FIQ and FIQ2, New Q-site inhibitors for photosynthetic electron transport: synthesis and the relationship between stereochemistry and biological activity

Robert J. Pilling and Donald A. Whiting *

Department of Chemistry, The University of Nottingham, University Park, Nottingham, UK NG7 2RD

Received (in Cambridge) 12th May 1999, Accepted 4th June 1999

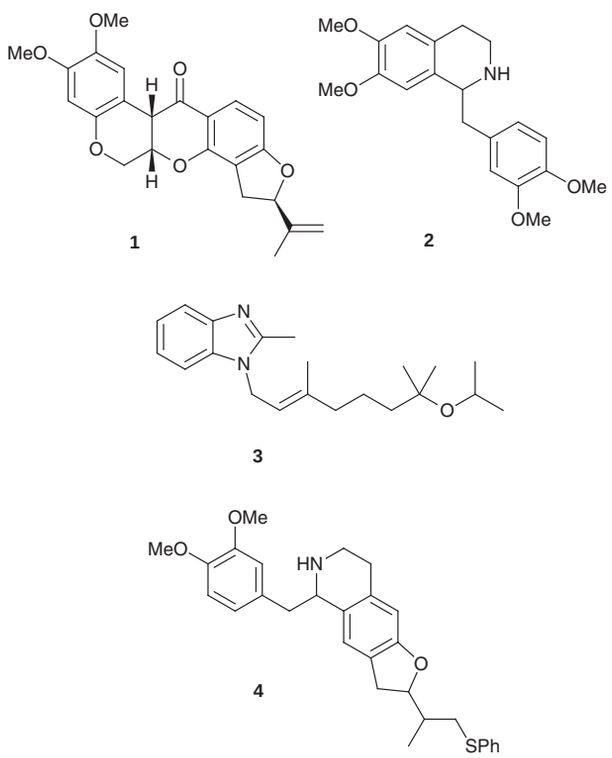
The synthetic hexahydrofuroisoquinoline **4** has, as a mixture of stereoisomers, been identified as a potent and specific inhibitor of electron transport in photosynthesis. We now report that the biological activity of **4** is, surprisingly, independent of configuration at C-1″ and C-2. A new inhibitor **26** has been synthesised, with similar inhibitory activity; the *S*-enantiomer displays *ca*. twice the activity of the *R*-form.

Introduction

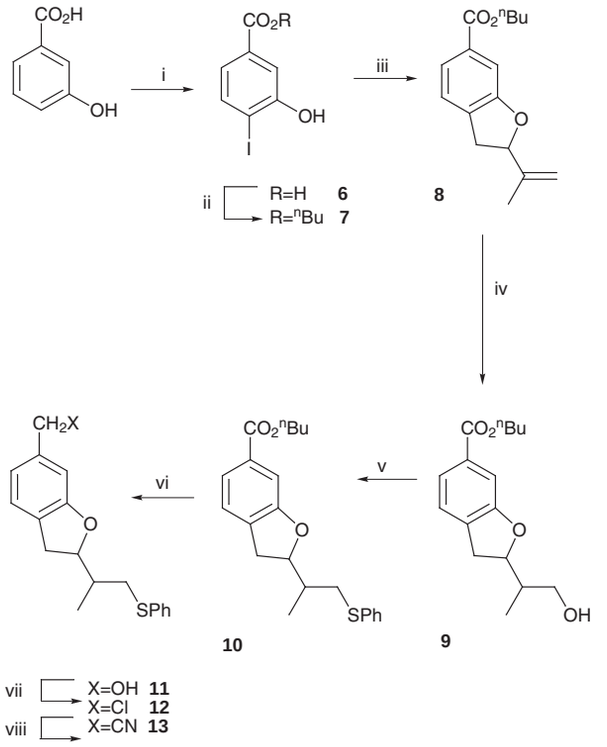
Electron transport chains are of great importance in respiration, where they mediate the reduction of oxygen by NADH and $FADH_2$ cofactors in mitochondria, and in photosynthesis, where they mediate the oxidation of water by $NADP^+$ in chloroplasts; in both cases ATP is formed. There are broad similarities between these two systems, both of which involve a number of complexes containing protein units and redox-active metal centred sites. In respiration, electron transport from complexes I and II into complex III (the bc complex) is effected by a quinone shuttle mechanism using ubiquinone (coenzyme Q), while in photosynthesis a quinone shuttle system is operated by plastoquinone, feeding electrons to the bf complex. A number of electron transport (ET) inhibitors operate at the quinone binding sites (Q sites).[1] In respiration these include *e.g.* rotenone **1**,[2] stigmatellin,[3] and antimycin,[4] while in photosynthesis *N′*-(3,4-dichlorophenyl)-*N*,*N*-dimethylurea,[5] tridecylstigmatellin[1d,6] and MOA-stilbene (methoxyacrylate stilbene)[7] are known Q site blockers. Other complex I inhibitors *e.g.* the myxalamides and fenazaquin may also be Q site inhibitors.

In earlier papers[8,9] dealing with complex I inhibitors of respiration we compared, using molecular modelling, the diverse structures of some natural and synthetic compounds, and on the basis of these comparisons we set out to synthesise a number of 'molecular hybrids', as a strategy for the discovery of new inhibitors with potential as pesticides. This work produced a number of new inhibitors with features drawn from rotenone and tetrahydropapaverine **2** and rotenone and the benzimidazole **3**. The most active of these products was the furoisoquinoline **4** (FIQ) which, as a racemic mixture of all diastereoisomers, displayed *ca.* 2% of the activity of the classic inhibitor rotenone. As a result of discussion with Professor Peter Rich, FIQ was tested as a Q site inhibitor in photosynthesis, and found to be the most effective and most selective inhibitor known at that time.[6] In view of the interest in FIQ it appeared to us necessary to determine which one of the eight stereoisomers was responsible for the biological activity, before pursuing new synthetic work to capitalise on this lead. In this paper we report on this search, and show that, to our surprise, the biological activity of FIQ is independent of the stereochemistry at two of the three stereogenic centres. A related new and equally effective inhibitor, FIQ2, was synthesised and it was demonstrated that one enantiomer of FIQ2 was more active than the other.

Initially we explored the viability of HPLC separation of



FIQ **4** diastereoisomers, using a sample containing an approximately equimolar mixture of all four racemates.[9] Using the free amine, no separation was observed at all, with either normal or reversed phase HPLC; the corresponding trifluoroacetamides **5** were more tractable but still only two peaks could be obtained on HPLC (normal phase). We therefore set out to modify the original synthetic approach to allow separation of diastereoisomers at an earlier stage. After some experimentation the route shown in Schemes 1 and 2 was settled on. Thus (Scheme 1; yields are shown in the scheme captions) 3-hydroxybenzoic acid was iodinated using iodine and potassium iodide in ammonia (see Experimental section for a safety note) and the *n*-butyl ester **7** was formed from the corresponding acid chloride. Reaction of the iodophenol **7** with isoprene and palladium acetate afforded the dihydrobenzofuran **8**. Hydroboration yielded the primary alcohol **9** as a mixture of diastereoisomers which could readily be separated by flash chromatography.

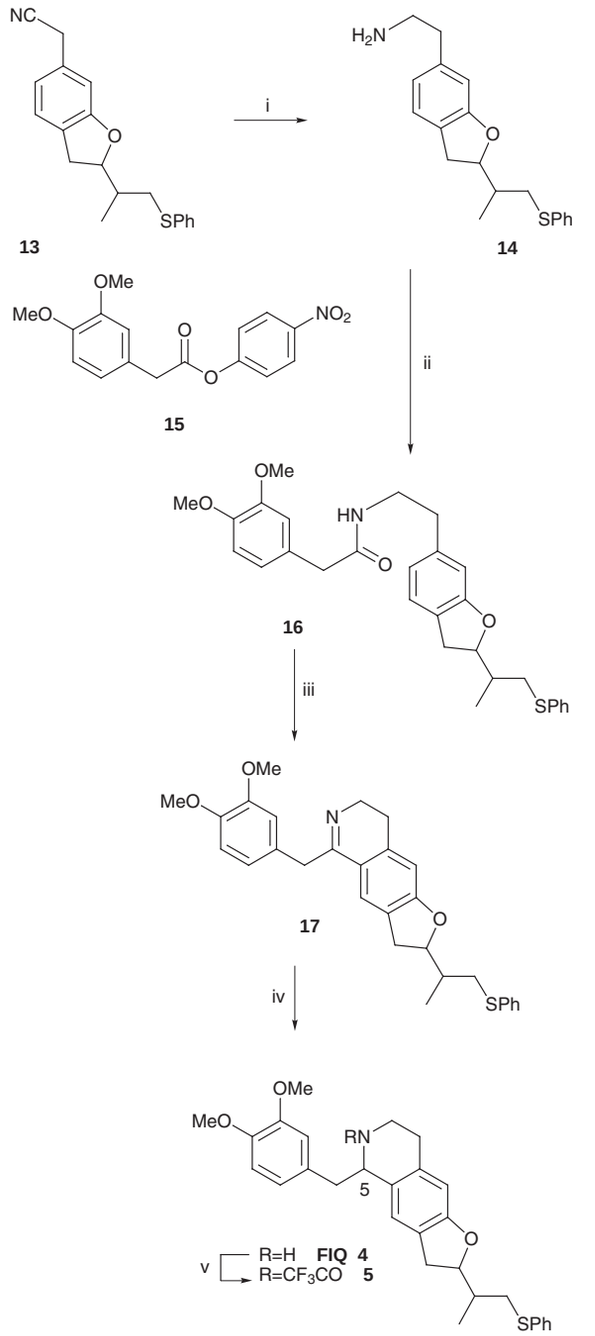


Scheme 1 *Reagents, conditions and yields*: i, Kl, I_2, NH_3(aq), 25 °C, 10 min, 62%; ii, $SOCl_2$, ^nBuOH, 65 °C, 20 h, 93%; iii, isoprene, $Pd(OAc)_2$, $^nBu_4NCl$, NaOAc, DMF, 140 °C, 24 h, 65%; iv, BH_3–THF, THF, 0 °C, 4 h; H_2O_2, NaOH, 2 h, 83%; v, PhSSPh, $^nBu_3P$, pyridine, 24 h, 80%; vi, $LiAlH_4$, diethyl ether, 30 min, 82%, vii, $SOCl_2$, 80 °C, 30 min, 74%; viii, KCN, KI, $^nBu_4Cl$, 18-crown-6, 82 °C, 6 h, 92%.

The choice of the butyl ester was crucial in achieving a clean separation. Using in the first instance the diastereoisomeric mixture the alcohol **9** was converted into the phenyl sulfide **10**, and hence to the nitrile **13** *via* the benzylic alcohol **11** and the chloride **12**. Reduction of the nitrile **13** (Scheme 2) gave the labile amine **14** which, without further purification, was acylated with *p*-nitrophenyl 3,4-dimethoxyphenylacetate **15** to provide the amide **16**. Bischler–Napieralski cyclisation gave the imine **17**, which was reduced with sodium borohydride to the target **4**, readily acylated with trifluoroacetic anhydride to the trifluoroacetamide **5**.

In planning the above approach we anticipated that enantioselective hydroboration and imine reduction might be introduced, to open the way to obtain separate enantiomers of FIQ. However the next step was to obtain each of the four racemates for biological screening. This was achieved by the strategy set out in Scheme 3. Separate diastereoisomers **9A** and **9B** of the alcohol **9**, of undetermined configuration, were converted into FIQ giving rise to two mixtures **4AA/AB** and **4BA/BB**. These were separated by HPLC as their trifluoroacetamides, finally providing after hydrolysis four separate racemates of FIQ, albeit of unknown configuration at this stage. These four products were then assayed for their ability to inhibit electron transport in photosynthesis, using pea thylakoids and monitoring single and multiple turnover kinetics and steady state photosynthetic activity.[10] To our considerable surprise all four compounds showed very similar activities to each other and to the original mixture and these results were confirmed by repeated testing.

