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The Synthesis of C_2-Symmetric and Axially Chiral Compounds for Recognition and Catalysis

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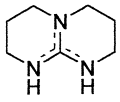
Abstract—Axially chiral amidines and guanidines, some possessing C_2-symmetry, have been targeted as potential chiral catalysts for reactions of α,β-unsaturated carboxylic acids or esters. The key step in each synthesis required the coupling of two sterically demanding aromatic compounds to form atropisomeric biaryl species.

Guanidines and amidines have been used widely as recognition elements for anionic substrates; they remain protonated over a wide pH range and form organised hydrogen bonded complexes. In particular, the symmetrical heterocyclic core (**1**) forms the basis of many compounds designed to recognise carboxylate, phosphate and nitronate functionalities. Mendoza et al employed a guanidinium moiety in the design of a compound for the efficient resolution of L-tryptophan and L-phenylalanine,[1,2] and in a catalyst designed to induce chirality in the Michael reactions of α,β-unsaturated esters.[3] Davis et al employed a bicyclic amidinium in the recognition of nitronate species in pursuit of a system for the induction of chirality in the Henry reaction;[4] this was subsequently realised by Najera et al. using an acyclic guanidinium species.[5] Axially chiral biaryl amidinium species have been investigated previously.[6]

The aim of this current work was to design a compound that would recognise and bind specifically an α,β-unsaturated substrate, either an oxoanion or a neutral species, and behave as a temporary, catalytic chiral auxiliary. The axial chirality of the compound must enable attack on an α,β-unsaturated substrate from one face only, attack from the other face being hindered by a large blocking group (Fig. 1).



(**1**)

The blocking group must be of a size sufficient to effect good facial selectivity; our chosen strategy of assembling the axially chiral targets using a biaryl coupling required an aromatic residue. However, the steric bulk of the blocking group in the target molecules must not hinder the approach of the guest α,β-unsaturated substrate, nor must it prevent the substrate from being able to access and associate with the binding site on the host amidine or guanidine. Essentially, the incoming substrate must be able to 'see' the binding site. The ability of the target molecules to accommodate α,β-unsaturated substrates and, hence, induce asymmetry in reactions of the substrates was assessed using very simple molecular modelling techniques.[7] A rigid tricyclic amidine or guanidine moiety was chosen to serve as the recognition site for two series of compounds possessing axial chirality. Atropisomers can exist for all the target compounds due to restricted rotation around the biaryl C–C bond. However, different conformations can be envisaged for each atropisomer of most of the target hosts and this became important in our later investigations.

Conformation **A** of the atropisomer of C_2-symmetric compound (**2**) was energetically favoured over conformation **B**. The tricyclic moiety of conformation **A** and the methyl group of conformation **B** provide facial selectivity in each case. In both cases, the recognition site is accessible (Figs. 2 and 3). The C_2-symmetric bis(amidine) (**3**) gave similar results, the favoured conformation having a dihedral angle of 47°.

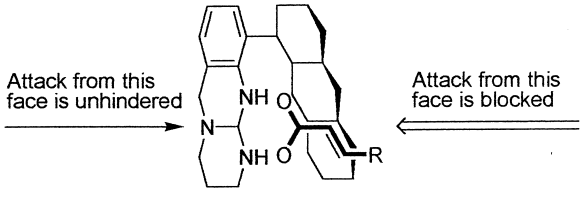


Figure 1.

Keywords: guanidines; amidines; molecular recognition; axial chirality.
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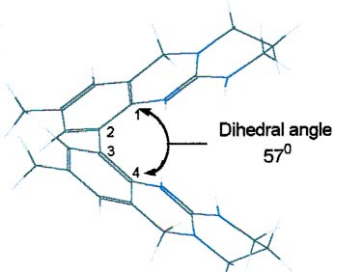


Figure 2.

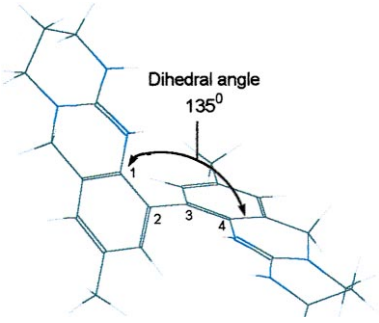
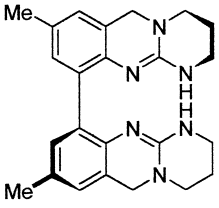
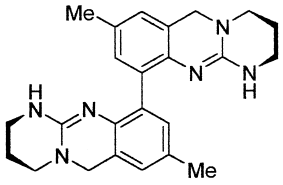


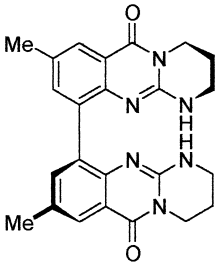
Figure 3.



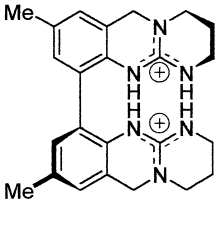
(**2**)
Conformation A



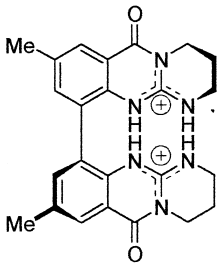
(**2**)
Conformation B



(**3**)



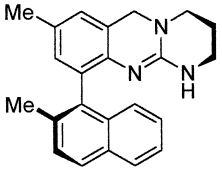
(**4**)



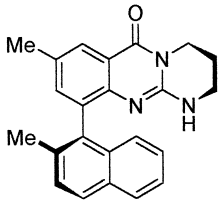
(**5**)

The corresponding diprotonated bis(guanidine) (**4**) and bis(amidine) (**5**) were examined, as these species would actually bind oxoanion substrates. Protonation of either compound (**2**) or (**3**) increases the dihedral angle between the two tricyclic moieties to 124° for (**4**) and 135° for (**5**), presumably through mutual repulsion of the protonated basic centres. The favoured atropisomeric conformations of compounds (**4**) and (**5**) still have recognition sites that are blocked from one face.

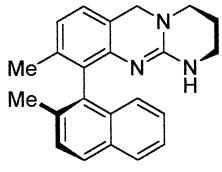
A naphthyl moiety was chosen as the directing group in a series of axially chiral compounds. The naphthyl group provides effective facial discrimination in the favoured atropisomeric conformations of guanidine (**6**) (dihedral angle 68°) and amidine (**7**) (dihedral angle 62°). Modelling also confirmed that the rotational mobility about the biaryl axes of guanidine (**8**) (dihedral angle 107°) and amidine (**9**) (dihedral angle 103°) is extremely restricted by the addition of a second *ortho* methyl substituent.



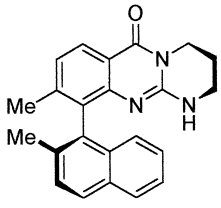
(**6**)



(**7**)

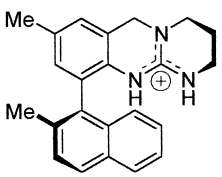


(**8**)

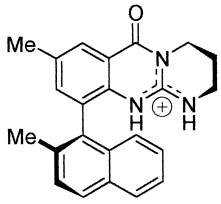


(**9**)

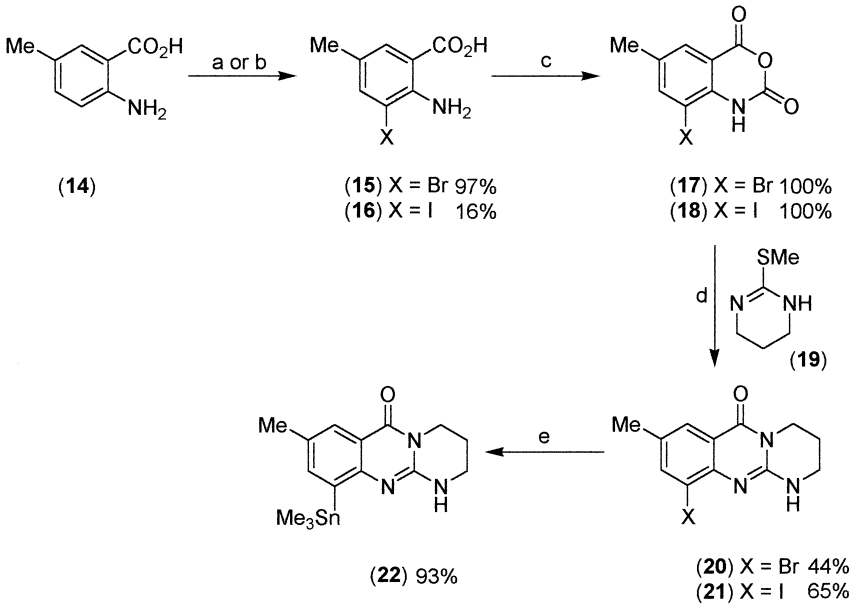
The dihedral angles of the preferred atropisomeric conformations of protonated compounds (**10**) (dihedral angle 61°), (**11**) (dihedral angle 68°), (**12**) (dihedral angle 103°) and (**13**) (dihedral angle 105°) are virtually unchanged from their nonprotonated counterparts.



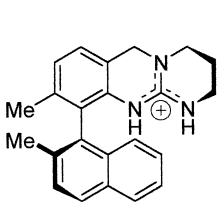
(**10**)

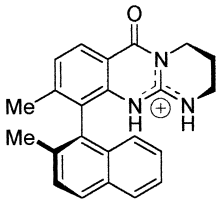


(**11**)



Scheme 1. (a) Br_2, AcOH. (b) I_2 AcOH. (c) 20% $COCl_2$ in toluene, 60°C. (d) (**19**), DMF, 100°C, N_2. (e) $(Me_3Sn)_2$, $Pd(PPh_3)_2Cl_2$, THF, 80°C, N_2.

