), 2.97 (1 H, dd, *J* 14 and 7) and 2.91 (1 H, dd, *J* 14 and 8) (4-CH_2), 2.7 (1 H, dd, *J* 15.5 and 6.5) and 2.63 (1 H, dd, *J* 15.5 and 8) (2-CH_2) and 1.11 (3 H, t, *J* 7, OCH_2CH_3).

Ethyl 3-(4″-bromobiphenyl-4′-yl)-4-phenylbutanoate 9

In a reaction similar to that for the preparation of the butanoate **8**, the BnCu–TMEDA complex [prepared by dissolving CuI (4.2 g, 21.72 mmol, 2 equiv.) in a mixture of THF (80 ml) and TMEDA (4 ml, 23.93 mmol, 2.2 equiv.) followed by addition of BnMgCl (1.17 M solution in THF; 19 ml, 21.75 mmol, 2 equiv.) was allowed to react with ethyl 4-(4′-bromophenyl)cinnamate **7** (3.6 g, 10.88 mmol in 55 ml of THF) in the presence of TMSCl (54.38 mmol; 7.1 ml, 5 equiv.) to give the butanoate **9** as a *white solid* (3.7 g, 81%); mp 49 °C; R_F 0.54 (hexane–acetone, 9:1); *m/z* 422 and 424 (M^+, 10%), 423 (10), 333 (70), 332 (68), 290 (98), 289 (100), 253 (40), 211 (42), 179 (70), 178 (85), 165 (35), 152 (32), 91 (73) and 65 (28) (Found: M^+, 422.0878 and 424.0863. $C_{24}H_{23}O_2Br$ requires M^+, 422.0881 and 424.0862); ν_{max}(liquid film)/cm^{-1} 1728 (C=O), 1524, 1248 and 930; δ_H($CDCl_3$) 7.53 (2 H, d, *J* 8.5, H-3″,5″), 7.45 (2 H, d, *J* 8.5, H-2″,6″), 7.43 (2 H, d, *J* 8.5, H-3′,5′), 7.26–7.05 (7 H, m, Ph), 3.99 (2 H, q, *J* 7, OCH_2CH_3), 3.52–3.42 (1 H, m, H-3), 2.96 (1 H, dd, *J* 14 and 7.5) and 2.91 (1 H, dd, *J* 14 and 8) (4-CH_2), 2.69 (1 H, dd, *J* 16 and 7) and 2.62 (1 H, dd, *J* 16 and 8.5) (2-CH_2) and 1.12 (3 H, t, *J* 7, OCH_2CH_3).

3-(Biphenyl-4′-yl)-1,2,3,4-tetrahydronaphthalen-1-one 10

Anhydrous $AlCl_3$ (240 mg, 1.79 mmol, 3 equiv.) was added to a solution of the butanoate **8** (200 mg, 0.581 mmol) in dry toluene (4 ml). The mixture was kept at 90 °C for 16 h after which it was treated with 3 M hydrochloric acid (3 ml), concentrated by solvent removal under reduced pressure and extracted with ethyl acetate (2 × 20 ml). The combined extracts were washed with water (20 ml), dried (Na_2SO_4) and evaporated to dryness to yield the tetralone **10** as a white solid (0.152 g, 88%) following preparative TLC (hexane–acetone, 9:1); mp 95 °C (lit.,[1] 92–94 °C); R_F 0.3; ν_{max}(liquid film)/cm^{-1} 1683 (C=O), 2260, 1386 and 897; δ_H($CDCl_3$) 8.09 (1 H, dd, *J* 8 and 1.5, H-8), 7.62–7.28 (12 H, m, Ph), 3.57–3.46 (1 H, m, H-3), 3.31–3.18 (2 H, m, 4-CH_2), 3.02 [1 H, ddd, *J* 14, 4 and 2, H-2(eq)] and 2.87 [1 H, dd, *J* 16.5 and 12.5, H-2(ax)].

3-(4″-Bromobiphenyl-4′-yl)-1,2,3,4-tetrahydronaphthalen-1-one 11

Treatment of the butanoate **9** (200 mg, 0.4728 mmol) with $AlCl_3$ (190 mg, 1.43 mmol, 3 equiv.) in dry toluene (4 ml) as described above, gave the tetralone **11** (153 mg, 86%); mp 153 °C (lit.,[1] 156–158 °C); R_F 0.29 (hexane–acetone, 9:1); ν_{max}(liquid film)/cm^{-1} 1689 (C=O), 1605, 1488 and 906; δ_H($CDCl_3$) 8.09 (1 H, dd, *J* 8 and 1.5, H-8), 7.62–7.28 (11 H, m, Ph), 3.57–3.46 (1 H, m, H-3), 3.31–3.18 (2 H, m, 4-CH_2), 3.02 [1 H, ddd, *J* 16.5, 4 and 2, H-2(eq)] and 2.86 [1 H, dd, *J* 16.5 and 12.5, H-2(ax)].