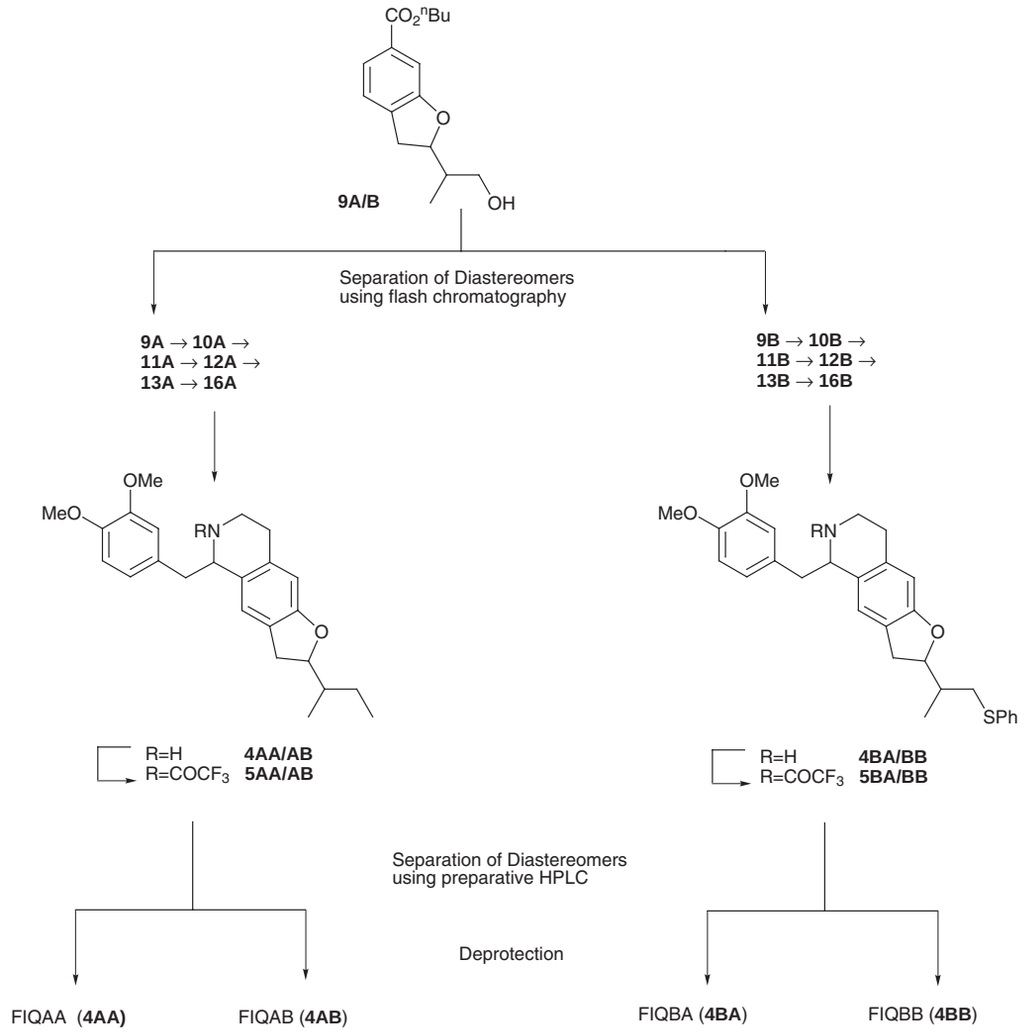
These results suggested to us that the inhibitory activity of FIQ could not depend on more than one of the stereogenic centres. It seemed to us most likely that this centre would be that adjacent to nitrogen, as this centre controls the relationship to natural isoquinoline alkaloids. Rather than pursue the above scheme through enantioselective hydroboration *etc*., we decided to synthesise a modified target, FIQ2 **26**, in which two



Scheme 2 *Reagents, conditions and yields*: i, $LiAlH_4$, $AlCl_3$, diethyl ether, 20 h; ii, DBU, dichloromethane, 16 h, 58% (combined yield for steps i and ii); iii, $POCl_3$, toluene, 100 °C, 1 h; iv, $NaBH_4$, methanol, 1 h, 76% (combined yield for steps iii and iv); v, $(CF_3CO)_2O$, pyridine.

stereocentres were eliminated, reasoning that the inhibitory effects of this compound should be similar to those of FIQ if those centres were not significant.

The synthetic approach to racemic FIQ2 is set out in Scheme 4. Methyl 3-hydroxy-4-iodobenzoate **18** was reacted with but-3-yn-1-ol in refluxing pyridine in the presence of cuprous oxide, a modification[11] of the Castro reaction. The benzofuran **19** was formed in very satisfactory yield, and converted into the thioether **20** using diphenyl disulfide and tributylphosphine. The rest of the synthesis paralleled the chemistry of Schemes 2 and 3; the benzylic alcohol **21** was prepared from the ester **20**, and converted into the nitrile **23** by way of the benzylic chloride **22**. Reduction of the nitrile **23** with lithium aluminium hydride and aluminium chloride gave the unstable amine **24**, which was reacted with the *p*-nitrophenyl ester **15** to afford the key amide **25**. Cyclisation with phosphorus oxychloride followed by



Scheme 3

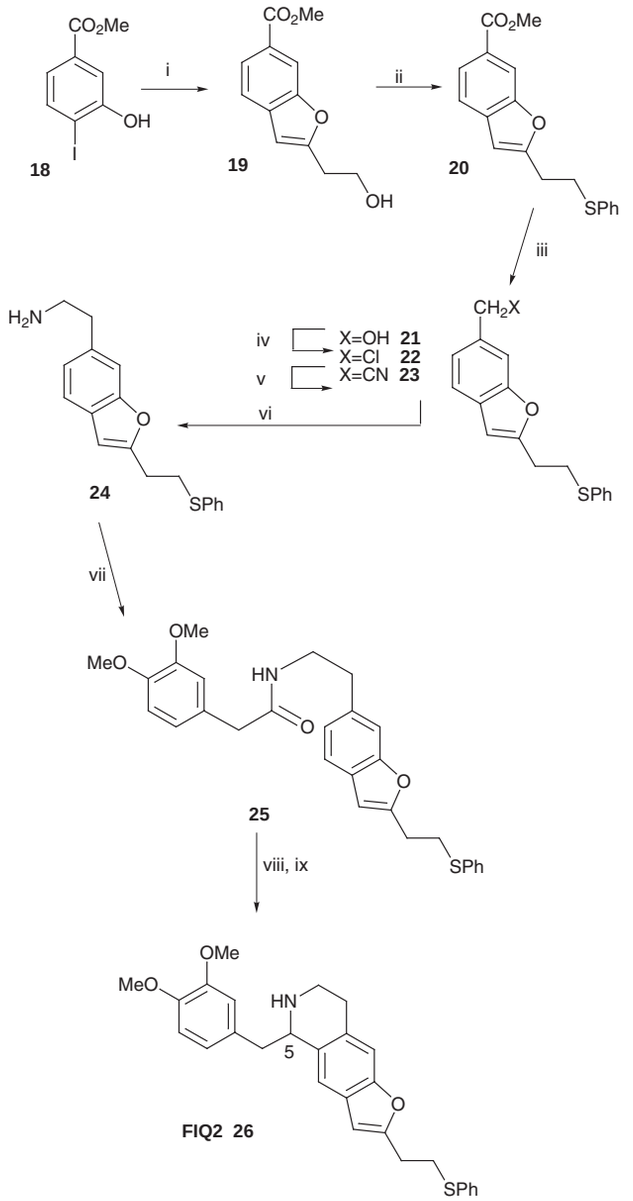
hydride reduction of the intermediate imine gave the desired racemic FIQ2 **26**. Biological evaluation revealed that this racemate exhibited very similar inhibitory properties to those of our previous samples of FIQ, thus supporting our proposition that the C-2 and C-1″ centres of FIQ were of little or no importance in affecting the activity of FIQ.

One final point remained to be established. Was the biological activity of FIQ in fact contingent on the absolute stereochemistry of C-5? To settle the matter we embarked on the synthesis of the separate enantiomers of FIQ2, at sufficient ee to give significant results in the assays. After investigating several possible approaches the protocol of Scheme 5 was adopted. Thus the imine **27** was reduced with sodium tris-(*N*-benzyloxycarbonyl-(*S*)-proline)borohydride[12] to yield an optically active sample of (−)-FIQ **26a**. A portion of this product was converted to the corresponding trifluoroacetamide and analysed by HPLC on a chiral column: the results indicated an ee of better than 60%. To improve the ee the urea **28a** was formed, following the work of Brossi *et al.*[13] Column chromatography of this urea gave only partial separation of diastereoisomers but nevertheless the ee was improved to 85%, estimated by PMR. Base hydrolysis of the urea to regenerate FIQ2 presented the problem of concurrent elimination of thiophenol, but reaction and isolation conditions were devised to eliminate this problem, and the urea **28a** afforded a specimen of *S*-(−)-FIQ2 **26a** with 85% ee. The assignment of absolute configuration depends on comparison with literature examples[12] of reduction of isoquinoline imines with sodium tris(*N*-benzyloxycarbonyl-(*S*)-proline)borohydride. Repetition of this sequence using the (*R*)-proline complex provided the *R*-(+)-enantiomer, **26b** 82% ee. The final biological tests showed that the *S*-(−)-enantiomer of FIQ2 exhibited approximately twice the inhibitory activity of the *R*-(+)-enantiomer, after correcting for the enantiomeric purities.

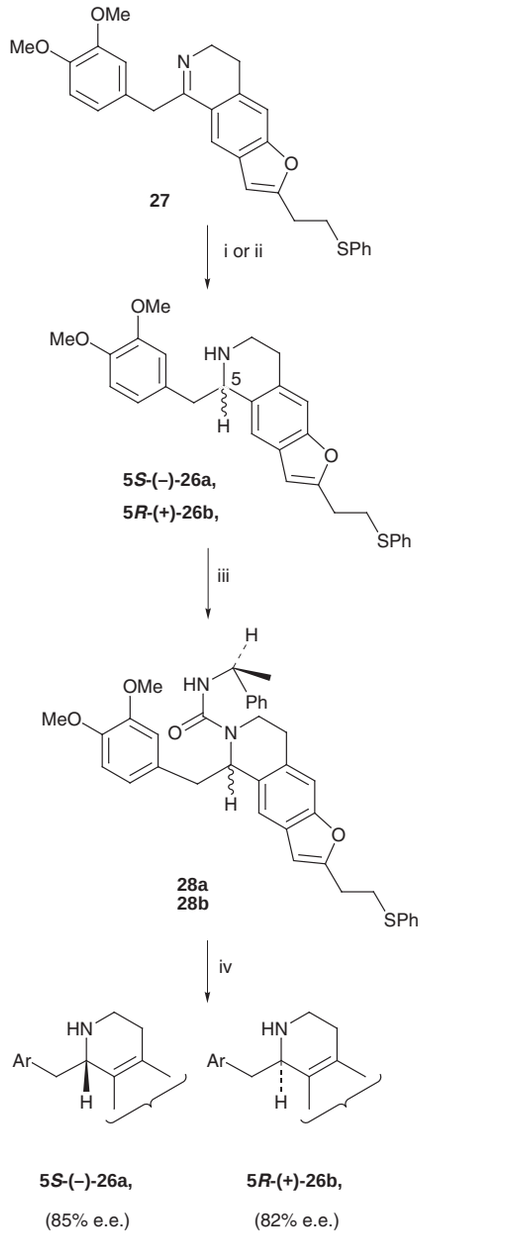
Thus it appears that although these compounds show high biological potency, and are specific in their action on the bf complex, their activities show remarkably little dependence on stereochemistry. This may indicate that FIQ and FIQ2 act in a different manner to other known Q site inhibitors, and biological studies are in hand to test possible alternative mechanisms of action.