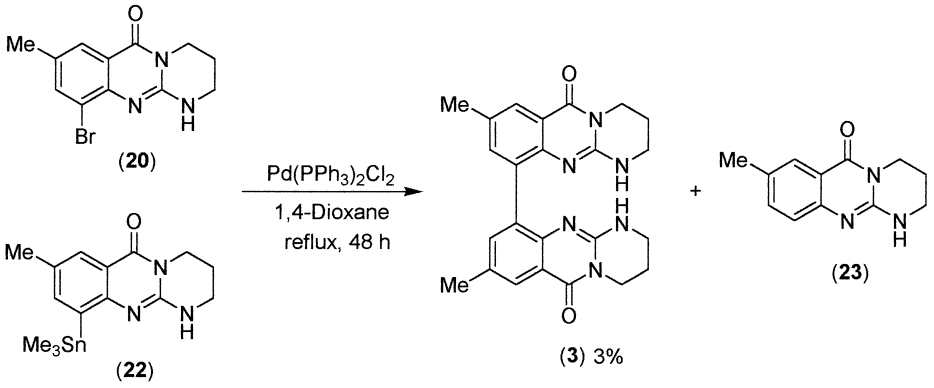




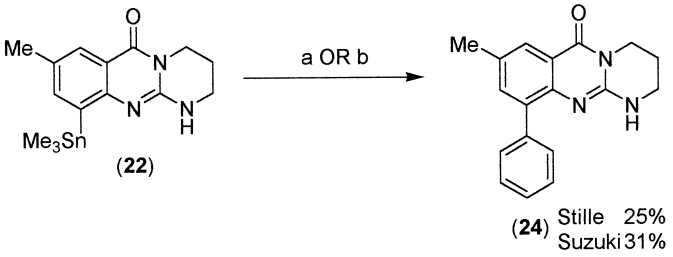
The modelling has demonstrated that a tricyclic amidine/guanidine based skeleton can support a facial directing group without sterically hindering the binding site. These positive results encouraged the synthesis of the proposed compounds.

The first series of compounds investigated possess C_2-symmetry. We envisaged that a convergent strategy could be employed, using a common building block to give both partners for a biaryl bond forming reaction. The synthesis of pyrimido[2,1-b]quinazoline derivatives was achieved in good yield (Scheme 1). Thus, bromination of 2-amino-5-methylbenzoic acid (**14**) afforded 2-amino-3-bromo-5-methylbenzoic acid (**15**) exclusively. Similarly, iodination of compound (**14**) yielded iodide (**16**). Treatment of bromide (**15**) or iodide (**16**) with phosgene (as a solution in toluene) afforded isatoic anhydrides (**17**) and (**18**), respectively, in quantitative yield. Condensation of anhydrides (**17**) and (**18**) with 2-methylthio-1,4,5,6-tetrahydropyrimidine (**19**) delivered the desired tricyclic compounds (**20**) and (**21**) in 44% and 65% yield, respectively. Bromide (**20**) was subsequently reacted with hexamethylditin to give stannane (**22**). The above route to pyrimido[2,1-b]quinazoline derivatives was adopted in favour of the direct fusion of 2-methylthio-1,4,5,6-tetrahydropyrimidine (**19**) with anthranilic acids (**15**) and (**16**) as the latter process gave unsatisfactory yields with these substrates.

The synthesis of C_2-symmetric compound (**3**) via a biaryl bond forming reaction was investigated using Stille, Suzuki and Ullmann protocols. Only the reaction of bromide (**20**) with stannane (**22**) using Stille methodology delivered compound (**3**), albeit in very low (3%) yield (Scheme 2). The palladium catalysed coupling reaction was attempted



Scheme 2.



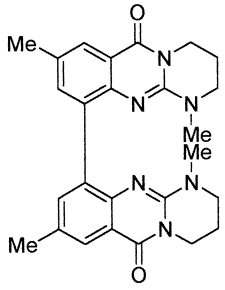
Scheme 3. (a) PhI, $Pd(PPh_3)_4$, 1,4-dioxane, reflux, 48 h. (b) $PhB(OH)_2$, $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 (aq), reflux, 24 h.

many times using different catalysts and conditions, but the majority of experiments yielded the reduced compound (**23**) (previously prepared using an alternative procedure[8]) in high yield, together with recovered bromide (**20**).

Stannane (**22**) was reacted with iodobenzene using similar conditions to yield coupled product (**24**) in 25% yield, and with phenylboronic acid to give (**24**) in 31% yield (Scheme 3).

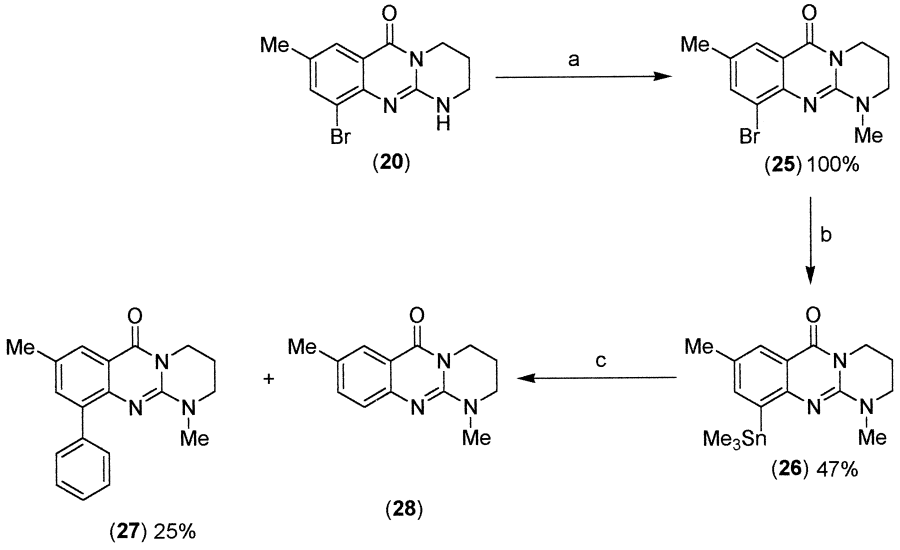
Many examples of Stille couplings of sterically demanding substrates are cited in the literature.[9,10,11,12] We considered possible reasons (other than steric hindrance) for the repeated isolation of reduced material from the cross-coupling reactions. The metallated intermediate can only be acquiring a proton from the solvent, atmosphere or from the starting materials themselves. Rigorous precautions were always taken to ensure that anhydrous conditions were employed under an inert atmosphere. We decided subsequently to protect the secondary amine function in bromide (**20**) to remove the acidic proton from the starting material. There is precedent for this manoeuvre in the work of Stille et al.[13] Our main concern was not ease of cleavage of the protecting group: rather, we required a group that would not increase the steric constraints of the reaction too greatly. After establishing that the cross-coupling reaction was viable, alternative protecting groups could be examined.

Quantitative methylation of bromide (**20**) gave the protected building block (**25**) (Scheme 4). Subsequent reaction of compound (**25**) with hexamethylditin delivered stannane (**26**) in 47% (based on recovered starting material); no coupled product was detected in the product mixture. Stannane (**26**) was reacted with iodobenzene using palladium catalysis to yield the coupled product (**27**) in 25% yield, though the major product was again reduced starting material (**28**) (prepared for reference by methylation of compound (**23**)). However, reaction of methylated bromide (**25**) with stannane (**26**) under analogous conditions did not yield the desired C_2-symmetric compound (**29**), the compounds isolated from the reaction being recovered bromide (**25**) and reduced material (**28**).

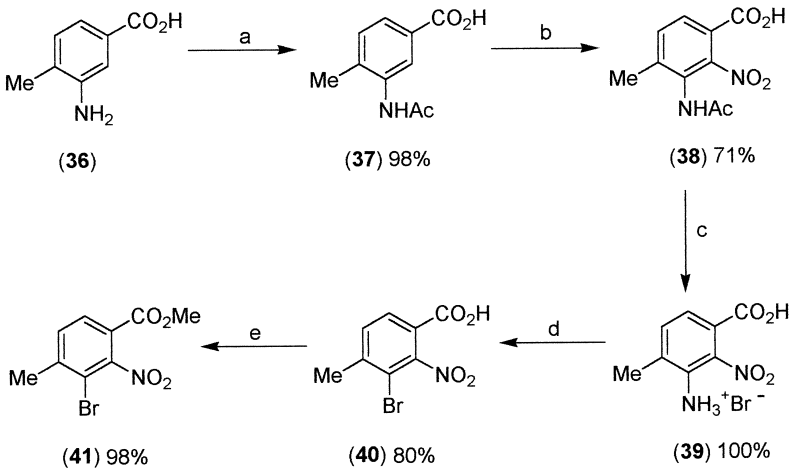


(**29**)

Suzuki methodology was also employed but with a similar

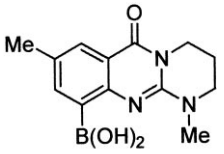


Scheme 4. (a) NaH, THF, MeI. (b) $(Me_3Sn)_2$, $Pd(PPh_3)_4$, 1,4-dioxane, 120°C, 4 h. (c) PhI, $Pd(PPh_3)_4$, 1,4-dioxane, reflux, 3 h.