3-(Biphenyl-4′-yl)-1,2,3,4-tetrahydronaphthalen-1-ol (mixture of *cis*,*trans* isomers) 12

Sodium boranuide (51 mg, 1.342 mmol, 4 equiv.) was added to a solution of the ketone **10** (100 mg, 0.3355 mmol) in EtOH–THF (1:1 mixture; 5 ml). The mixture was stirred for 4 h after which the excess of boranuide was destroyed by the addition of acetone prior to removal of the solvents *in vacuo* and the addition of water (5 ml). The mixture was extracted with ether (3 × 10 ml) and the combined extracts were dried (Na_2SO_4), and evaporated to yield a white solid (98 mg, 98%); R_F 0.37 (hexane–benzene–acetone, 6:3:1); δ_H($CDCl_3$) 7.67–7.08 (13 H, m, Ph), 5.05–4.95 [1 H, m, H-1 (*cis*,*trans*)], 3.48–3.36 [1 H, m, H-3 (*trans*)], 3.2–2.9 [3 H, m, 2-CH_2 (*cis*,*trans*), 4-CH (*cis*)], 2.57–2.49 [1 H, m, H-3 (*cis*)], 2.38–2.30 (1 H, m) and 2.19–2.09 (1 H, m) [4-CH_2 (*trans*)], 2.04–1.91 [1 H, m, 4-CH (*cis*)] and 2.0–1.8 (br s, OH).

3-(4″-Bromobiphenyl-4′-yl)-1,2,3,4-tetrahydronaphthalen-1-ol (mixture of *cis*,*trans* isomers) 13

Similar treatment of the bromo ketone **11** (100 mg, 0.2652 mmol) with sodium boranuide (40 mg, 1.061 mmol, 4 equiv.) in EtOH–THF (1:1; 5 ml) gave the product **13** as a white solid (97 mg, 97%); R_F 0.38 (hexane–benzene–acetone, 6:3:1); δ_H($CDCl_3$) 7.67–7.10 (12 H, m, Ph), 5.05–4.95 [1 H, m, H-1

(*cis*,*trans*)], 3.48–3.36 [1 H, m, H-3 (*trans*)], 3.2–2.9 [3 H, m, 2-CH_2 (*cis*,*trans*), 4-CH (*cis*)], 2.57–2.49 [1 H, m, H-3 (*cis*)], 2.38–2.30 (1 H, m) and 2.19–2.09 (1 H, m) [4-CH_2 (*trans*)], 2.04–1.91 [1 H, m, 4-CH (*cis*)] and 2.0–1.8 (br s, OH).

3-[3′-(Biphenyl-4″-yl)-1′,2′,3′,4′-tetrahydro-1′-naphthyl]-4-hydroxychromen-2-one 1 (diphenacoum)

A mixture of the 4-hydroxycoumarin **16** (106 mg, 0.6532 mmol, 2 equiv.) and the tetralol **12** (98 mg, 0.3266 mmol) under an HCl(g) atmosphere was heated at 160 °C for 30 min. Flash chromatography (hexane–benzene–acetone, 6:3:1) of the mixture afforded the title compound **1** (0.115 g, 78%; *trans*:*cis*, 3:2); *trans*-isomer: 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; $\delta_H(C_6D_6)$ 7.63 (1 H, dd, *J* 8 and 1.5, H-5), 7.52–7.48 (2 H, m, Ph), 7.4 (2 H, d, *J* 8, Ph), 7.26–6.72 (12 H, m, Ph), 6.17 (br s, OH), 4.84 (1 H, dd, *J* 6 and 2.5, H-1′), 3.10–2.99 (1 H, m, H-3′), 2.88–2.79 (1 H, m) and 2.68–2.58 (1 H, m) (4′-CH_2), 2.53–2.45 (1 H, m) and 2.18–2.06 (1 H, m) (2′-CH_2); *cis*-isomer: 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; $\delta_H(C_6D_6)$ 7.72–7.62 (br s, OH), 7.54 (2 H, dd, *J* 8 and 1.5, H-5), 7.47 (2 H, d, *J* 8, Ph), 7.29–6.77 (13 H, m, Ph), 5.02–4.92 (1 H, br s, H-1′), 2.85–2.65 (4 H, br s) and 2.4–2.3 (1 H, br s) (2′-CH_2, H-3′, 4′-CH_2).

3-[3′-(4‴-Bromobiphenyl-4″-yl)-1′,2′,3′,4′-tetrahydro-1′-naphthyl]-4-hydroxychromen-2-one 2 (brodifacoum)

A condensation similar to that described above between the tetralol **13** (100 mg, 0.2638 mmol) and 4-hydroxycoumarin **16** (86 mg, 0.5276 mmol, 2 equiv.) at 160 °C for 30 min gave the title compound **2** (0.103 g, 74%, *trans*:*cis*, 11:9); *trans*-isomer: 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; $\delta_H(C_6D_6)$ 7.63 (1 H, dd, *J* 8 and 1.5, H-5′), 7.49 (1 H, dd, *J* 8 and 1.5, Ph), 7.39 (1 H, d, *J* 8, Ph), 7.32 (2 H, d, *J* 8, H-3‴,5‴), 7.26–6.70 (11 H, m, Ph), 4.86–4.81 (1 H, br s, H-1′), 3.10–2.99 (1 H, m, H-3′), 2.88–2.79 (1 H, m) and 2.68–2.58 (1 H, m) (4′-CH_2), 2.53–2.45 (1 H, m) and 2.18–2.06 (1 H, m) (2′-CH_2); *cis*-isomer: 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; $\delta_H(C_6D_6)$ 7.66–7.63 (br s, OH), 7.54 (1 H, dd, *J* 8 and 1.5, H-5′), 7.48 (1 H, d, *J* 8, Ph), 7.37–6.76 (14 H, m, Ph), 5.02–4.92 (1 H, br s, H-1′), 2.85–2.65 (4 H, br s) and 2.4–2.3 (1 H, br s) (2′-CH_2, H-3′, 4′-CH_2).

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