Experimental

Infrared spectra were recorded using a Perkin-Elmer 1600 FTIR spectrophotometer as either solutions in chloroform or films. High resolution mass spectra were acquired on a VG Micromass 70E or an AEI MS-902 mass spectrometer using EI or FAB (*m*-nitrobenzyl alcohol (NBA) matrix). Optical rotations were recorded using a Jasco DIP-370 digital polarimeter. Proton NMR spectra were recorded on a Bruker WM 250 (250 MHz) spectrometer, a Bruker AM 400 (400 MHz) spectrometer or a Bruker DRX 500 (500 MHz) spectrometer using solutions in deuteriated chloroform with an internal tetramethylsilane standard. Coupling constants (*J*) are reported in Hz and abbreviations used are s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sex, sextet; m, multiplet; dd, double doublet *etc.*; ap s, apparent singlet; ap d, apparent doublet *etc.* for partially



Scheme 4 *Reagents, conditions and yields*: i, but-3-yn-1-ol, Cu_2O, pyridine, reflux, 24 h, 78%; ii, PhSSPh, $^nBu_3P$, pyridine, 24 h, 78%; iii, $LiAlH_4$, diethyl ether, 1 h, 80%; iv, $SOCl_2$, 50 °C, 45 min, 93%; v, KCN, KI^nBu_4NCl, 18-crown-6, acetonitrile, reflux, 6 h, 90%; vi, $LiAlH_4$, $AlCl_3$, diethyl ether, 5 h; vii, **15**, DBU, dichloromethane, 12 h, 75% (combined yield for steps vi and vii); viii, $POCl_3$, toluene, 3 h, ix, $NaBH_4$, methanol, 3 h, 76% (combined yield for steps viii and ix).

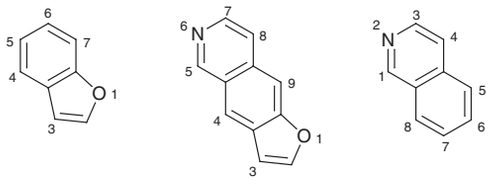


Scheme 5 *Reagents, conditions and yields*: i, sodium tris(*N*-benzyloxycarbonyl-(*S*)-proline)borohydride, dichloromethane, −30 °C, 12 h, 25%, 60% ee; ii, sodium tris(*N*-benzyloxycarbonyl-(*R*)-proline)-borohydride, dichloromethane, −30 °C, 12 h, 25%, 60% ee; iii, (+)-*S*-1-phenylethyl isocyanate, dichloromethane, 2 h, 76%; iv, NaOEt (0.25 equiv.), butanol, reflux, 2.5 h.

resolved peaks and br, broad. Carbon-13 NMR spectra were recorded on either a Bruker DRX 500 (125 MHz) spectrometer or a Bruker DRX 400 (100 MHz) spectrometer. The multiplicities indicated were obtained using a DEPT sequence. The assignment of proton and carbon spectra was assisted, where necessary, by obtaining ^1H–^1H and ^1H–^{13}C COSY spectra. Thin layer chromatography (TLC) used Merck silica gel 60 F_{254} precoated plates and preparative thin layer chromatography (pTLC) was performed using Analtech silica gel preparative plates. Flash column chromatography used Fluka silica gel 60 (220–440 mesh). High performance liquid chromatography (HPLC) was performed as indicated using a Waters 440 UV detector (254 nm) with normal phase semi-prep (Dynamax silica, 8 mm × 25 cm) and prep (Dynamax silica 2 cm × 25 cm) columns and a reversed phase semi-prep (Dynamax C_{18}, 8 mm × 25 cm) column. Analytical chiral HPLC was performed using a Chiracel OD column at ambient temperature with UV detection at 254 nm. Organic solvents and reagents were dried from the following as required: THF and Et_2O (sodium-benzophenone ketyl), methanol (from magnesium methoxide onto 3 Å molecular sieves), DCM and chlorotrimethylsilane (calcium hydride). Petrol refers to petroleum ether (bp 40–60 °C) which was distilled prior to use. Where anhydrous conditions were required, reactions were performed using oven-dried apparatus and nitrogen atmospheres. Drying of organic solutions used magnesium sulfate and solvent evaporation was achieved using a rotary evaporator.

Note on nomenclature

The numbering systems below were used for the following ring systems and their derivatives. Where selected diastereoisomers were prepared of unknown relative stereochemistry, these compounds were arbitrarily labelled A, B, AA, AB *etc.* Unless reported otherwise, products containing mixtures of diastereoisomers were obtained in an approx. 1 : 1 ratio (by NMR).



3-Hydroxy-4-iodobenzoic acid 6

A solution of iodine (23.4 g, 92 mmol) and potassium iodide (18.2 g, 110 mmol) in water (100 cm^3) was added to a stirred solution of 3-hydroxybenzoic acid (13.8 g, 100 mmol) in concentrated aqueous ammonia (200 cm^3) over 10 min. The solution was stirred for a further 25 min, then acidified by addition of concentrated hydrochloric acid (180 cm^3). The resulting thick white precipitate was isolated by filtration. Further product was obtained by extracting the filtrate with ethyl acetate (2 × 250 cm^3). After evaporation of the ethyl acetate the solid residue was combined with the precipitate, washed with water and recrystallised (water–ethanol 5:1), yielding the title compound as a white crystalline solid (13.0 g, 62%): mp 224–225 °C (lit.[14] 226 °C); δ_H(250 MHz, d_6-DMSO) 7.14 (1H, dd, *J* 1.8, 8.1, 6-H), 7.44 (1H, d, *J* 1.8, 2-H), 7.81 (1H, d, *J* 8.1, 5-H).

(**SAFETY NOTE**: the rate of addition of iodine was controlled to avoid any build up of unreacted iodine complex. Efficient paddle stirring was used and the reaction apparatus was scrutinised for any signs of nitrogen triiodide which might be formed from splashing inside the flask. No larger scale reactions were attempted.)

***n*-Butyl 3-hydroxy-4-iodobenzoate 7**

Thionyl chloride (30 cm^3) was added dropwise to a stirred solution of 3-hydroxy-4 iodobenzoic acid **6** (8.5 g, 32 mmol) in butanol (150 cm^3). The solution was then refluxed for 20 h. On cooling, water (100 cm^3) was added cautiously and the excess butanol was removed as an azeotrope. The resulting residue was taken up in dichloromethane (100 cm^3) and washed with saturated aqueous sodium hydrogen carbonate (3 × 50 cm^3) and saturated aqueous sodium chloride (50 cm^3). Drying and evaporation yielded the *title compound* as a crystalline solid (9.6 g, 93%): mp 72–73 °C (cyclohexane–ethyl acetate) (Found *m*/*z*: 319.992 (28%), $C_{11}H_{13}O_3I$ requires: M^+, 319.991); $\nu_{max}(CCl_4)/cm^{-1}$ 3450 (OH), 2961, 2934, 2875, 1715 (C=O), 1573 (Ar), 1318, 1302, 1102; δ_H(270 MHz) 0.97 (3H, t, *J* 7.5, ^{n}Bu, CH_3), 1.45 (2H, ap sex, ^{n}Bu, CH_2), 1.69–1.80 (2H, m, ^{n}Bu, CH_2), 4.32 (2H, t, *J* 6.6, ^{n}Bu, CH_2), 5.76 (1H, br s, OH), 7.33 (1H, dd, *J* 2.0, 8.3, 6-H), 7.65 (1H, d, *J* 2.0, 2-H), 7.75 (1H, d, *J* 8.3, 5-H); δ_C(100 MHz) 13.8 (^{n}Bu, CH_3), 19.2 (^{n}Bu, CH_2), 30.7 (^{n}Bu, CH_2), 65.5 (^{n}Bu, CH_2), 91.4 (C), 115.9 (CH), 122.8 (CH), 132.2 (C), 138.8 (CH), 155.5 (C), 166.5 (C=O); *m*/*z* 320 (M, 28%), 264 (M − ^{n}Bu, 100), 247 (M − O^{n}Bu, 51), 92 (14).

***n*-Butyl 2,3-dihydro-2-isopropenylbenzofuran-6-carboxylate 8**

Isoprene (5.5 g, 81 mmol) was added to a solution of *n*-butyl 3-hydroxy-4-iodobenzoate **7** (5.0 g, 16 mmol), palladium(II) acetate (180 mg, 0.80 mmol), sodium acetate (4.6 g, 56 mmol) and tetrabutylammonium chloride (4.5 g, 16 mmol) in anhydrous DMF (100 cm^3). The stirred mixture was heated at 80 °C for 24 h. Once cool, ethyl acetate (100 cm^3) was added and the reaction mixture was filtered through kieselguhr. The solvents were evaporated (50 mmHg then 0.1 mmHg) and the resulting residue was taken up in ethyl acetate, washed with water (3 × 50 cm^3), dried and evaporated. Chromatography (petrol–ethyl acetate 15:1) yielded the *title compound* as a racemic yellow oil (2.7 g, 65%) (Found *m*/*z*: 260.140 (78%), $C_{16}H_{20}O_3$ requires: M^+, 260.141); $\nu_{max}(CCl_4)/cm^{-1}$ 3088 (C=CH_2), 2949, 2874, 1714 (C=O), 1589 (Ar), 1493 (Ar), 1457, 1378, 1343, 1312, 1111, 1088, 972, 904; δ_H(400 MHz) 0.97 (3H, t, *J* 7.5, ^{n}Bu, CH_3), 1.76 (3H, s, 3′-H_3), 1.47 (2H, ap sex, ^{n}Bu, CH_2), 1.70–1.76 (2H, m, ^{n}Bu, CH_2), 3.07 and 3.38 (2H, 2 × dd, *J* 8.0, 16.4 and 9.5, 16.4, 3-H_2), 4.30 (2H, t, *J* 6.6, ^{n}Bu, CH_2), 4.92 and 5.09 (2H, 2 × s, 1′-H_2), 5.22 (1H, ap t, 2-H), 7.19 (1H, d, *J* 7.7, 4-H), 7.43 (1H, d, *J* 1.4, 7-H), 7.57 (1H, dd, *J* 1.4, 7.7, 5-H); δ_C(100 MHz) 13.8 (^{n}Bu, CH_3), 17.2 (3′-CH_3), 19.4 (^{n}Bu, CH_2), 30.9 (^{n}Bu, CH_2), 34.8 (3-CH_2), 64.8 (^{n}Bu, CH_2), 86.1 (2-CH), 110.0 (CH), 112.3 (1′-CH_2), 122.5 (CH), 124.5 (CH), 131.0 (C), 132.2 (C), 143.7 (2′-C), 160.0 (C), 166.6 (C=O); *m*/*z* 260 (M, 78%), 245 (M − CH_3, 25), 189 (42), 187 (M − ^{n}BuO, 43), 159 (M − CO_2-^{n}Bu, 100), 57 (31).