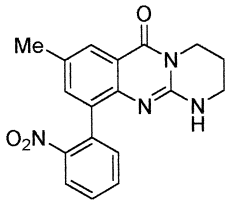
Scheme 5. (a) Ac_2O, AcOH, reflux, 30 min. (b) Fuming HNO_3, 0°C. (c) Aqueous HBr, reflux, 12 h. (d) Aqueous HBr, $NaNO_2$, CuBr, 0°C. (e) MeOH, H_2SO_4, reflux, 14 h.

outcome to the reactions of bromide (**25**) and stannane (**26**) as described above. Isolation of the boronic acid (**30**) from reaction of bromide (**25**) with butyllithium, quenching of the anion with trimethyl borate and subsequent hydrolysis proved difficult. Homocoupling was attempted using the method described by Keay et al., by in situ formation of the boronic acid (**30**) and subsequent addition of a palladium catalyst;[14] again, the major product isolated was reduced material (**28**).

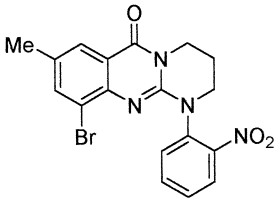


(**30**)

In an alternative strategy, (**20**) was reacted with 2-bromonitrobenzene under palladium catalysed Ullmann coupling conditions. The nitrobenzene derivative was expected to be an active coupling partner in the Ullmann reaction, delivering the anticipated product (**31**) in high yield. However, the reaction did not deliver the desired biaryl product, instead giving *N*-arylated compound (**32**) in 36% yield, together with 2,2′-dinitrobiphenyl, unreacted bromide (**20**) and reduced compound (**23**).

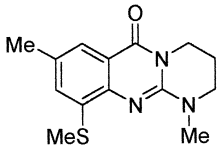


(**31**)



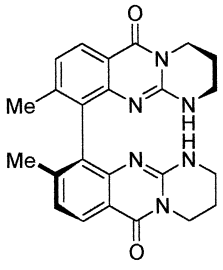
(**32**)

We assume that *N*-alkylation occurred because of the acidic proton in bromide (**20**). A different result was obtained from the attempted homocoupling of methylated bromide (**25**) in DMSO under Ullmann conditions. The major product from the reaction was not the desired homocoupled compound; rather, sulfide (**33**) was isolated in 60% yield. Similar results have been reported previously by Tamborski and Chen and by Soulen and Griffith for the attempted homocoupling of fluorinated aryls.[15,16]

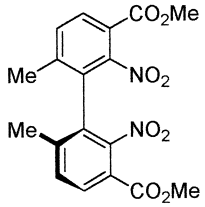


(**33**)

An alternative, divergent strategy was employed for the synthesis of C_2-symmetric compound (**34**), relying upon the preparation of biphenyl (**35**) as the key intermediate.

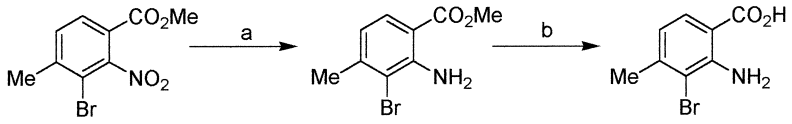


(**34**)



(**35**)

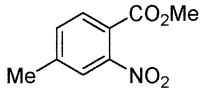
Synthesis of compound (**35**) was achieved in six steps from 3-amino-4-methylbenzoic acid (**36**) (Scheme 5). Acylation of the acid (**36**) gave amide (**37**), nitration of which gave two regioisomeric compounds in a 4:1 ratio. The regioisomers were readily separated by fractional crystallisation, giving the desired compound (**38**) in 71% yield. Cleavage of the amide using hydrobromic acid delivered salt (**39**). Subsequent diazotisation and Sandmeyer bromination gave 3-bromo-4-methyl-2-nitrobenzoic acid (**40**) in 80% yield. Esterification was necessary as the Ullmann coupling shows low tolerance to the presence of free carboxylic acid functions; this was best achieved using acid catalysis to give methyl ester (**41**) in 98% yield.



(**41**) (**44**) 87% (**45**) 87%

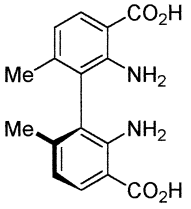
Scheme 6. (a) Fe, EtOH, conc. HCl, reflux, 12 h. (b) KOH, MeOH, reflux 12 h.

Homocoupling of (**41**) under Ullmann conditions yielded the desired biphenyl compound (**35**) in 63% yield. However, this reaction proved to be rather capricious and varying amounts of debrominated material (**42**) were always isolated in preparations using freshly activated copper powder, anhydrous reagents and high temperatures.[17] This is in contrast with results obtained by Kanojia et al. in the coupling of sterically demanding substrates under identical conditions.[18]



(**42**)

The next step after the homocoupling of bromide (**41**) was the reduction of the nitro groups in (**35**) to amines and saponification of the methyl esters to yield bis(aminoacid) (**43**). Compound (**43**) could then be further elaborated to give compound (**34**) using the methodology employed for the synthesis of bromide (**20**). Reduction of 2,2′-dinitro-1,1′-biphenyl to the corresponding diamine in high yield has been reported using the conditions of West.[19,20] Bromide (**41**) was chosen as a model to test our strategy (Scheme 6): compound (**41**) was reduced using West conditions to give amine (**44**) in 87% yield, subsequent saponification delivered aminoacid (**45**) in good yield.



(**43**)

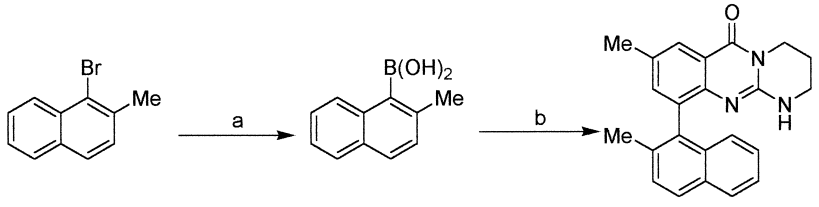
As with the convergent route, it proved difficult to homocouple the sterically demanding bromide (**41**); it should be noted that the present strategy relies upon the homocoupling of a compound with two substituents *ortho* to the bromide substituent. Hence, reduction of key biphenyl (**35**) was not attempted because of the small amount available. However, the chemistry outlined above indicates that the divergent strategy provides a promising route to C_2-symmetric target (**34**). Not only does this route avoid the coupling of two sterically demanding tricyclic units but the synthesis of intermediate biphenyl (**35**) is achieved without the need to use expensive catalysts.

After encountering problems in our attempts to prepare biaryl compounds with C_2-symmetry, we directed our efforts towards the preparation of simpler compounds with axial chirality. Compound (**7**) was chosen as the target. No repulsion between the two basic centres found in compounds (**3**) and (**34**) would be present in the corresponding naphthyl substituted compound (**7**). Furthermore, coupling of bromide (**20**) and the naphthyl moiety should not present so many problems in terms of steric effects.

1-Bromo-2-methylnaphthalene (**46**) was converted into boronic acid (**47**) via the Grignard intermediate (Scheme 7).[21] Boronic acid (**47**) was then coupled with the bromide (**20**) under optimised Suzuki coupling conditions to give compound (**7**) in 27% yield.

Naphthyl substituted compound (**7**) obviously exists as enantiomeric atropisomers: ^{1}H NMR nOe experiments indicated that the preferred conformation of this compound is as depicted. Although racemisation is possible, there is much literature precedent suggesting that the energy required to rotate through the biaryl bond of 2-substituted 1,1′-biaryl systems is high enough to make this unfavourable and, therefore, pure enantiomers can be stored at room temperature for long periods of time. In light of these and other studies, axially chiral compound (**7**) would not be prone to racemisation under mild reaction conditions. Compound (**7**) was resolved into its enantiomeric forms by analytical chiral HPLC but attempts to effect a classical resolution have so far been unsuccessful.

Protonated axially chiral compound (**11**) proved to be a



(**46**) (**47**) 79% (**7**) 27%

Scheme 7. (a) Mg, THF, heat 1 h; $B(OMe)_3$, RT, 2 h; aqueous HCl, RT 4 h. (b) (**20**), $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, 2 M aqueous ethanolic $Ba(OH)_2$, reflux, 24 h, Ar.

suitable system for the recognition of anionic substrates (association constant K for sodium acetate in $CDCl_3$ is $8.9\times10^2\ M^{-1}$, measured by analysis of ^1H NMR spectra of protonated (**11**) in the presence of varying amounts of sodium acetate). A strong association with neutral esters was also evidenced by significant changes in the ^1H NMR spectra of protonated compound (**11**) in the presence of ethyl acetate. This implies that reduction to the guanidine may not be necessary for catalytic activity. We are currently studying the use of protonated species (**11**) as an asymmetric catalyst in several important reactions of α,β-unsaturated substrates and will report our findings in due course.

Experimental

Melting points were determined using a Reithert Kofler melting point microscope apparatus and are uncorrected. Microanalyses were carried out using a Perkin–Elmer 240 elemental analyser. Infrared spectra were obtained using a Perkin–Elmer Paragon 100 FT-IR spectrometer; samples were analysed either as potassium bromide discs, as mulls in Nujol or as solutions in $CHCl_3$. Nuclear magnetic resonance (NMR) spectra were acquired using either a Jeol GSX270 FT-NMR at 270 MHz or a Bruker DPX300 FT-NMR at 300 MHz; samples were analysed as solutions in $CDCl_3$ or d_6-DMSO solution. Low resolution mass spectra were acquired using a AEI MS12 mass spectrometer (EI, 70 eV) or by the EPSRC Mass Spectrometry Service (Swansea). High resolution mass spectra were recorded by the EPSRC Mass Spectrometry Service (Swansea) and the mass spectrometry service at Reading University.