***n*-Butyl 2,3-dihydro-2-(2′-hydroxy-1′-methylethyl)benzofuran-6-carboxylate 9**

Borane–THF complex (1 M in THF, 2.2 cm^3, 22 mmol) was added dropwise to a stirred solution of the alkene **8** (5.8 g, 22 mmol) in THF (40 cm^3) at 0 °C. After 6 h the excess hydride was destroyed by the careful addition of water (20 cm^3). 2 M Aqueous sodium hydroxide (12 cm^3) and 30% hydrogen peroxide (8.0 cm^3) were added. Upon stirring for a further 2 h the mixture was extracted with ether (3 × 50 cm^3) and the combined organic layers were dried and evaporated. Chromatography (ether–petrol 2:1) yielded the *title compound* as a pale yellow oil and as a mixture of two diastereoisomers (5.1 g, 83%) (Found *m*/*z*: 278.152 (100%), $C_{16}H_{22}O_4$ requires: M^+, 278.152); $\nu_{max}(CCl_4)/cm^{-1}$) 3626 (OH), 3060, 2994, 2876, 1713 (C=O), 1590 (Ar), 1494, 1458, 1385, 1344, 1294, 1083, 978; *m*/*z* 278 (M, 100%), 247 (M − CH_2OH, 68), 219 (M − C_3H_6OH), 191 (38), 147 (50), 57 (^{n}Bu, 81).

Flash column chromatography yielded the separate diastereoisomers **9A** and **9B**, of undetermined configuration.

Alcohol **9A**: δ_H(400 MHz) 0.95–0.99 (6H, m, 1′-CH_3 and ^{n}Bu, CH_3), 1.47 (2H, ap sex, ^{n}Bu, CH_2), 1.70–1.77 (2H, m, ^{n}Bu, CH_2), 2.04–2.11 (1H, m, 1′-H), 2.28 (1H, br s, OH), 3.03 and 3.30 (2H, dd, *J* 8.7, 16.2 and 8.9, 16.2, 3-H_2), 3.70–3.78 (2H, m, 2′-H_2), 4.29 (2H, t, *J* 6.6, ^{n}Bu), 4.72 (1H, ap q, 2-H), 7.20 (1H, d, *J* 7.7, 4-H), 7.39 (1H, s, 7-H), 7.58 (1H, d, *J* 7.7, 5-H); δ_C(100 MHz) 12.8 (CH_3), 13.8 (^{n}Bu, CH_3), 19.3 (^{n}Bu, CH_2), 30.8 (^{n}Bu, CH_2), 34.1 (3-CH_2), 41.0 (1′-CH), 64.9 (^{n}Bu, CH_2), 66.1 (2′-CH_2), 87.3 (2-CH), 110.1 (CH), 122.6 (CH), 124.5 (CH), 130.8 (C), 132.2 (C), 159.5 (C), 166.6 (C=O).

Alcohol **9B**: δ_H(400 MHz) 0.95–1.04 (6H, m, 1′-CH_3 and ^{n}Bu, CH_2), 1.42–1.51 (2H, m, ^{n}Bu, CH_2), 1.70–1.79 (2H, m, ^{n}Bu, CH_2), 1.99–2.10 (1H, m, 1′-H), 2.05 (1H, br s, OH), 3.08 and 3.29 (2H, dd, *J* 9.5, 16.6 and 8.3, 16.6, 3-H_2), 3.66–3.76 (2H, m, 2′-H_2), 4.29 (2H, t, *J* 6.6, ^{n}Bu, CH_2), 4.98 (1H, ap dt, 2-H), 7.20 (1H, d, *J* 7.7, 4-H), 7.39 (1H, d, *J* 1.3, 7-H), 7.59 (1H, dd, *J* 1.3, 7.7, 5-H); δ_C(100 MHz) 10.9 (CH_3), 13.8 (^{n}Bu, CH_3), 19.4 (^{n}Bu, CH_2), 30.9 (^{n}Bu, CH_2), 33.1 (3-CH_2), 40.5 (1′-CH), 64.9 (^{n}Bu, CH_2), 65.3 (2′-CH_2), 84.8 (2-CH), 109.9 (CH), 122.4 (CH), 124.5 (CH), 130.8 (C), 132.6 (C), 160.0 (C), 166.7 (C=O).

***n*-Butyl 2,3-dihydro-2-(1′-methyl-2′-phenylthioethyl)benzofuran-6-carboxylate 10**

Tri-*n*-butylphosphine (3.9 g, 19 mmol) was added to a solution of diphenyl disulfide (4.2 g, 19 mmol) and the alcohol **9B** (1.8 g, 6.5 mmol) in dry pyridine (10 cm^3). The solution was stirred for 24 h, then heated at 60 °C for a further 2 h. On cooling, dichloromethane (30 cm^3) was added and the reaction mixture was washed with 2 M aqueous sodium hydroxide (2 × 20 cm^3), 2 M hydrochloric acid (3 ×0 cm^3) and saturated aqueous sodium chloride (20 cm^3). The organic layer was dried and evaporated. Chromatography (petrol–ethyl acetate 15:1) yielded the *sulfide* **10B** as a light yellow oil (2.0 g, 80%) (Found *m*/*z*: 370.162 (6%), $C_{22}H_{26}O_3S$ requires: M^+, 370.160); $\nu_{max}(CCl_4)/cm^{-1}$ 2961, 2933, 2875, 1710 (C=O), 1588 (Ar), 1290, 1085, 963; δ_H(400 MHz) 0.97 (3H, t, *J* 7.4, ^{n}Bu, CH_3), 1.08 (3H, d, *J* 6.8, 1′-CH_3), 1.43–1.50 (2H, m, ^{n}Bu, CH_2), 1.69–1.76 (2H, m, ^{n}Bu, CH_2), 1.98–2.08 (1H, m, 1′-H), 2.87 (1H, dd, *J* 7.8, 13.0, 2′-*H*H), 2.99 (1H, dd, *J* 5.4, 16.5, 3-*H*H), 3.17 (1H, dd,

J 5.9, 13.0, 2′-H*H*), 3.27 (1H, dd, *J* 9.4, 16.5, 3-H*H*), 4.29 (2H, t, *J* 6.6, ^{n}Bu, CH_2), 4.96 (1H, ap dt, 2-H), 7.15–7.40 (7H, m, ArH), 7.55 (1H, dd, *J* 1.4, 7.7, ArH); δ_C(100 MHz) 13.8 (CH_3), 19.4 (^{n}Bu, CH_2), 30.9 (^{n}Bu, CH_2), 32.9 (3-CH_2), 37.1 (2′-CH_2), 38.2 (1′-CH), 64.9 (^{n}Bu, CH_2), 85.2 (2-CH), 109.9 (CH), 122.4 (CH), 124.5 (CH), 126.1 (CH), 129.1 and 129.2 (*o*/*m*-SPh, 4 × CH), 130.9 (C), 132.3 (C), 136.6 (C), 160.1 (C), 166.6 (C=O) [missing ^{n}Bu, CH_3)—coincides with 13.8 (CH_3)]; *m*/*z* 370 (M, 6%), 232 (19), 218 (5), 123 (CH_2SPh, 100), 83 (55).

The same experimental procedure was employed to prepare the diastereoisomeric sulfide **10A** from the alcohol **9A**.

10A: δ_H(400 MHz) 0.97 (3H, t, *J* 7.4, ^{n}Bu, CH_3), 1.10 (3H, d, *J* 6.8, 1′-CH_3), 1.47 (2H, ap sex, ^{n}Bu, CH_2), 1.69–1.76 (2H, m, ^{n}Bu, CH_2), 2.05–2.20 (1H, m, 1′-H), 2.80 (1H, dd, *J* 8.7, 13.0, 2′-*H*H), 2.98 and 3.24 (2H, 2 × dd, *J* 8.4, 16.5 and 9.2, 16.5, 3-H_2), 3.36 (1H, dd, *J* 4.1, 13.0, 2′-H*H*), 4.29 (2H, t, *J* 6.6, ^{n}Bu), 4.73 (1H, ap q, 2-H), 7.10–7.41 (7H, m, ArH), 7.56 (1H, dd, *J* 1.4, 7.7, ArH); δ_C(100 MHz) 14.9 (CH_3), 13.8 (^{n}Bu, CH_3), 19.4 (^{n}Bu, CH_2), 30.9 (^{n}Bu, CH_2), 33.1 (3-CH_2), 36.8 (2′-CH_2), 38.4 (1′-CH), 64.9 (^{n}Bu, CH_2), 85.5 (2-CH), 110.0 (CH), 122.4 (CH), 124.6 (CH), 126.0 (CH), 129.0 and 129.1 (*o*/*m*-SPh, 4 × CH), 130.9 (C), 132.3 (C), 136.7 (C), 159.8 (C), 166.6 (C=O).

[2,3-Dihydro-2-(1′-methyl-2′-phenylthioethyl)benzofuran-6-yl]-methanol 11

A solution of the *n*-butyl ester **10** (4.5 g, 14 mmol) in dry ether (50 cm^3) was added, over 10 min, to a stirred suspension of lithium aluminium hydride (2.7 g, 71 mmol) in dry ether (100 cm^3). After stirring for 30 min, excess hydride was destroyed by the careful addition of firstly ethyl acetate (25 cm^3) and then water (50 cm^3). The reaction mixture was subsequently acidified with 2 M hydrochloric acid (100 cm^3). After stirring for 15 min, the organic layer was decanted and the aqueous phase further extracted with ethyl acetate (3 × 100 cm^3). The combined organic layers were dried and evaporated. Chromatography (petrol–ethyl acetate 5:1) yielded the title compound as a pale yellow oil and as a mixture of two diastereoisomers (3.4 g, 82%) (Found *m*/*z*: 300.119 (100%), $C_{18}H_{20}O_2S$ requires: M^+, 300.118). Repetition of this reaction using the separate stereoisomers **10A** and **10B** afforded the diastereoisomers **11A** and **11B**.

11A: δ_H(400 MHz) 1.09 (3H, d, *J* 6.8, 1′-CH_3), 1.74 (1H, br s, OH), 2.05–2.22 (1H, m, 1′-H), 2.78 (1H, dd, *J* 8.8, 13.0, 2′-*H*H), 2.92 and 3.19 (2H, 2 × dd, *J* 8.4, 15.7 and 9.0, 15.7, 3-H_2), 3.36 (1H, dd, *J* 4.1, 13.0, 2′-H*H*), 4.61 (2H, s, 6-CH_2), 4.68 (1H, ap q, 2-H), 6.78 (1H, s, ArH), 6.81 (1H, d, *J* 7.5, ArH), 7.11 (1H, d, *J* 7.5, ArH), 7.16 (1H, d, *J* 7.3, ArH), 7.22–7.29 (2H, m, ArH), 7.30–7.38 (2H, m, ArH).

11B: δ_H(400 MHz) 1.08 (3H, d, *J* 6.8, 1′-CH_3), 1.70 (1H, br s, OH), 2.00–208 (1H, m, 1′-H), 2.84 (1H, dd, *J* 8.0, 13.0, 2′-*H*H), 2.94 (1H, dd, *J* 8.0, 15.8, 3-*H*H), 3.17 (1H, dd, *J* 5.7, 13.0, 2′-H_2), 3.21 (1H, dd, *J* 9.5, 15.8, 3-H*H*), 4.61 (2H, s, 6-CH_2), 4.91 (1H, ddd, *J* 4.3, 8.0, 9.5, 2-H), 6.78 (1H, s, ArH), 6.81 (1H, d, *J* 7.5, ArH), 7.11 (1H, d, *J* 7.5, ArH), 7.15–7.37 (5H, m, ArH).

[2,3-Dihydro-2-(1′-methyl-2′-phenylthioethyl)benzofuran-6-yl]-ethanenitrile 13

A solution of the aryl methanol **11** (2.2 g, 7.3 mmol) and freshly distilled thionyl chloride (12.0 cm^3) was heated at 50 °C for 45 min. On cooling, the solution was poured into ice cooled water (50 cm^3) and extracted with ethyl acetate (2 × 50 cm^3). The organic layer was washed with saturated aqueous sodium hydrogen carbonate (2 × 50 cm^3) and saturated aqueous sodium chloride (50 cm^3), dried and evaporated. Chromatography (petrol–ethyl acetate 20:1) yielded the benzylic chloride **12** as a pale yellow oil and as a mixture of two diastereoisomers (1.7 g, 74%): δ_H(400 MHz) 1.08 (3H, d, *J* 6.8, 1′-CH_3), 2.00–2.16 (1H, m, 1′-H), 2.79 and 2.84 (1H, 2 × dd, *J* 9.1, 13.0 and 8.0, 13.0, 2′-H*H*), 2.89–3.24 and 3.37 (3H, m and dd, *J* 4.2, 13.0, 2′-*H*H and 3-H_2), 4.52 (2H, s, 6-CH_2), 4.69 and 4.91 (1H, ap q and ap dt, 2-H), 6.75–6.86 (2H, m, ArH), 7.06–7.37 (6H, m, ArH). The chloride **12** (720 mg, 2.3 mmol), potassium iodide (38 mg, 0.23 mmol), tetrabutylammonium chloride (40 mg, 0.15 mmol), 18-crown-6 (50 mg, 0.19 mmol) and potassium cyanide (450 mg, 6.9 mmol) were added to acetonitrile (25 cm^3). The stirred suspension was refluxed for 6 h. On cooling, the solvent was evaporated and chromatography (petrol–ethyl acetate 2:1) yielded the title compound as a pale yellow oil and as a mixture of two diastereoisomers (560 mg, 79%) (Found *m*/*z*: 309.118 (92%), $C_{19}H_{19}NOS$ requires: M^+, 309.119).

The diastereoisomers **13A** and **13B** were prepared from the separate alcohols **11A** and **11B** using the above procedure.

13A: δ_H(400 MHz) 1.09 (3H, d, *J* 6.8, 1′-CH_3), 2.05–2.20 (1H, m, 1′-H), 2.80 (1H, dd, *J* 8.7, 13.0, 2′-*H*H), 2.93 (1H, dd, *J* 8.4, 15.8, 3-*H*H), 3.19 (1H, dd, *J* 9.1, 15.8, 3-H*H*), 3.35 (1H, dd, *J* 4.2, 13.0, 2′-H*H*), 3.68 (2H, s, 6-CH_2), 4.71 (1H, ap q, 2-H), 6.72 (1H, s, ArH), 6.78 (1H, d, *J* 9.1, ArH), 7.12 (1H, d, *J* 7.2, ArH), 7.18 (1H, d, *J* 7.2, ArH), 7.20–7.40 (4H, m, ArH); δ_C(100 MHz) 14.8 (CH_3), 23.6 (6-C*C*H_2), 32.7 and 36.8 (3-CH_2 and 2′-CH_2), 38.4 (1′-CH), 86.7 (2-CH), 108.9 (CH), 118.0 (C), 120.0 (CH), 125.3 (CH), 125.9 (CH), 126.9 (C), 129.0 (*m*/*o*-SPh, 4 × CH), 130.0 (C), 136.7 (C), 160.4 (C).

13B: δ_H(400 MHz) 1.07 (3H, d, *J* 6.8, 1′-CH_3), 1.98–2.12 (1H, m, 1′-H), 2.84 (1H, dd, *J* 7.8, 13.0, 2′-*H*H), 2.93 (1H, dd, *J* 8.0, 15.8, 3-*H*H), 3.15 (1H, dd, *J* 5.8, 13.0, 2′-H*H*), 3.20 (1H, dd, *J* 9.5, 15.8, 3-H*H*), 3.65 (2H, s, 6-CH_2), 4.93 (1H, ddd, *J* 4.3, 8.0, 9.5, 2-H), 6.70 (1H, s, ArH), 6.76 (1H, d, *J* 7.9, ArH), 7.10 (1H, d, *J* 7.6, ArH), 7.15–7.37 (5H, m, ArH); δ_C(100 MHz) 13.8 (CH_3), 23.5 (6-C*C*H_2), 32.5 and 37.0 (3-CH_2 and 2′-CH_2), 38.2 (1′-CH), 85.4 (2-CH), 108.8 (CH), 118.0 (C), 119.9 (CH), 125.3 (CH), 126.0 (CH), 126.8 (C), 129.0 and 129.2 (*m*/*o*-SPh, 4 × CH), 130.0 (C), 136.6 (C), 160.7 (C).

N-{2′-[2″,3″-Dihydro-2″-(1‴-methyl-2‴-phenylthioethyl)benzofuran-6″-yl]ethyl}-2-(3‴″,4‴″-dimethoxyphenyl)ethanamide 16

A solution of aluminium chloride (1.6 g, 12 mmol) in ether (10 cm^3) was added to a suspension of lithium aluminium hydride (460 mg, 12 mmol) in ether (50 cm^3). After stirring for 15 min the arylethanenitrile **13** (730 mg, 2.4 mmol) dissolved in ether (10 cm^3), was added. The mixture was stirred for a further 6 h, then cooled to 0 °C and quenched by the addition of water (10 cm^3) and 5% aqueous ammonia (50 cm^3). The ether layer was decanted and the aqueous layer further extracted with ether (3 × 50 cm^3). The combined organic layers were dried and evaporated yielding the crude amine **14** as a light brown oil (570 mg). 4-Nitrophenyl 2-(3′,4′-dimethoxyphenyl)ethanoate **15** (570 mg, 1.8 mmol) and DBU (270 mg, 1.8 mmol) were added to a solution of the crude amine (570 mg) in dichloromethane (10 cm^3). The mixture was stirred for 12 h, after which the solvent was evaporated and the residue taken up in ethyl acetate (20 cm^3). This was washed with 2 M aqueous sodium hydroxide (2 × 10 cm^3), 2 M hydrochloric acid (2 × 10 cm^3) and saturated aqueous sodium chloride (10 cm^3). Chromatography (dichloromethane–ethyl acetate 1:0→2.5:1) yielded the title compound as a pale yellow oil and as a mixture of two diastereoisomers (650 mg, 58%) (Found *m*/*z*: 491.212 (73%), $C_{29}H_{33}NO_4S$ requires: M^+, 491.213). Repetition of this procedure using separate stereoisomers **13A** and **13B** gave the amides **16A** and **16B**.

16A: δ_H(250 MHz) 1.09 (3H, d, *J* 6.7, 1‴-CH_3), 2.05–2.20 (1H, m, 1‴-H), 2.66 (2H, t, *J* 6.8, 2′-H_2), 2.79 (1H, dd, *J* 8.8, 13.0, 2‴-*H*H), 2.89 and 3.15 (2H, 2 × dd, *J* 8.5, 15.5 and 9.1, 15.5, 3″-H_2), 3.36 (1H, dd, *J* 4.3, 13.0, 2‴-H*H*), 3.42–3.47 (2H, m, 1′-H_2), 3.47 (2H, s, 2-H_2), 3.82 and 3.86 (6H, 2 × s, 2 × OCH_3), 4.66 (1H, ap q, 2″-H), 5.47 (1H, br t, *J* 6.4, NH), 6.43–6.50 (2H, m, ArH), 6.67–6.74 (2H, m, ArH), 6.81 (1H, d, *J* 8.0, ArH), 6.97 (1H, d, *J* 7.4, ArH), 7.06–7.38 (5H, m, ArH);

δ_C(100 MHz) 14.9 (CH_3), 32.8 (2‴-CH_2), 35.5 (2′-CH_2), 36.9 (3″-CH_2), 38.4 (1‴-CH), 40.7 (2-CH_2), 43.4 (1′-CH_2), 55.8 and 55.9 (2 × OCH_3), 86.4 (2″-CH), 109.4 (CH), 111.6 (CH), 112.5 (CH), 120.7 (CH), 121.7 (CH), 124.7 (CH), 124.9 (C), 125.8 (CH), 127.3 (C), 128.9 (*o*/*m*-SPh, 4 × CH), 136.6 (C), 139.0 (C), 148.4 (C), 149.3 (C), 160.0 (C), 171.1 (C=O).

16B: δ_H(250 MHz) 1.09 (3H, d, *J* 6.7, 1‴-CH_3), 2.00–2.15 (1H, m, 1‴-H), 2.66 (2H, t, *J* 6.8, 2′-H_2), 2.84 (1H, dd, *J* 8.0, 13.0, 2‴-*H*H), 2.89 (1H, dd, *J* 8.0, 15.8, 3″-*H*H), 3.17 (1H, dd, 9.1, 15.8, 3″-H*H*), 3.32–3.47 (3H, m, 2‴-H*H* and 1′-H_2), 3.47 (2H, s, 2-H_2), 3.84 and 3.88 (6H, 2 × s, 2 × OCH_3), 4.88 (1H, ap dt, 2″-H), 5.47 (1H, br t, *J* 6.4, NH), 6.43–6.50 (2H, m, ArH), 6.67–6.74 (2H, m, ArH), 6.81 (1H, d, *J* 8.0, ArH), 6.97 (1H, d, *J* 7.4, ArH), 7.06–7.38 (5H, m, ArH); δ_C(100 MHz) 13.9 (CH_3), 32.6 (2‴-CH_2), 35.5 (2′-CH_2), 37.1 (3″-CH_2), 38.2 (1‴-CH), 40.7 (2-CH_2), 43.4 (1′-CH_2), 55.8 and 55.9 (2 × OCH_3), 85.2 (2″-CH), 109.2 (CH), 111.6 (CH), 112.5 (CH), 120.6 (CH), 121.7 (CH), 124.6 (CH), 124.9 (C), 126.0 (CH), 127.3 (C), 128.9 and 129.1 (*o*/*m*-SPh, 4 × CH), 136.8 (C), 139.0 (C), 148.4 (C), 149.3 (C), 160.3 (C), 171.1 (C=O).

2,3,5,6,7,8-Hexahydro-5-(3′,4′-dimethoxybenzyl)-2-(1″-methyl-2″-phenylthioethyl)furo[2,3-*g*]isoquinoline (FIQ, 4)

A solution of a mixture of the diastereoisomers of the amide **16** (650 mg, 13 mmol) and phosphorus oxychloride (1.2 g, 7.8 mmol) in toluene (15 cm^3) was heated at 100 °C for 1 h. On cooling, the volatiles were evaporated (0.5 mmHg) and the residue was taken up in dichloromethane (20 cm^3). This organic phase was washed with 5% aqueous ammonia (2 × 20 cm^3) and saturated aqueous sodium chloride (20 cm^3). After drying and evaporation the resulting crude imine **17** (650 mg) was dissolved in methanol (20 cm^3) and treated with sodium borohydride (1.0 g, 27 mmol). After stirring for 3 h the solvent was evaporated, water (10 cm^3) was added and the mixture was basified with 5% aqueous ammonia (15 cm^3). This aqueous phase was extracted with ether (20 cm^3), which itself was subsequently washed with 5% aqueous ammonia (2 × 15 cm^3), dried and evaporated to yield the title compound as a pale yellow oil and as a mixture of four diastereoisomers (470 mg, 76%) (Found *m*/*z* (FAB): 476.227 (7%), $C_{29}H_{33}NO_3S$ requires: M^+, 476.226), with NMR and TLC behaviour indistinguishable from an authentic sample.[9] This procedure was then repeated using separate amides **16A** and **16B**, to provide two mixtures **4AA/AB** and **4BA/BB** which were converted into the corresponding trifluoroacetamides **5AA/AB** and **5BA/BB**, by treatment with pyridine (2 equiv.) and trifluoroacetic anhydride (4 equiv.) in dichloromethane at ambient temperature. The mixtures **5AA/AB** and **5BA/BB** were then separated by HPLC (semi-preparative reversed phase column) using small (*ca.* 5 mg) batches; attempts to separate larger quantities led to significant sample decomposition. In this way, HPLC pure samples of racemates **5AA**, **5AB**, **5BA** and **5BB** were isolated.