All solvents were purified and distilled before use. Acetonitrile was doubly distilled from P_2O_5 and then stored in a dark bottle over 4 Å molecular sieves. THF and dioxan were dried by refluxing over sodium until benzophenone held a purple colour. Dimethyl sulphoxide was passed through a column (20 g/L) of activated 3 or 4 Å molecular sieves. Thin layer chromatography was carried out using foil backed alumina or silica plates. Flash column chromatography was carried out using Janssen silica gel (particle size 0.035–0.07 mm). Chromatotron radial chromatography was performed on plates prepared using silica gel 60 PF_{254}.

Activation of copper powder/copper bronze

Copper bronze or copper powder (1 g) was treated with a 2% solution of iodine in acetone (50 mL) for 5–10 min. The copper was filtered off and washed with a 50% solution of concentrated hydrochloric acid in acetone (25 mL). The resulting slurry was filtered and washed with acetone. The copper was then dried in vacuo at 300°C for 4 h. The activated copper was used immediately.

2-Amino-3-bromo-5-methylbenzoic acid (15). To a stirred solution of 2-amino-5-methyl-benzoic acid (**14**) (25 g, 166 mmol) in glacial acetic acid (250 mL) at room temperature was added bromine (10 mL, 198 mmol) dropwise. A yellow precipitate formed immediately and the suspension was stirred for a further 3 h. The precipitate was filtered, washed with distilled water (250 mL) and dried in vacuo to give the *title compound* (**15**) (37 g, 97%) as an off-white solid, mp 205°C (lit[22] 207°C); (Found: C, 41.47; H, 3.21; N, 5.87. $C_8H_9BrNO_2$ requires C, 41.74; H, 3.48; N, 6.09%); ν_{max} (KBr disc) 3471, 3367, 2918, 1680, 1573, 1548, 1465, 1421, 1310, 1273, 1237, 1067, 939, 869, 791 and 708 cm^{-1}; δ_H (270 MHz, d_6DMSO) 7.60 (1H, d, *J*=2.0 Hz, *H*-2), 7.49 (1H, d, *J*=2.0 Hz, *H*-4), 2.17 (3H, s, *Me*); *m/z* (EI) 231 (67 M^+), 229 (69 M^+), 213 (99), 211 (100), 184 (27), 182 (23), 132 (15), 104 (36), 77 (41%).

2-Amino-3-iodo-5-methylbenzoic acid (16). To a stirred solution of 2-amino-5-methylbenzoic acid (**14**) (5 g, 33 mmol) in glacial acetic acid (50 mL) was added iodine crystals (9 g, 35 mmol). The mixture was heated at reflux for three days. The mixture was cooled to room temperature and petroleum ether (bp 40–60°C) (30 mL) was added. The mixture was filtered, the filtrate was concentrated in vacuo, and dichloromethane was added to give the *title compound* (**16**) (1.37 g, 16%) as a yellow solid, mp 211°C; (Found: C, 34.73; H, 2.69; N, 5.1; $C_8H_8INO_2$ requires C, 34.68; H, 2.91; N, 5.06%);. ν_{max} (Nujol) 3417, 3376, 3314, 1787, 1726, 1660, 1576, 1537, 1502, 1378, 1321, 1304, 1239, 1170, 934, 898, 872, 792, 762, 722 and 700 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.75 (1H, d, *J*=2.0 Hz, *H*-2), 7.69 (1H, d, *J*=2.0 Hz, *H*-4) 2.21 (2H, s, N*H*), 2.17 (3H, s, *Me*); *m/z* (EI) 277 (100 M^+), 260 (22), 259 (88), 230 (11), 209 (11), 164 (5), 146 (16), 132 (13), 105 (12), 104 (19), 77 (35%).

8-Bromo-6-methyl-1*H*-3,1-benzoxazine-2,4-dione (17). 2-Amino-5-methyl-benzoic acid (**15**) (15.0 g, 65 mmol) was dissolved in a solution of 20% phosgene in toluene (50 mL) and stirred at 60°C for 24 h. A further amount of a solution of 20% phosgene in toluene (50 mL) was added and heating continued. Aliquots (0.5 mL) were taken at 6 h intervals and heating continued until no starting material remained by ^1H NMR. The solvent was evaporated in vacuo to yield the *title compound* (16.70 g, 100%) (**17**) as an off-white solid, mp 249–250°C; (Found: C, 42.22, H, 2.11, N, 5.45; $C_9H_6BrNO_3$ requires C, 42.19, H, 2.34, N, 5.47%); ν_{max} (Nujol) 3217, 1787, 1723, 1612, 1378, 1328, 1256, 1207, 1142, 1054, 1006, 929, 880, 850, 801, 742, 723 and 708 cm^{-1}; δ_H (270 MHz, d_6DMSO) 11.01 (1H, s, N*H*) 7.89 (1H, d, *J*=2.0 Hz, *H*-5), 7.77 (1H, d, *J*=2.0 Hz, *H*-7), 2.33 (3H, s, *Me*); *m/z* (EI) 257 (21 M^+) 255 (22 M^+) 213 (96), 211 (100), 184 (27), 182 (26), 132 (21), 104 (29), 103 (26), (77) (53), 76 (29%).

8-Iodo-6-methyl-1*H*-3,1-benzoxazine-2,4-dione (18). 2-Amino-3-iodo-5-methylbenzoic acid (**16**) (1.3 g, 4.7 mmol) was dissolved in a solution of 20% phosgene in toluene (50 mL) and stirred at 60°C for 24 h. A further amount of a solution of 20% phosgene in toluene (50 mL) was added and heating continued. Aliquots (0.5 mL) were taken at 6 h intervals and heating continued until no starting material remained by ^1H NMR. The solvent was evaporated in vacuo to yield the *title compound* (**18**) (1.4 g, 100%) as a cream solid, mp 231–233°C; ν_{max} ($CHCl_3$) 3254, 1789, 1723, 1610, 1501, 1329, 1254, 1216, 1141, 1056, 1008, 927, 880, 826, 698, 670 and 615 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.92 (1H, d, *J*=2.0 Hz, *H*-5), 7.89 (1H, d, *J*=2.0 Hz, *H*-7), 2.38 (3H, s, *Me*); *m/z* (EI) 303 (100 M^+), 260 (32), 230 (39), 151 (10), 133 (39), 132 (57), 104 (43), 103 (55), 92 (61), 91 (91), 78 (20), 77 (59%); HRMS (CI, NH_3) M^+ found 302.9404. $C_9H_6INO_3$ requires 302.9392.

10-Bromo-8-methyl-1,2,3,4-tetrahydropyrimido[2,1-b]-quinazolin-6-one (20). To a stirred solution of 8-bromo-6-methyl-1*H*-3,1-benzoxazine-2,4-dione (**17**) (12.8 g, 50 mmol) in dimethylformamide (250 mL) was added 2-methylsulfanyl-1,4,5,6-tetrahydropyrimidine (**19**) (6.5 g, 50 mmol). The mixture was heated to 100°C for 4 h and a stream of nitrogen was bubbled continuously through the mixture. The mixture was cooled and distilled water (500 mL) was added to give an off white precipitate. The precipitate was filtered, washed with water (2×50 mL), then petroleum ether (bp 40–60°C) (2×50 mL). The precipitate was dissolved in dichloromethane (250 mL), the solution was dried over magnesium sulphate and the solvent evaporated in vacuo to give an off-white solid. Recrystallisation (dichloromethane–diethyl ether) gave the *title compound* (**20**) (6.47 g, 44%) as a white crystalline solid, mp 252°C; ν_{max} (KBr disc) 3297, 2947, 1664, 1622, 1579, 1488, 1294, 1232, 1219, 1018, 814, 790 and 675 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.87 (1H, d, *J*=2.0 Hz, *H*-7), 7.69 (1H, d, *J*=2.0 Hz, *H*-9), 5.63 (1H, br s; N*H*), 4.09 (2H, t, *J*=6.5 Hz, CH_2), 3.48 (2H, t, *J*=6.5 Hz, CH_2), 2.36 (3H, s, *Me*), 2.11 (2H, m, CH_2); *m*/*z* (EI) 295 (93 M^+), 293 (100 M^+), 240 (12), 238 (14), 213 (17), 211 (19), 129 (12), 103 (23), 77 (15), 76 (10%); HRMS (CI, NH_3) M^++H found 294.0229. $C_{12}H_{12}BrN_3O$ requires 294.0242.

10-Iodo-8-methyl-1,2,3,4-tetrahydropyrimido[2,1-b]quinazolin-6-one (21). To a stirred solution of 8-iodo-6-methyl-1*H*-3,1-benzoxazine-2,4-dione (**18**) (1.3 g, 3.8 mmol) in dimethylformamide (25 mL) was added 2-methylsulfanyl-1,4,5,6-tetrahydropyrimidine (**19**) (0.5 g, 3.8 mmol). The mixture was heated to 100°C for 4 h and a stream of nitrogen was bubbled continuously through the mixture. The mixture was cooled and distilled water (50 mL) was added to give a pale yellow precipitate. The precipitate was filtered, washed with water (2×50 mL), then petroleum ether (bp 40–60°C) (2×50 mL). The precipitate was dissolved in dichloromethane (75 mL), the solution was dried over magnesium sulphate and the solvent evaporated in vacuo to give an off-white solid. Recrystallisation (dichloromethane–diethyl ether) gave the *title compound* (**21**) (0.84 g, 65%) as a pale yellow solid, mp 241–243°C; (Found: C, 41.98; H, 3.69; N, 12.19; $C_{12}H_{12}IN_3O$ requires C, 42.25; H, 3.55; N, 12.32%); ν_{max} (KBr disc) 3299, 1664, 1623, 1578, 1496, 1473, 1371, 1317, 1292, 1235 and 790 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.93 (1H, d, *J*=2.0 Hz, *H*-7), 7.86 (1H, d, *J*=2.0 Hz, *H*-9), 4.05 (2H, t, *J*=6.0 Hz, CH_2), 3.46 (2H, t, *J*=6.0 Hz, CH_2), 2.32 (3H, s, *Me*), 2.08 (2H, m, CH_2); *m*/*z* (EI) 341 (100 M^+), 286 (24), 259 (32), 214 (30), 132 (19), 103 (28), 83 (27), 77 (24), 55 (34%).