5AA: δ_H(400 MHz) 1.10 (3H, d, *J* 6.8, 1″-CH_3), 2.05–2.17 (1H, m, 1″-H), 2.55–3.48 (8H, m, 3-H_2, 7-H_2, 8-H_2, 2″-H_2), 3.07 (2H, d, *J* 6.2, 1′-CH_2), 3.73 and 3.84 (6H, 2 × s, 2 × OCH_3), 4.67 (1H, ap q, 2-H), 5.54 (1H, t, *J* 6.2, 5-H), 6.50–6.56 (3H, m, ArH), 6.71 (1H, s, ArH), 6.72 (1H, d, *J* 8.3, ArH), 7.14–7.38 (5H, m, ArH); δ_C(100 MHz) 14.9 (CH_3), 29.3 (CH_2), 32.8 (CH_2), 36.9 (CH_2), 38.5 (1″-CH), 40.8 (CH_2), 41.8 (CH_2), 55.8 (5-CH), 55.8 and 55.9 (2 × OCH_3), 86.5 (2-CH), 108.6 (CH), 111.1 (CH), 112.8 (CH), 121.9 (CH), 124.0 (CH), 125.6 (C), 125.9 (CH), 126.8 (C), 129.0 and 129.1 (*o*/*m*-SPh, 4 × CH_3), 129.5 (C), 133.3 (C), 136.8 (C), 148.0 (C), 148.8 (C), 155.9 (q, CF_3), 158.9 (C=O).

5AB: δ_H(400 MHz) 1.08 (3H, d, *J* 6.7, 1″-CH_3), 2.05–2.17 (1H, m, 1″-H), 2.55–3.50 (8H, m, 3-H_2, 7-H_2, 8-H_2, 2″-H_2), 3.07 (2H, d, *J* 6.2, 1′-CH_2), 3.77 and 3.85 (6H, 2 × s, 2 × OCH_3), 4.67 (1H, ap q, 2-H), 5.54 (1H, t, *J* 6.2, 5-H), 6.50–6.56 (3H, m, ArH), 6.71 (1H, s, ArH), 6.74 (1H, d, *J* 8.0, ArH), 7.14–7.38 (5H, m, ArH); δ_C(100 MHz) 14.9 (CH_3), 29.3 (CH_2), 32.8 (CH_2), 36.9 (CH_2), 38.4 (1″-CH), 40.8 (CH_2), 41.8 (CH_2), 55.8 (5-CH), 55.8 and 55.9 (2 × OCH_3), 86.5, (2-CH), 108.6 (CH), 111.1 (CH), 112.8 (CH), 121.9 (CH), 124.1 (CH), 125.6 (C), 125.9 (CH), 126.8 (C), 129.0 and 129.1 (*o*/*m*-SPh, 4 × CH_3), 129.5 (C), 133.3 (C), 136.8 (C), 148.0 (C), 148.8 (C), 155.9 (q, CF_3), 158.9 (C=O).

5BA: δ_H(400 MHz) 1.08 (3H, d, *J* 6.7, 1″-CH_3), 2.00–2.10 (1H, m, 1″-H), 2.55–3.45 (8H, m, 3-H_2, 7-H_2, 8-H_2, 2″-H_2), 3.07 (2H, d, *J* 6.2, 1′-CH_2), 3.73 and 3.84 (6H, 2 × s, 2 × OCH_3), 4.85–5.00 (1H, m, 2-H), 5.54 (1H, t, *J* 6.2, 5-H), 6.50–6.56 (3H, m, ArH), 6.71 (1H, s, ArH), 6.72 (1H, d, *J* 8.0, ArH), 7.14–7.38 (5H, m, ArH); δ_C(100 MHz) 13.8 (CH_3), 29.3 (CH_2), 32.6 (CH_2), 37.1 (CH_2), 38.2 (1″-CH), 40.8 (CH_2), 41.7 (CH_2), 55.8 (5-CH), 55.8 and 55.9 (2 × OCH_3), 85.2 (2-CH), 108.4 (CH), 111.1 (CH), 112.8 (CH), 121.9 (CH), 123.9 (CH), 125.6 (C), 126.0 (CH), 126.7 (C), 129.0 and 129.2 (*o*/*m*-SPh, 4 × CH_3), 129.5 (C), 133.4 (C), 136.6 (C), 148.0 (C), 148.8 (C), 155.9 (q, CF_3), 159.2 (C=O).

5BB: δ_H(400 MHz) 1.06 (3H, d, *J* 6.8, 1″-CH_3), 1.98–2.05 (1H, m, 1″-H), 2.55–3.47 (8H, m, 3-H_2, 7-H_2, 8-H_2, 2″-H_2), 3.07 (2H, d, *J* 6.2, 1′-CH_2), 3.77 and 3.85 (6H, 2 × s, 2 × OCH_3), 4.85–5.00 (1H, m, 2-H), 5.54 (1H, t, *J* 6.2, 5-H), 6.48–6.58 (3H, m, ArH), 6.70–6.75 (2H, m, ArH), 7.14–7.38 (5H, m, ArH); δ_C(100 MHz) 13.8 (CH_3), 29.3 (CH_2), 32.6 (CH_2), 37.1 (CH_2), 38.2 (1″-CH), 40.8 (CH_2), 41.9 (CH_2), 55.8 (5-CH), 55.8 and 55.9 (2 × OCH_3), 85.2 (2-CH), 108.4 (CH), 111.1 (CH), 112.8 (CH), 121.9 (CH), 124.0 (CH), 125.6 (C), 126.0 (CH), 126.7 (C), 129.0 and 129.2 (*o*/*m*-SPh, 4 × CH_3), 129.5 (C), 133.4 (C), 136.6 (C), 148.0 (C), 148.8 (C), 155.9 (q, CF_3), 159.2 (C=O).

The above trifluoroacetamides were hydrolysed by stirring in a (1 : 1) methanol–aq. sodium bicarbonate mixture to afford the desired four racemates of FIQ, **4AA**, **4AB**, **4BA** and **4BB** (*ca.* 5 mg each).

4AA: δ_H(400 MHz) 1.10 (3H, d, *J* 6.7, 1″-CH_3), 1.86 (1H, br s, NH), 2.10–2.15 (1H, m, 1″-H), 2.67–2.93, 3.15–3.22 and 3.39 (10H, 2 × m and dd, *J* 4.0, 12.9, 3-H_2, 7-H_2, 8-H_2, 1′-CH_2, 2″-H_2), 3.84 and 3.87 (6H, 2 × s, 2 × OCH_3), 4.10 (1H, dd, *J* 1.2, 7.9, 5-H), 4.64 (1H, ap q, 2-H), 6.52 (1H, s, ArH), 6.74–6.85 (3H, m, ArH), 7.02 (1H, s, ArH), 7.22 (1H, ap t, ArH), 7.27–7.31 (2H, m, ArH), 7.34–7.36 (2H, m, ArH).

4AB: δ_H(400 MHz) 1.10 (3H, d, *J* 6.7, 1″-CH_3), 1.86 (1H, br s, NH), 2.10–2.15 (1H, m, 1″-H), 2.67–2.93, 3.15–3.22 and 3.37 (10H, 2 × m and dd, *J* 4.1, 13.0, 3-H_2, 7-H_2, 8-H_2, 1′-CH_2, 2″-H_2), 3.86 and 3.87 (6H, 2 × s, 2 × OCH_3), 4.10 (1H, dd, *J* 1.2, 7.9, 5-H), 4.64 (1H, ap q, 2-H), 6.52 (1H, s, ArH), 6.74–6.85 (3H, m, ArH), 7.02 (1H, s, ArH), 7.22 (1H, ap t, ArH), 7.27–7.31 (2H, m, ArH), 7.34–7.36 (2H, m, ArH).

4BA: δ_H(400 MHz) 1.09 (3H, d, *J* 6.7, 1″-CH_3), 1.85 (1H, br s, NH), 2.01–2.06 (1H, m, 1″-H), 2.70–3.01 and 3.17–3.25 (10H, 2 × m, 3-H_2, 7-H_2, 8-H_2, 1′-CH_2, 2″-H_2), 3.83 and 3.87 (6H, 2 × s, 2 × OCH_3), 4.10 (1H, dd, *J* 1.2, 7.9, 5-H), 4.98 (1H, ap dt, 2-H), 6.53 (1H, s, ArH), 6.73 (1H, s, ArH), 6.76–6.88 (2H, m, ArH), 7.02 (1H, s, ArH), 7.18 (1H, ap t, ArH), 7.27–7.31 (2H, m, ArH), 7.34–7.36 (2H, m, ArH).

4BB: δ_H(400 MHz) 1.09 (3H, d, *J* 6.7, 1″-CH_3), 1.85 (1H, br s, NH), 2.01–2.06 (1H, m, 1″-H), 2.70–2.98 and 3.15–3.21 (10H, 2 × m, 3-H_2, 7-H_2, 8-H_2, 1′-CH_2, 2″-H_2), 3.85 and 3.87 (6H, 2 × s, 2 × OCH_3), 4.10 (1H, dd, *J* 1.2, 7.9, 5-H), 4.97 (1H, ap dt, 2-H), 6.53 (1H, s, ArH), 6.75 (1H, s, ArH), 6.76–6.88 (2H, m, ArH), 7.02 (1H, s, ArH), 7.18 (1H, ap t, ArH), 7.27–7.31 (2H, m, ArH), 7.34–7.36 (2H, m, ArH).

Methyl 2-(2′-hydroxyethyl)benzofuran-6-carboxylate 19

Copper(I) oxide (7.0 g, 49 mmol) was added to a solution of methyl 3-hydroxy-4-iodobenzoate (19.5 g, 70 mmol) and but-3-yn-1-ol (5.3 g, 75 mmol) in dry pyridine (150 cm^3). The mixture was heated at 100 °C for 24 h. On cooling, ethyl acetate (200 cm^3) was added and the solution was filtered through

kieselguhr. The filtrate was washed with 2 M hydrochloric acid (3 × 200 cm^3) and saturated aqueous sodium chloride (200 cm^3), dried and evaporated. Chromatography (petrol–ethyl acetate 2:1) yielded the *title compound* as a light yellow oil (12 g, 78%): mp 59–60 °C (cyclohexane–ethyl acetate) (Found: C 65.79, H 5.65%, *m/z*: 220.073 (38%), $C_{12}H_{12}O_4$ requires: C 65.43, H 5.55%, M^+, 220.074); $\nu_{max}(CCl_4)/cm^{-1}$ 3622 (OH), 2953, 2889, 1714 (C=O), 1620 (C=C), 1594 (Ar), 1577 (Ar), 1300, 1081, 1045, 987; δ_H(400 MHz) 2.98 (2H, t, *J* 6.4, 1′-H_2), 3.17 (1H, br s, OH), 3.85 (3H, s, OCH_3), 3.93 (2H, t, *J* 6.4, 2′-H_2), 6.46 (1H, s, 3-H), 7.41 (1H, d, *J* 8.1, 4-H), 7.81 (1H, dd, *J* 1.3, 8.1, 5-H), 7.99 (1H, br s, 7-H); δ_C(100 MHz) 31.9 (1′-CH_2), 51.9 (OCH_3), 59.9 (2′-CH_2), 103.5 (3-CH_2), 112.1 (CH), 119.7 (CH), 123.9 (CH), 124.9 (C), 133.1 (C), 153.9 (C), 159.6 (C), 167.3 (C=O); *m/z* 220 (M, 38%), 189 (M − CH_2OH, 100), 161 (M − CO_2Me, 6), 130 (M − $C_3H_6O_3$, 20).

Methyl 2-(2′-phenylthioethyl)benzofuran-6-carboxylate 20

Tri-*n*-butylphosphine (27 g, 130 mmol) was added to a solution of diphenyl disulfide (28 g, 130 mmol) and the alcohol **19** (11.0 g, 50 mmol) in pyridine (100 cm^3). After stirring for 24 h, ethyl acetate (200 cm^3) was added and the reaction mixture was washed with 2 M aqueous sodium hydroxide (3 × 150 cm^3), 2 M hydrochloric acid (2 × 150 cm^3) and saturated aqueous sodium chloride (150 cm^3). The organic phase was then dried and evaporated. Chromatography (petrol–ethyl acetate 10:1) yielded the *title compound* as a crystalline solid (15.2 g, 78%): mp 57–58 °C (cyclohexane–ethyl acetate) (Found: C 69.23, H 5.16%, *m/z*: 312.082 (48%), $C_{18}H_{16}O_3S$ requires: C 69.21, H 5.17%, M^+, 312.082); $\nu_{max}(CCl_4)/cm^{-1}$ 2952, 1713 (C=O), 1620 (C=C), 1578 (Ar), 1482, 1438, 1298, 1082, 987, 978; δ_H(400 MHz) 3.07 (2H, t, *J* 7.4, 1′-H), 3.26 (2H, t, *J* 7.4, 2′-H), 3.90 (3H, s, OCH_3), 6.45 (1H, s, 3-H), 7.16 (1H, br t, *J* 7.5, ArH), 7.26 (2H, br d, *J* 7.5, ArH), 7.36 (2H, br t, *J* 7.5, ArH), 7.46 (1H, d, *J* 8.1, 4-H), 7.91 (1H, dd, *J* 1.2, 8.1, 5-H), 8.08 (1H, d, *J* 1.2, 7-H); δ_C(100 MHz) 28.8 (1′-CH_2), 31.5 (2′-CH_2), 51.9 (OCH_3), 103.4 (3-CH), 112.3 (CH), 119.9 (CH), 124.0 (CH), 125.5 (C), 128.3 (CH), 128.9 and 129.8 (*o*/*m*-SPh, 4 × CH), 133.0 (C), 135.4 (C), 154.0 (C), 159.0 (C), 167.1 (C=O); *m/z* 312 (M, 48%), 281 (M − OCH_3, 5), 203 (M − Ph, 6), 189 (M − CH_2SPh, 18), 123 (CH_2SPH, 100).

[2-(2′-Phenylthioethyl)benzofuran-6-yl]methanol 21

A solution of the methyl ester **20** (11 g, 35 mmol) in ether (50 cm^3) was added over 10 min, to a stirred suspension of lithium aluminium hydride (3.4 g, 89 mmol) in ether (350 cm^3). After stirring for 1 h, excess hydride was destroyed by the careful addition of firstly ethyl acetate (50 cm^3) and then water (200 cm^3). The reaction mixture was subsequently acidified with 2 M hydrochloric acid (200 cm^3). After stirring for 15 min, the organic layer was decanted and the aqueous phase further extracted with ethyl acetate (3 × 200 cm^3). The combined organic fractions were dried and evaporated. Recrystallisation (cyclohexane) of the residue yielded the *title compound* as a crystalline solid (7.9 g, 80%): mp 58–60 °C (cyclohexane) (Found: C 72.01, H 5.70%, *m/z*: 284.088 (94%), $C_{17}H_{16}O_2S$ requires: C 71.81, H 5.68%, M^+, 284.087); $\nu_{max}(CCl_4)/cm^{-1}$ 3606 (OH), 2932, 1583 (Ar), 1482, 1439, 1383, 1281, 1114, 963, 870; δ_H(400 MHz) 1.79 (1H, br s, OH), 3.07 (2H, t, *J* 7.4, 1′-H_2), 3.28 (2H, t, *J* 7.4, 2′-H_2), 4.75 (2H, s, 6-CH_2), 6.43 (1H, s, 3-H), 7.17–7.46 (8H, m, ArH); δ_C(100 MHz) 28.9 (1′-CH_2), 31.9 (2′-CH_2), 65.7 (6-CCH_2), 103.1 (3-CH), 109.7 (CH), 120.5 (CH), 122.0 (CH), 126.5 (CH), 128.3 (C), 129.1 and 129.9 (*o*/*m*-SPh, 4 × CH), 135.9 (C), 136.9 (C), 155.0 (C), 157.3 (C); *m/z* 284 (M, 94%), 267 (M − OH, 12), 174 (M − SPh, 28), 161 (100), 123 (CH_2SPh, 89).

6-Chloromethyl-2-(2′-phenylthioethyl)benzofuran 22

A solution of the arylmethanol **21** (7.6 g, 27 mmol) and freshly distilled thionyl chloride (20 cm^3, 170 mmol) was heated at 50 °C for 45 min. Afterwards the solution was poured into ice cooled water (100 cm^3) and extracted with ethyl acetate (2 × 100 cm^3). The combined organic extracts were then washed with saturated aqueous sodium hydrogen carbonate (2 × 100 cm^3) and saturated aqueous sodium chloride (100 cm^3), dried and evaporated. Chromatography (petrol–ethyl acetate 20:1) yielded the *title compound* as a crystalline solid (7.6 g, 93%) (Found *m/z*: 302.052 (28%), $C_{17}H_{15}ClOS$ requires: M^+, 302.053); ν_{max} $(CCl_4)/cm^{-1}$ 2964, 2932, 1583, 1482, 1440, 1315, 1281, 1116, 968; δ_H(400 MHz) 3.07 (2H, t, *J* 7.4, 1′-H_2), 3.28 (2H, t, *J* 7.4, 2′-H_2), 4.69 (2H, s, 6-CH_2), 6.44 (1H, s, 3-H), 7.17–7.46 (8H, m, ArH); δ_C(100 MHz) 28.9 (1′-CH_2), 31.9 (2′-CH_2), 47.0 (6-CH_2), 103.3 (3-CH), 111.3 (CH), 120.7 (CH), 123.5 (CH), 126.5 (CH), 129.0 (C), 129.1 and 129.9 (*o*/*m*-SPh, 4 × CH), 133.2 (C), 135.6 (C), 154.7 (C), 157.9 (C); *m/z* 302 (M, 28%), 267 (M − Cl, 6), 192 (7), 179 (M − CH_2SPh, 15), 144 (12), 123 (CH_2SPh, 58), 72 (22), 58 (100).

[2-(2′-Phenylthioethyl)benzofuran-6-yl]ethanenitrile 23

A stirred solution of the benzylic chloride **22** (6.0 g, 20 mmol), potassium iodide (330 mg, 2.0 mmol), tetrabutylammonium chloride (350 mg, 1.3 mmol), 18-crown-6 (350 mg, 1.3 mmol) and potassium cyanide (3.9 g, 60 mmol) in acetonitrile (70 cm^3) was refluxed for 6 h. On cooling the solvent was evaporated and chromatography (petrol–ethyl acetate 2:1) yielded the *title compound* as a crystalline solid (5.2 g, 90%): mp 50–51 °C (cyclohexane–ethyl acetate) (Found: C 73.74, H 5.06, N 4.58%, *m/z*: 293.087 (73%), $C_{18}H_{15}NOS$ requires: C 73.70, H 5.16, N 4.78%, M^+, 293.088); $\nu_{max}(CCl_4)/cm^{-1}$ 2930, 2254 (CN), 1583 (Ar), 1484, 1439, 1283, 1118, 968; δ_H(400 MHz) 3.08 (2H, t, *J* 7.4, 1′-H_2), 3.28 (2H, t, *J* 7.4, 2′-H_2), 3.82 (2H, s, 6-CH_2), 6.45 (1H, s, 3-H), 7.13 (1H, d, *J* 8.0, ArH), 7.17–7.22 (1H, m, ArH), 7.25–7.31 (2H, m, ArH), 7.36–7.38 (3H, m, ArH), 7.46 (1H, d, *J* 8.0, ArH); δ_C(100 MHz) 23.8 (6-CCH_2), 28.8 (1′-CH_2), 31.9 (2′-CH_2), 103.2 (3-CH), 110.6 (CH), 118.3 (CN), 121.1 (CH), 122.6 (CH), 125.4 (C), 126.5 (CH), 129.0 (C), 129.1 and 130.0 (*o*/*m*-SPh, 4 × CH), 135.9 (C), 155.1 (C), 157.8 (C); *m/z* 293 (M, 73%), 267 (M − CN, 5), 183 (M − SPh, 18), 170 (M − CH_2SPh, 22), 123 (CH_2SPh, 100), 77 (C_6H_5, 4).

N-{2′-[2″-(2‴-Phenylthioethyl)benzofuran-6″-yl]ethyl}-2-(3‴′,4‴′-dimethoxyphenyl)ethanamide 25

A solution of aluminium chloride (1.7 g, 13 mmol) in ether (20 cm^3) was added to a suspension of lithium aluminium hydride (500 mg, 13 mmol) in ether (20 cm^3). After stirring for 15 min, a solution of the ethanenitrile **23** (750 mg, 2.6 mmol) in ether (10 cm^3) was added. The mixture was stirred for a further 5 h, then cooled to 0 °C and quenched by the addition of water (20 cm^3), 5% aqueous ammonia (20 cm^3) and water (20 cm^3). The ether layer was decanted and the aqueous layer further extracted with ether (3 × 40 cm^3). The combined organic extracts were dried and evaporated yielding the crude amine **24** as a light brown oil (760 mg). 4-Nitrophenyl 2-(3′,4′-dimethoxyphenyl)ethanoate (830 mg, 2.6 mmol), and DBU (400 mm^3, 2.6 mmol) were added to a solution of the crude amine (760 mg) in dichloromethane (10 cm^3). The mixture was stirred for 12 h, after which the solvent was evaporated and the residue taken up in ethyl acetate (400 mm^3). This was washed with 2 M aqueous sodium hydroxide (2 × 30 cm^3), 2 M hydrochloric acid (2 × 30 cm^3) and saturated aqueous sodium chloride (30 cm^3). Upon drying and evaporation, the resulting residue was recrystallised (ethyl acetate–cyclohexane) to yield the *title compound* as a crystalline solid (760 mg, 75%): mp 83–85 °C (cyclohexane–ethyl acetate) (Found: C 70.52, H 6.19, N 3.05%, *m/z*: 475.184 (29%), $C_{28}H_{29}NO_4S$ requires: C 70.71, H 6.15, N 2.95%, M^+, 475.182); $\nu_{max}(CCl_4)/cm^{-1}$ 3424 (CONH), 2937, 2838, 1659 (C=O), 1590 (Ar), 1464, 1264, 1141, 1027;

δ_H(400 MHz) 2.82 (2H, t, *J* 6.7, 2′-H_2), 3.08 (2H, t, *J* 7.5, 1‴-H_2), 3.29 (2H, t, *J* 7.5, 2‴-H_2), 3.47 (2H, s, 2-H_2), 3.49 (2H, t, *J* 6.7, 1′-H_2), 3.77 and 3.85 (6H, 2 × s, 2 × OCH_3), 5.63 (1H, br s, NH), 6.41 (1H, s, 3″-H), 6.65 (1H, d, *J* 1.8, 2⁗-H), 6.68 (1H, dd, *J* 1.8, 8.1, ArH), 6.76 (1H, d, *J* 8.1, ArH), 6.85 (1H, dd, *J* 0.9, 7.9, ArH), 7.10 (1H, s, Ar), 7.18–7.40 (6H, m, ArH); δ_C(100 MHz) 28.8 (1‴-CH_2), 32.0 (2‴-CH_2), 35.7 (2′-CH_2), 41.1 (1′-CH_2), 43.6 (2-CH_2), 55.9 and 56.0 (2 × OCH_3), 103.0 (3″-CH), 111.0 (CH), 111.7 (CH), 112.5 (CH), 120.4 (CH), 121.7 (CH), 123.5 (CH), 126.5 (CH), 126.9 (C), 127.3 (C), 129.1 and 129.9 (*o*/*m*-SPh, 4 × CH), 134.6 (C), 135.7 (C), 148.4 (C), 149.4 (C), 155.1 (C), 156.8 (C), 171.3 (C=O); *m*/*z* 475 (M, 29%), 280 ($C_{18}H_{16}OS$, 100), 195 ($C_{10}H_{13}NO_3$, 19), 170 ($C_{12}H_{10}O$, 30), 157 ($C_{11}H_9O$, 86), 151 ($CH_2Ph(OMe)_2$, 64), 123 (46), 77 (C_6H_5, 7).