10-(Trimethylstannyl)-8-methyl-1,2,3,4-tetrahydropyrimido[2,1-b]quinazolin-6-one (22). 10-Bromo-8-methyl-1,2,3,4-tetrahydro-2*H*-pyrimido[2,1-*b*]quinazolin-6-one (**20**) (2.0 g, 6.8 mmol), hexamethylditin (2.9 g, 9 mmol) and bis(triphenylphosphine) palladium(II) dichloride (0.4 g, 0.58 mmol) were dissolved in 1,4-dioxane (50 mL) under Argon. The stirred mixture was heated at 120°C for 4 h and then cooled to room temperature. The mixture was filtered and the solvent evaporated in vacuo to give a brown solid. Purification of the crude product by chromatography (CH_2Cl_2) gave the *title compound* (**22**) (2.39 g, 93%) as a yellow solid, mp 216°C; (Found: C, 47.60; H, 5.55; N, 11.08; $C_{15}H_{21}N_3OSn$ requires C, 47.65; H, 5.6; N, 11.11%); ν_{max} (KBr disc) 3290, 1665, 1578, 1475, 1444, 1369, 1282, 1223, 1161, 1118, 1019, 800, 175 and 696 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.85 (1H, m, *H*-7), 7.50 (1H, d, *J*=2.0 Hz, *H*-9), 5.00 (1H, br s, N*H*), 4.08 (2H, m, CH_2), 3.48 (2H, m, CH_2), 2.38 (3H, s, Ar*Me*), 2.11 (2H, m, CH_2), 0.29 (9H, t, *J*=26 Hz, SnMe_3); *m*/*z* (EI) 379 (3 M^++H), 334 (19), 277 (23), 262 (100), 215 (42), 183 (100), 108 (59), 77 (13%).

8-Methyl-10-(8′-methyl-6′-oxy-1′,2′,3′,4′-tetrahydropyrimido[2,1-b]quinazolin-10′-yl)-1,2,3,4-tetrahydropyrimido[2,1-b]quinazolin-6-one (3). 10-Bromo-8-methyl-1,2,3,4-tetrahydropyrimido[2,1-b]quinazolin-6-one (**20**) (0.117 g, 0.4 mmol), 10-(Trimethylstannyl)-8-methyl-1,2,3,4-tetrahydropyrimido[2,1-b]quinazolin-6-one (**22**) (0.15 g, 0.4 mmol) and bis(triphenylphosphine) palladium(II) dichloride (56 mg) were dissolved in dry 1,4-dioxane (20 mL) under argon. The mixture was heated at reflux for 48 h and then cooled to room temperature. The mixture was filtered and the solvent evaporated in vacuo to give an orange solid. Purification of the crude product by chromatography (33% ethyl acetate/petroleum ether (bp 40–60°C), then methanol) gave the *title compound* (**3**) (5 mg, 3%) as a yellow solid, mp 297–300°C; ν_{max} (KBr disc) 3404, 1683, 1592, 1477, 1438, 1318, 1291, 1101, 787, 746 and 692 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.89 (2H, d, *J*=2.0 Hz, 2×*H*-7), 7.29 (2H, d, *J*=2.0 Hz, 2×*H*-9), 3.97 (4H, t, *J*=4.0 Hz, CH_2), 3.16 (4H, br t, *J*=5.5 Hz, CH_2), 2.32 (6H, s, Me), 1.93 (4H, m, CH_2); *m*/*z* (EI) 428 (88 M^+), 427 (80), 413 (24), 388 (14), 387 (14), 344 (17), 330 (21), 293 (27), 290 (27), 281 (24), 278 (41), 277 (100%); HRMS (CI, NH_3) M^+−H found 427.1872. $C_{24}H_{23}N_6O_2$ requires 427.1882.

8-Methyl-1,2,3,4-tetrahydropyrimido[2,1-b]quinazolin-6-one (23). 2-Amino-5-methylbenzoic acid (**14**) (1.0 g, 6.6 mmol) and 2-methylsulfanyl-1,4,5,6-tetrahydropyrimidine (**19**) (840 mg, 6.6 mmol) were ground separately into fine powders and then thoroughly mixed together to give a creamy paste. The mixture was heated at 160°C for 30 min under argon to give a viscous dark brown oil. Purification of the crude product by chromatography (50% ethyl acetate/petroleum ether (bp 40–60°C), then methanol) followed by crystallisation (ethanol) gave the *title compound* (**23**) (596 mg, 42%) as an off-white crystalline solid, mp 241–242°C; ν_{max} ($CHCl_3$) 3443, 3285, 1664, 1578, 1489, 1475, 1446, 1371, 1341, 1318, 1294, 1216, 1166, 1115, 1100, 1044, 1019, 974, 930, 888, 875, 812, 708 and 669 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.82 (1H, s, *H*-7), 7.32 (1H, d, *J*=8.0 Hz, *H*-10), 7.08 (1H, d, *J*=8.0 Hz, *H*-9), 6.07 (1H, br s; N*H*), 4.01 (2H, t, *J*=6.0 Hz, CH_2), 3.42 (2H, t, *J*=6.0 Hz, CH_2), 2.29 (3H, s, *Me*), 2.02 (2H, t, *J*=6.0 Hz, CH_2); *m*/*z* (EI) 215 (33), 165 (20), 151 (60), 133 (100), 116 (28), 106 (29), 104 (49), 78 (26), 77 (29%); HRMS (CI, NH_3) M^++H found 216.1134. $C_{12}H_{14}N_3O$ requires 216.1137.

8-Methyl-10-phenyl-1,2,3,4-tetrahydropyrimido[2,1-b]-quinazolin-6-one (24). *Stille conditions:* Iodobenzene (70 mg, 0.34 mmol, 0.39 mL), 10-(trimethylstanyl)-8-methyl-1,2,3,4-tetrahydropyrimido[2,1-*b*]quinazolin-6-one (**22**) (100 mg, 0.34 mmol), and tetrakis(triphenylphosphine)

palladium(0) (20 mg) were added to anhydrous 1,4-dioxane (3 mL) and the mixture was heated at reflux for 3 h under argon. The mixture was cooled to room temperature and filtered. The filtrate was diluted with dichloromethane (150 mL) and the solution was washed with brine (100 mL) and water (50 mL). The organic solution was dried over magnesium sulphate and the solvent evaporated in vacuo to yield a brown oil. Purification of the crude product by chromatography (50% ethyl acetate/petroleum ether (bp 40–60°C)) gave the *title compound* (**24**) (21 mg, 25%) as an off-white solid, mp 202–205°C; (Found: C, 74.30; H, 5.97; N, 14.19; $C_{18}H_{17}N_3O$ requires C, 74.20; H, 5.88; N, 14.42%); ν_{max} (KBr disc) 3443, 3240, 3167, 1672, 1611, 1483, 1442, 1370, 1318, 1298, 1279, 1222, 1161, 800, 758 and 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.99 (1H, s, *H*-7), 7.74 (2H, d, *J*=7.5 Hz, 2×*Ar*), 7.45 (1H, d, *J*=2 Hz, *H*-9), 7.38 (2H, t, *J*=7.5 Hz, *Ar*), 7.28 (1H, t, *J*=7.5 Hz, *Ar*), 7.12 (1H br s, N*H*), 3.94 (2H, t, *J*=6.0 Hz, CH_2), 2.80 (2H, t, *J*=6.0 Hz, CH_2), 2.43 (3H, s, *Me*), 1.78 (2H, m, CH_2); *m/z* (EI) 291 (100 M^+), 277 (42), 217 (27), 180 (36), 152 (25), 133 (21), 86 (56), 84 (95), 77 (60%).

Suzuki conditions: To a solution of 10-bromo-8-methyl-1,2,3,4-tetrahydropyrimido[2,1-*b*]quinazolin-6-one (**20**) (200 mg, 0.68 mmol) in anhydrous 1,4-dioxane (10 mL) was added bis(triphenylphosphine) palladium(II) dichloride (40 mg) and the mixture stirred at room temperature for 20 min under argon. A solution of phenylboronic acid (83 mg, 0.68 mmol) in 2 M aqueous sodium carbonate (1 mL) was added and the mixture was heated at reflux for 24 h. The mixture was cooled to room temperature and filtered. The filtrate was diluted with dichloromethane (150 mL) and the solution was washed with brine (50 mL). The mixture was dried over magnesium sulphate and the solvent evaporated in vacuo to give a pale yellow solid. Purification of the crude product by chromatography (50% ethyl acetate/petroleum ether (bp 40–60°C)) gave the *title compound* (**24**) (63 mg, 31%) as an off-white solid, identical by IR and ^1H NMR spectroscopy to material obtained using Stille conditions.

10-Bromo-1,8-dimethyl-1,2,3,4-tetrahydropyrimido[2,1-b]quinazolin-6-one (25). 10-Bromo-8-methyl-1,2,3,4-tetrahydropyrimido[2,1-*b*]quinazolin-6-one (**20**) (500 mg, 1.7 mmol) was dissolved in anhydrous THF (5 mL) at room temperature. Sodium hydride (136 mg, 3.4 mmol, 60% dispersion in oil) was added slowly to the stirred solution, followed by methyl iodide (284 mg, 2.0 mmol). The mixture was stirred in the dark for 24 h. The mixture was diluted with iced water (20 mL) and saturated aqueous sodium carbonate (20 mL) was added. The mixture was extracted with dichloromethane (2×150 mL), the organic phase was dried over magnesium sulphate and the solvent evaporated in vacuo to yield the *title compound* (**25**) (522 mg, 100%) as a white solid, mp 263°C; (Found: C, 50.61; H, 4.57; N, 13.59; $C_{13}H_{14}BrN_3O$ requires C, 50.67; H, 4.58; N, 13.64%); ν_{max} ($CHCl_3$) 1662, 1637, 1618, 1581, 1560, 1541, 1508, 1478, 1458, 1411, 1361, 1340, 1312, 1290, 1217, 1047, 958, 929, 876, 845 and 626 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.76 (1H, s, *H*-7), 7.62 (1H, s, *H*-9), 4.02 (2H, t, *J*=6.0 Hz, CH_2), 3.44 (2H, t, *J*=6.0 Hz, CH_2), 3.25 (3H, s N*Me*), 2.29 (3H, s, Ar*Me*), 2.03 (2H, m, CH_2); *m/z* (EI) 309 (100 M^+), 307 (100 M^+), 280 (48), 278 (47), 254 (14), 253 (14), 252 (16), 213 (13), 211 (17), 129 (16), 104 (9), 103 (30), 102 (18), 69 (48%).

1,8-Dimethyl-10-(trimethylstannyl)-1,2,3,4-tetrahydropyrimido[2,1-b]quinazolin-6-one (26). 10-Bromo-1,8-dimethyl-1,2,3,4-tetrahydropyrimido[2,1-*b*]quinazolin-6-one (**25**) (0.4 g, 1.3 mmol), hexamethylditin (0.55 g, 1.7 mmol) and tetrakis(triphenylphosphine) palladium(0) (100 mg) were dissolved in 1,4-dioxane (10 mL) under argon. The stirred mixture was heated at 120°C for 4 h and then cooled to room temperature. The mixture was filtered and the solvent evaporated in vacuo to give a grey solid. Purification of the crude product by chromatography (20% ethyl acetate/petroleum ether (bp 40–60°C)) gave the *title compound* (**26**) (240 mg, 47%) as a white solid, mp 241–244°C; ν_{max} (KBr disc) 1671, 1579, 1504, 1449, 1412, 1341, 1313, 1292, 1246, 1182, 1065, 956 and 880 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.61 (1H, s, *H*-7), 7.28 (1H, s, *H*-9), 3.89 (2H, t, *J*=6.0 Hz, CH_2), 3.22 (2H, t, *J*=6.0 Hz, CH_2), 2.97 (3H, s, N*Me*), 2.15 (3H, s, Ar*Me*), 1.89 (2H, m, CH_2), 0.09 (9H, t, *J*=26.5 Hz, $SnMe_3$); *m/z* (EI) 393 (7 M^++H), 392 (3 M^+), 378 (100), 376 (88), 374 (51), 189 (7%); HRMS (CI, NH_3) M^++H found 394.0952. $C_{16}H_{24}N_3OSn$ requires 394.0940.

1,8-Dimethyl-10-phenyl-1,2,3,4-tetrahydropyrimido[2,1-b]quinazolin-6-one (27). Iodobenzene (67 mg, 0.32 mmol, 0.37 mL), 1,8-dimethyl-10-(trimethylstannyl)-1,2,3,4-tetrahydropyrimido[2,1-*b*]quinazolin-6-one (**26**) (100 mg, 0.32 mmol), and tetrakis(triphenylphosphine) palladium(0) (20 mg) were added to anhydrous 1,4-dioxane (3 mL) and the mixture was heated at reflux for 3 h under argon. The mixture was cooled to room temperature and filtered. The filtrate was diluted with dichloromethane (150 mL) and the solution was washed with brine (100 mL) and water (50 mL). The organic solution was dried over magnesium sulphate and the solvent evaporated in vacuo to yield a red oil. Purification of the crude product by chromatography (petroleum ether (bp 40–60°C), then ethyl acetate) gave the *title compound* (**27**) (21 mg, 25%) as an off-white solid, mp 214–216°C; ν_{max} (KBr disc) 1658, 1582, 1512, 1477, 1407, 1315, 1287, 1229, 893, 801, 718 and 695 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.91 (1H, br s, *H*-7), 7.71 (2H, d, *J*=7.5 Hz, Ar), 7.46 (1H, d, *J*=2.0 Hz, *H*-9), 7.41 (2H, t, *J*=7.5 Hz, *Ar*), 7.32 (1H, t, *J*=7.5 Hz, *Ar*), 4.12 (2H, t, *J*=7.0 Hz, CH_2), 3.41 (2H, t, *J*=7.0 Hz, CH_2), 3.10 (3H, s, N*Me*) 2.43 (3H, s, Ar*Me*), 2.08 (2H, m, CH_2); *m/z* (EI) 305 (100 M^+), 276 (27), 125 (15), 111 (26), 97 (38), 85 (28), 71 (41%); HRMS (CI, NH_3) M^++H found 306.1609. $C_{19}H_{20}N_3O$ requires 306.1606.

1,8-Dimethyl-1,2,3,4-tetrahydropyrimido[2,1-b]quinazolin-6-one (28). 8-Methyl-1,2,3,4-tetrahydropyrimido[2,1-*b*]quinazolin-6-one (**23**) (215 mg, 1.0 mmol) was dissolved in anhydrous THF (5 mL) at room temperature. Sodium hydride (80 mg, 2.0 mmol, 60% dispersion in oil) was added slowly to the stirred solution, followed by methyl iodide (170 mg, 1.2 mmol). The mixture was stirred in the dark for 24 h. The mixture was diluted with iced water (20 mL) and saturated aqueous sodium carbonate (20 mL) was added. The mixture was extracted with dichloromethane (2×50 mL), the organic phase was dried over magnesium sulphate and the solvent evaporated in vacuo to yield the *title compound* (**28**) (296 mg, 96%) as a white

solid, mp 220°C; ν_{max} (KBr) 1661, 1504, 1410, 1380, 1313, 1295, 1198 and 839 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.79 (1H, d, *J*=0.5 Hz, *H*-7), 7.30 (1H, dd, *J*=8.5 and 0.5 Hz, *H*-10), 7.17 (1H, d, *J*=8.5 Hz, *H*-9), 4.04 (2H, t, *J*=6.0 Hz, CH_2), 3.37 (2H, t, *J*=6.0 Hz, CH_2), 3.16 (3H, s N*Me*), 2.31 (3H, s, Ar*Me*), 2.02 (2H, m, CH_2); *m/z* (EI) 229 (100 M^+), 200 (77), 174 (20), 133 (20), 104 (15), 77 (13%); HRMS (CI, NH_3) M^++H found 230.1296. $C_{13}H_{16}N_3O$ requires 230.1293.

10-Bromo-8-methyl-1-(2′-nitrophenyl)-1,2,3,4-tetrahydropyrimido[2,1-b]quinazolin-6-one (32). To a stirred solution of 10-bromo-8-methyl-1,2,3,4-tetrahydropyrimido[2.1-b]quinazolin-6-one (**20**) (100 mg, 0.34 mmol) and 2-bromonitrobenzene (68 mg, 0.34 mmol) in dry dimethyl sulphoxide (3 mL) was added freshly activated copper bronze (42 mg, 0.68 mmol). The stirred mixture was heated at 120°C for 8 h under argon. The mixture was cooled to room temperature, diluted with chloroform (100 mL) and the solution was washed with brine (2×100 mL). The organic layer was dried over magnesium sulphate and the solvent evaporated in vacuo to give a yellow/brown solid. Purification of the crude product by chromatography (ethyl acetate) gave the *title compound* (**32**) (80 mg, 63%) as a pale yellow solid, mp 283°C; (Found: C, 51.91; H, 3.67; N, 13.44; $C_{18}H_{15}BrN_4O_3$ requires C, 52.06; H, 3.64; N, 13.49%); ν_{max} ($CHCl_3$) 3020, 1670, 1574, 1559, 1540, 1531, 1507, 1498, 1480, 1458, 1442, 1355, 1314, 1216, 771 and 669 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 8.04 (1H, dd, *J*=7.5 and 1.5 Hz, *H*-3′), 7.74 (1H, d, *J*=1.0 Hz, *H*-7), 7.64 (1H, dt, *J*=7.5 and 1.5 Hz, *H*-4′), 7.51 (1H, d, *J*=1.0 Hz, *H*-9′), 7.38 (2H, m, *H*-5′ and *H*-6′), 4.17 (2H, br t, *J*=6.0 Hz, CH_2), 3.85 (2H, br m, CH_2), 2.33 (2H, br m, CH_2), 2.25 (3H, s, *Me*); *m/z* (EI) 417 (6), 415 (6), 371 (15), 369 (15), 296 (100), 294 (96), 240 (11), 238 (13), 213 (21), 211 (23), 116 (14), 102 (17), 77 (22%).

1,8-Dimethyl-10-methylsulfanyl-1,2,3,4-tetrahydropyrimido[2,1-b]quinazolin-6-one (33). To a solution of 10-bromo-1,8-dimethyl-1,2,3,4-tetrahydropyrimido[2,1-*b*]quinazolin-6-one (**25**) (150 mg, 0.48 mmol) in dry dimethyl sulphoxide (3 mL) was added freshly activated copper bronze (75 mg) and the mixture was heated at reflux for 18 h under argon. The solution was cooled to room temperature and filtered. The filtrate was diluted with ethyl acetate (100 mL) and washed with brine (2×100 mL), aqueous ammonia (5 mL) and water (2×50 mL). The organic phase was dried over magnesium sulphate and the solvent evaporated in vacuo to give a pale yellow solid. Purification of the crude product by chromatography (50% ethyl acetate/petroleum ether (bp 40–60°C)) gave the *title compound* (**33**) (107 mg, 81%) as a white solid, mp 271°C; (Found: C, 60.79; H, 5.97; N, 15.32; $C_{14}H_{17}N_3OS$ requires C, 61.06; H, 6.22; N, 15.26%); ν_{max} (KBr disc) 2966, 1660, 1507, 1443, 1365, 1310, 1295, 1203 and 827 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.55 (1H, d, *J*=1.5 Hz, *H*-7), 7.03 (1H, d, *J*=1.5 Hz, *H*-9), 4.02 (2H, t, *J*=6.0 Hz, CH_2), 3.38 (2H, t, *J*=6.0 Hz, CH_2), 2.40 (3H, s S*Me*), 2.32 (3H, s, N*Me*), 2.02 (2H, m, CH_2); *m/z* (EI) 275 (100 M^+), 229 (90), 215 (30), 201 (35), 161 (10), 121 (10), 106 (20) 78 (30%).

3-Acetylamino-4-methylbenzoic acid (37). To a stirred solution of 3-amino-4-methylbenzoic acid (**36**) (10 g, 66 mmol) in glacial acetic acid (70 mL) contained in a flask equipped for reflux was added acetic anhydride (10 mL) slowly in 4–5 portions. An off-white precipitate formed after a few minutes. The mixture was stirred for a further 30 min, cooled to room temperature and filtered. The precipitate was washed with diethyl ether (2×150 mL) and dried in vacuo to give the *title compound* (**37**) (12.5 g, 98%) as an off-white solid, mp 272–274°C (lit[23] 275–276°C); ν_{max} (KBr disc) 3236, 3023, 1684, 1646, 1618, 1581, 1545, 1430, 1412, 1375, 1323, 1303, 1273, 1235, 1139, 1104, 1022, 937, 905, 848 and 746 cm^{-1}; δ_H (270 MHz, d_6DMSO) 9.38 (1H, br s, CO_2H); 8.01 (1H, br s, *H*-2), 7.60 (1H, d, *J*=8.0 Hz, *H*-6), 7.28 (1H, d, *J*=8.0 Hz, *H*-5), 2.24 (3H, s, CO*Me*), 2.06 (3H, s, Ar*Me*); *m/z* (EI) 193 (33 M^+), 151 (100), 136 (37), 119 (29), 106 (40), 91 (40%); HRMS (CI, NH_3) M^++H found 194.0815. $C_{10}H_{12}NO_3$ requires 194.0817.

3-Acetylamino-4-methyl-2-nitrobenzoic acid (38). To an solution of 3-acetylamino-4-methylbenzoic acid (**37**) (11.5 g, 59 mmol) cooled to 0°C was added fuming nitric acid (22 mL) slowly over 90 min, not allowing the temperature of the mixture to rise above 5°C. The mixture was stirred at 0°C for 2 h. The mixture was poured on to ice (110 g) and left to stand for 12 h. The precipitate was filtered, washed with cold water (100 mL) and dried in vacuo to give a pale yellow solid. Recrystallisation of the crude product (glacial acetic acid) gave the *title compound* (**38**) (10 g, 71%) as a white solid, mp 157°C (lit[24] 155–156°C); (Found: C, 50.55; H, 4.21; N, 11.79; $C_{10}H_{10}N_2O_5$ requires C, 50.42; H, 4.23; N, 11.76%); ν_{max} (KBr disc) 3345, 2930, 1720, 1645, 1547, 1519, 1375, 1269, 1206, 1177, 1144, 1044, 852, 804, 790, 776 and 625 cm^{-1}; δ_H (270 MHz, d_6DMSO) 10.35 (1H, br s, CO_2H), 7.86 (1H, d, *J*=8.0 Hz, *H*-6), 7.08 (1H, d, *J*=8.0 Hz, *H*-5), 2.47 (3H, s, CO*Me*), 2.23 (3H, s, Ar*Me*); *m/z* (EI) 220 (31), 196 (61), 161 (22), 152 (20), 103 (38), 77 (19), 43 (100%).

3-Amino-4-methyl-2-nitrobenzoic acid hydrobromide (39). A solution of 3-acetylamino-4-methyl-2-nitrobenzoic acid (**38**) (10 g, 42 mmol) in aqueous hydrobromic acid (48% w/v) (150 mL) was heated at reflux for 12 h. The mixture was cooled to room temperature and the solvent evaporated in vacuo to give a yellow/orange solid. Recrystallisation of the crude product (acetone/petroleum ether (bp 40–60°C)) gave the *title compound* (**39**) (9.7 g, 100%) as an orange solid, mp 172°C (lit.[25]173–175°C); (Found: C, 34.79; H, 3.25; N, 10.32; $C_8H_9BrN_2O_4$ requires C, 34.68; H, 3.27; N, 10.11%); ν_{max} (KBr disc) 3480, 3372, 2925, 1706, 1618, 1519, 1443, 1332, 1256 and 1198 cm^{-1}; δ_H (270 MHz, d_6DMSO) 7.24 (1H, d, *J*=7.5 Hz, *H*-6), 6.84 (1H, d, *J*=7.5 Hz, *H*-5), 2.19 (3H, s, Ar*Me*); *m/z* (EI) 276 (2 M^+), 226 (2), 196 (27), 169 (3), 148 (4), 133 (3), 121 (5), 105 (8), 104 (8), 82 (94), 81 (38), 80 (100), 79 (39%).

3-Bromo-4-methyl-2-nitrobenzoic acid (40). To a solution of 3-amino-4-methyl-2-nitrobenzoic acid hydrobromide (**39**) (25 g, 109 mmol) aqueous hydrobromic acid (48% w/v) (300 mL) at 5°C was added a solution of sodium nitrite (13.5 g, 195 mmol) in water (15 mL) slowly, maintaining the temperature between 5–10°C. The mixture was shaken after each addition of the sodium nitrite solution until all red fumes were absorbed. Copper powder (1.5 g) was added to the mixture and the mixture heated very cautiously on a

water bath. Upon evolution of nitrogen the flask was cooled immediately to 0°C. After vigorous evolution of nitrogen had subsided the flask was heated at 30°C for 3 h. The mixture was cooled by the slow addition of iced water until a pale yellow precipitate formed. The precipitate was filtered and dried in vacuo to give the *title compound* (**40**) (17 g, 80%) as a pale yellow solid, mp 232–234°C; (Found: C, 36.85; H, 2.21; N, 5.37; $C_8H_6BrNO_4$ requires C, 36.95; H, 2.33; N, 5.39%); ν_{max} (Nujol) 1706, 1598, 1547, 1416, 1378, 1291, 1249, 1190, 1162, 1016, 935, 844, 797, 779, 722, 702 and 622 cm^{-1}; δ_H (270 MHz, d_6DMSO) 8.27 (1H, d, *J*=8.5 Hz, *H*-6). 7.99 (1H, d, *J*=8.5 Hz, *H*-5), 2.78 (3H, s, *Me*); *m/z* (EI) 261 (55), 259 (64), 231 (14), 229 (18), 215 (13), 213 (18), 187 (15), 185 (17), 171 (11), 169 (13), 133 (15), 132 (12), 106 (36), 105 (34), 90 (22), 89 (38), 78 (100), 77 (77%).

Methyl 3-bromo-4-methyl-2-nitrobenzoate (41). To a solution of 3-bromo-4-methyl-2-nitrobenzoic acid (**40**) (1 g, 3.8 mmol) in anhydrous methanol (3.8 mmol, 3 mL) was added concentrated sulphuric acid (0.5 mL) The mixture was heated at reflux for 14 h. The mixture was cooled to room temperature and diluted with dichloromethane (50 mL). The mixture was washed with water (2×50 mL), the organic phase was dried over magnesium sulphate and the solvent evaporated in vacuo to give a pale yellow solid. Purification of the crude product by chromatography (ethyl acetate) and crystallisation (dichloromethane/petroleum ether (bp 60–80°C)) gave the *title compound* (**41**) (1.02 g, 98%) as an off-white solid, mp 239°C; (Found: C, 39.40; H, 2.91; N, 5.24; $C_9H_8BrNO_4$ requires C, 39.44; H, 2.94; N, 5.11%); ν_{max} (KBr disc) 1734, 1548, 1438, 1364, 1296, 1244, 1201, 1163, 976, 845, 777, 718 and 702 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.92 (1H, d, *J*=8.0 Hz, *H*-d). 7.42 (1H, d, *J*=8.0 Hz, *H*-5), 3.90 (3H, s, CO_2*Me*), 2.54 (3H, s, Ar*Me*); *m/z* (EI) 275 (60), 273 (60), 244 (88), 242 (88), 214 (15), 212 (15), 170 (19), 168 (20), 133 (26), 91 (54), 90 (77), 89 (100), 77 (39), 63 (77%).

2,2′-Dinitro-6,6′-dimethyl-3,3′-dimethoxycarbonylbiphenyl (35). Methyl 3-bromo-4-methyl-2-nitrobenzoate (**41**) (100 mg, 0.36 mmol) and freshly activated copper powder (457 mg, 7.2 mmol) were mixed thoroughly. A further portion of copper powder (229 mg, 3.6 mmol) was placed on top of the mixture and the mixture was heated at 215°C for 72 h. The mixture was dissolved in methanol and the solution was filtered. The solvent was evaporated in vacuo to give an orange solid. Purification of the crude product by flash chromatography (50% ethyl acetate/petroleum ether (bp 40–60°C)) gave the *title compound* (**35**) (44 mg, 63%) as an off-white solid, mp 101°C; ν_{max} (KBr disc) 2961, 1733, 1607, 1552, 1538, 1435, 1368, 1280, 1240 and 1088 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.90 (2H, d, *J*=8.0 Hz, 2×*H*-4), 7.45 (2H, d, *J*=8.0 Hz, 2×*H*-5), 3.81 (3H, s, CO_2*Me*), 2.08 (3H, s, Ar*Me*); *m/z* (EI) 357 (21), 342 (39), 326 (36), 310 (100), 252 (43), 178 (39), 165 (90), 152 (68), 139 (42), 115 (25), 89 (29), 59 (60%); *m/z* (CI, NH_3) 406 (43 $M^+ + NH_4$), 359 (10), 329 (100), 271 (18%); HRMS (CI, NH_3) $M^+ + NH_4^+$ found 406.1240. $C_{18}H_{20}N_3O_8$ requires 406.1250.

Methyl 2-amino-3-bromo-4-methylbenzoate (44). To a solution of methyl 3-bromo-4-methyl-2-nitrobenzoate (**41**) (500 mg, 1.8 mmol) in absolute ethanol (50 mL) and concentrated hydrochloric acid (0.5 mL) was added iron pin dust (300 mg, (170 g/mol for each nitro group)) in 4 portions, allowing 5 min between each addition. The mixture was heated at reflux for 12 , cooled to room temperature and made alkali using a 1 M sodium hydroxide solution in 50% aqueous ethanol. The mixture was filtered, the filtrate was washed with brine (50 mL) and extracted with dichloromethane (2×50 mL). The organic phase was dried over magnesium sulphate and the solvent evaporated in vacuo to give the *title compound* (**44**) (380 mg, 87%) as an off-white solid, mp 198–200°C; ν_{max} (KBr disc) 3487, 3364, 2951, 1698, 1621, 1574, 1465, 1436, 1277, 1242, 1208, 1097 and 1008 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.74 (1H, d, *J*=8.0 Hz, *H*-6), 6.47 (1H, d, *J*=8.0 Hz, *H*-5), 5.66 (2H, br s, NH_2), 3.85 (3H, s, CO_2*Me*), 2.27 (3H, s, Ar*Me*); *m/z* (EI) 246 (93 M^++H), 245 (69 M^+), 244 (100 M^++H), 243 (64 M^+), 213 (32), 211, (32), 104 (7), 77 (7%); HRMS (CI, NH_3) M^++H found 243.9971. $C_9H_{11}BrNO_2$ requires 243.9973.

2-Amino-3-bromo-4-methylbenzoic acid (45). To a solution of methyl 2-amino-3-bromo-4-methylbenzoate (**44**) (200 mg, 0.82 mmol) in 75% aqueous methanol (50 mL) was added potassium hydroxide (45 mg, 0.8 mmol) slowly. The mixture was heated at reflux for 12 h. The mixture was cooled to room temperature, diluted with water (100 mL) and extracted with ethyl acetate (2×150 mL). The organic phase was dried over magnesium sulfate and the solvent evaporated in vacuo to give the title compound (**45**) (164 mg, 87%) as an off-white solid, mp 208°C; ν_{max} (KBr disc) 3471, 3367, 2921, 1684, 1572, 1549, 1466, 1421, 1311, 1274, 1238, 870, 792 and 709 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.75 (1H, d, *J*=8.0 Hz, *H*-6), 7.62 (1H, d, *J*=8.0 Hz, *H*-5), 6.47 (2H, br s, NH_2), 2.17 (3H, s, Ar*Me*); *m/z* (EI) 231 (74 M^+), 229 (74 M^+), 213 (100), 211 (85), 184 (16), 183 (13), 182 (9), 132 (5), 104 (37), 77 (31%); HRMS (CI, NH_3) M^++H found 229.9812. $C_8H_9BrNO_2$ requires 229.9817.

2-Methyl-1-naphthylboronic acid (47). To freshly activated magnesium turnings (1.04 g, 42.7 mmol) was added a solution of 1-bromo-2-methylnaphthalene (**46**) (8.6g, 38.8 mmol) in anhydrous THF (25 mL). The mixture was stirred and heated gently for 1 h. Trimethylborate (4.44 g, 42.7 mmol) was added slowly and the mixture was stirred at room temperature for 2 h. 1 M aqueous hydrochloric acid (12 mL) was added slowly to give a grey precipitate. The mixture was stirred at room temperature for a further 4 h, diluted with dichloromethane (100 mL) and washed with distilled water (2×50 mL). The organic phase was dried over magnesium sulphate and the solvent evaporated in vacuo to give a yellow oil. The oil was dissolved in petroleum ether (bp 60–80°C) (20 mL) and concentrated aqueous hydrochloric acid (1 mL) was added. The mixture was stirred at room temperature for 3 h, during which time a white precipitate formed. The precipitate was filtered and dried in vacuo to give the *title compound* (**47**) (5.7 g, 79%) as a white solid, mp 125–128°C (lit[21] 127°C); ν_{max} (KBr) 3318, 3045, 1595, 1565, 1510, 1427, 1398, 1347, 1333, 1297, 1265, 1162, 1141, 1067, 980, 810, 785, 742, 678 and 629 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.63–7.72 (3H, m, *Ar*), 7.29–7.39 (2H, m, *Ar*), 7.17 (1H, m, *Ar*), 5.05 (2H, s,

B(O*H*)$_2$), 2.45 (3H, s, Ar*Me*); *m*/*z* (EI) 186 (100 M^+), 168 (72), 167 (48), 142 (71), 141 (83), 115 (45%); HRMS (CI, NH_3) M^+ found 186.0844. $C_{11}H_{11}BO_2$ requires 186.0852.

8-Methyl-10-(2′-methyl-1′-naphthyl)-1,2,3,4,-tetrahydropyrimido[2,1-b]quinazolin-6-one (7). To a stirred solution of 10-bromo-8-methyl-1,2,3,4-tetrahydropyrimido[2,1-*b*]-quinazolin-6-one (**20**) (100 mg, 0.34 mmol) and bis(triphenylphosphine) palladium(II) chloride (20 mg) dissolved in anhydrous 1,4-dioxan (5 mL) was added a mixture of 2-methyl-1-naphthylboronic acid (**47**) (63 mg, 0.36 mmol) dissolved in a 2 M 50% aqueous ethanolic solution of barium hydroxide (5 mL). The mixture was heated at reflux for 24 h under argon. The mixture was cooled to room temperature and diluted with dichloromethane (100 mL). The mixture was filtered and the filtrate was washed with water (50 mL). The organic phase was dried over magnesium sulphate and the solvent evaporated in vacuo to give a pale yellow/orange solid. The reduced by-products were precipitated using dichloromethane and petroleum ether (bp 40–60°C) and filtered. The filtrate was concentrated in vacuo to give a red/orange solid. Purification of the crude product by flash chromatography (20% ethyl acetate/petroleum ether (bp 60–80°C)) gave the *title compound* (**7**) (33 mg, 27%) as a white solid, mp 136–137°C, ν_{max} ($CHCl_3$) 3439, 1664, 1599, 1487, and 1216 cm^{-1}; *m*/*z* (EI) 355 (77 M^+), 340 (100), 256 (36), 228 (77), 170 (31%); *m*/*z* (CI, NH_3) 356 (100% $M^+ + 1$); HRMS (EI) M^+ found 355.1676. $C_{23}H_{21}N_3O$ requires 355.1685.

^{1}H NMR data for the predominant atropisomeric conformation of compound (**7**): δ_H (300 MHz, $CDCl_3$) 7.95 (1H, s, *H*-7), 7.71 (1H, br t, *J*=6.5 Hz, *Ar*), 7.34 (1H, d, *J*=8.5 Hz, *Ar*) 7.29–7.33 (2H, m, 2×*Ar*), 7.22 (1H, s, *H*-9), 7.19 (2H, br t, *J*=6.0 Hz, 2×*Ar*), 3.97 (2H, t, *J*=6.0 Hz, CH_2), 5.15 (1H, br s, N*H*), 3.12 (2H, br t, *J*=6.0 Hz, CH_2), 2.36 (3H, s, Ar*Me*), 2.10 (3H, s, Ar*Me*), 1.92 (2H, m, CH_2).

^{1}H NMR data for the minor atropisomeric conformation of compound (**7**): δ_H (300 MHz, $CDCl_3$) 7.95 (1H, s, *H*-7), 7.71 (1H, br t, *J*=6.5 Hz, *Ar*), 7.34 (1H, d, *J*=8.5 Hz, *Ar*), 7.29–7.33 (2H, m, 2×*Ar*), 7.22 (1H, s, *H*-9), 7.19 (2H, br t, *J*=6.5 Hz, 2×*Ar*) 4.00 (2H, t, *J*=6.0 Hz, CH_2), 2.99–3.13 (2H, m, CH_2), 2.42 (3H, s, Ar*Me*), 2.17 (3H, s, Ar*Me*), 1.87 (2H, m, CH_2).

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