5,6,7,8-Tetrahydro-5-(3′,4′-dimethoxybenzyl)-2-(2″-phenylthioethyl)furo[2,3-*g*]isoquinoline (FIQ2, 26)

A solution of the arylethanamide **25** (730 mg, 1.5 mmol) and phosphorus oxychloride (1.5 cm^3, 9.8 mmol) in dry toluene (15 cm^3) was heated at 100 °C for 3 h. On cooling, the volatiles were evaporated (0.5 mmHg) and the residue was taken up in dichloromethane (30 cm^3) and washed with 5% aqueous ammonia (2 × 20 cm^3) and saturated aqueous sodium chloride (20 cm^3). After drying and evaporation, the resulting crude imine **27** (730 mg) was dissolved in methanol (30 cm^3) and sodium borohydride (1.2 g, 32 mmol) was added. After stirring for 3 h the solvent was evaporated and the residue partitioned between ether (20 cm^3) and water (20 cm^3). The layers were separated and the ether layer was washed with 5% aqueous ammonia (2 × 15 cm^3), dried and evaporated to yield the *title compound* as a racemic yellow oil (520 mg, 76%) (Found *m*/*z* (FAB): 460.195 (2%), $C_{28}H_{29}O_3NS$ requires: MH^+, 460.195); $\nu_{max}(CCl_4)/cm^{-1}$ 2936, 2838, 1587, 1514, 1465, 1266, 1139, 1028, 908, 878; δ_H(500 MHz) 2.87–2.98 and 3.22–3.30 (8H, 2 × m, 7-H_2, 8-H_2, 1′-CH_2, 2″-H_2), 3.07 (2H, t, *J* 7.4, 1″-H_2), 3.85 and 3.88 (6H, 2 × s, 2 × OCH_3), 4.28 (1H, dd, *J* 3.5, 9.6, 5‴-H), 6.39 (1H, s, ArH), 6.77 (1H, s, ArH), 6.80–6.85 (2H, m, ArH), 7.14 (1H, s, ArH), 7.15–7.39 (6H, s, ArH); δ_C(125 MHz) 28.8 (1″-CH_2), 30.7 (Ar-CH_2), 31.8 (2″-CH_2), 41.0 and 42.7 (7-CH_2 and 8-CH_2), 55.9 (2 × OCH_3), 57.5 (5-CH), 102.8 (3-CH), 110.6 (CH), 111.4 (CH), 112.5 (CH), 117.7 (CH), 121.4 (CH), 126.3 (CH), 126.8 (C), 129.0 and 129.7 (*o*/*m*-SPh, 4 × CH), 131.4 (C), 131.6 (C), 133.3 (C), 135.7 (C), 147.7 (C), 149.0 (C), 153.6 (C), 156.5 (C); *m*/*z* (FAB) 460 (MH, 2%), 401 (5), 327 (10), 281 (25), 221 (25), 207 (35), 154 (52), 147 (92), 136 (100).

The corresponding *trifluoroacetamide* was formed as an oil (57%) on treatment with trifluoroacetic anhydride (4 equiv.) and pyridine (2 equiv.) in dichloromethane (Found *m*/*z* (FAB): 556.174 (5%), $C_{30}H_{28}O_4F_3NS$ requires: MH^+, 556.177); ν_{max} $(CCl_4)/cm^{-1}$ 2936, 2838, 1682 (C=O), 1592 (Ar), 1464, 1267, 1141, 1027, 908; δ_H(500 MHz) 2.82 and 2.99 (2H, ap dt and ddd, *J* 5.1, 10.9 and 5.1, 9.1, 15.8), 3.08 (2H, t, *J* 7.5, 1″-H_2), 3.12–3.18 (2H, m, 1′-CH_2), 3.30 (2H, t, *J* 7.5, 2″-H_2), 3.61–3.66 and 3.78–3.83 (2H, 2 × m), 3.71 and 3.86 (6H, 2 × s, 2 × OCH_3), 5.71 (1H, t, 6.3, 5′-H), 6.39 (1H, s, 3-H), 6.50 (1H, d, *J* 1.9, 2′-H), 6.54 (1H, dd, 1.9, 8.1, 5′-H), 6.73 (1H, d, *J* 8.1, 6′-H), 7.06 (1H, s, ArH), 7.19 (1H, s, ArH), 7.20–7.25 (1H, m, ArH), 7.29–7.33 (2H, m, ArH), 7.35–7.44 (2H, m, ArH); δ_C(125 MHz) 28.7 (1″-CH_2), 29.3 (CH_2), 31.7 (CH_2), 41.3 (CH_2), 42.2 (CH_2), 55.7 and 55.8 (2 × OCH_3), 56.8 (CH), 102.9 (3-CH), 110.1 (CH), 110.9 (CH), 112.7 (CH), 119.3 (CH), 121.8 (CH), 126.4 (CH), 127.4 (C), 129.0 (*o*/*m*-SPh, 2 × CH), 129.3 (2 × C), 129.4 (C), 129.8 (*o*/*m*-SPh, 2 × CH), 135.5 (C), 147.9 (C), 148.6 (C), 153.9 (C), 156.1 (CF_3, q, *J* 36), 157.3 (C=O) [missing (1 × C)]; *m*/*z* (FAB) 556 (MH, 21%), 404 (100), 294 (10), 154 (23), 136 (17).

Formation of the β-phenethylurea 28

A solution of FIQ2 **26** (90 mg, 0.20 mmol) and (−)-(*S*)-1-phenylethyl isocyanate (30 mm^3, 0.20 mmol) in dichloromethane (5 cm^3) was stirred for 2 h. The solvent was then evaporated. Chromatography (petrol–ethyl acetate 1 : 1) yielded the *title compound* as a gum and a mixture of two diastereoisomers (90 mg, 76%) (Found *m*/*z* (FAB): 607.263 (33%), $C_{37}H_{38}O_4N_2S$ requires: MH^+, 607.263); $\nu_{max}(CCl_4)/cm^{-1}$ 3404 (NH), 2935, 2839, 1636 (C=O), 1494, 1465, 1374, 1139, 1028; *m*/*z* (FAB) 607 (MH, 23%), 455 (33), 308 (30), 157 (39), 154 (28), 147 (27), 136 (30), 115 (48), 91 (100), 73 (84).

Regeneration of FIQ2 26 from β-phenethylurea 28

A solution of the β-phenethylurea **28**, (50 mg, 0.083 mmol) and sodium ethoxide (1.4 mg) in butanol (10 cm^3) was refluxed for 1.5 h. Upon cooling, saturated aqueous sodium hydrogen carbonate (1 cm^3) was added and the biphasic mixture was evaporated (10 mmHg then 0.5 mmHg). Saturated aqueous sodium hydrogen carbonate (1 cm^3) was added to the residue, which was extracted with ether (3 × 1 cm^3). The combined organic fractions were dried and evaporated to yield the target amine.

Enantiomerically enriched *S*-(−) FIQ2 26a

A solution of the imine **27** (240 mg, 0.54 mmol in dichloromethane (10 cm^3) was added to a stirred suspension of sodium tris(*N*-benzyloxycarbonyl-(*S*)-proline)borohydride (0.61 g, 0.79 mmol) in dichloromethane (10 cm^3) at −30 °C. After stirring for 12 h, 2 M hydrochloric acid (10 cm^3) was added and the mixture was stirred at 60 °C for 1 h. On cooling, the mixture was basified (2 M sodium hydroxide) and the layers were separated. The organic layer was washed with 2 M sodium hydroxide (3 × 10 cm^3), dried and evaporated. Purification by pTLC (ethanol–ethyl acetate 1 : 4) yielded the *title compound* as a light yellow oil (60 mg, 25%, 60% ee). The ^{1}H NMR spectrum matched that of (±)-**26**, though trace contamination by pTLC plate binder was detected. Selectivity (60% ee) was determined by conversion to the trifloroacetamide derivative and analysis by chiral HPLC (OD column, isopropyl alcohol–hexane 17 : 83, 18 min (80%), 20 min (20%)) and confirmed by NMR analysis of the derived urea **28a**. This derivative was formed by the method given above.

Column chromatography of this product increased the de to 85% by NMR: δ_H(500 MHz) 1.24 (3H, d, *J* 6.2, N-CHCH_3), 2.82–2.89 (1H, m, 8-H), 2.95–3.02 (2H, m, 8-H and 1′-CH), 3.07 (2H, t, *J* 7.5, 2″-H_2), 3.12 (1H, d, *J* 7.9, 13.5, 1′-CH), 3.29 (2H, t, *J* 7.5, 1″-H_2), 3.42–3.48 (1H, m, 7-H), 3.75 and 3.88 (6H, 2 × s, 2 × OCH_3), 3.89–3.99 (1H, m, 7-H), 4.05–4.13 (1H, br m, NH), 4.89 (1H, br m, N-CH), 5.12 (1H, br m, 5-H), 6.37 (1H, s, 3-H), 6.58 (1H, s, ArH), 6.66 (1H, d, *J* 8.8, ArH), 6.79 (1H, d, *J* 8.1, ArH), 7.10 (1H, s, ArH), 7.19 (1H, s, ArH), 7.20–7.26 (4H, m, ArH), 7.29–7.33 (4H, m, ArH), 7.39 (2H, dd, *J* 1.0, 8.1, ArH) [peaks corresponding to the minor diastereoisomer were also observed]; δ_C(125 MHz) 22.4 (CH_3), 28.8 (CH_2), 28.9 (CH_2), 31.8 (CH_2), 39.2 (br, CH_2), 43.6 (CH_2), 49.8 (CH), 55.9 and 56.0 (2 × OCH_3), 58.8 (CH), 102.9 (CH), 110.2 (CH), 111.4 (CH), 112.5 (CH), 119.2 (CH), 121.8 (CH), 126.2 (2 × CH), 126.5 (CH), 127.0 (CH), 128.6 (2 × CH), 129.1 (2 × CH), 129.8 (2 × CH), 130.9 (C), 131.3 (C), 131.5 (C), 135.6 (C), 144.5 (C), 147.9 (C), 149.0 (C), 153.9 (C), 157.0 (C), 157.1 (C) [missing (1 × C) possibly broadened C=O signal not detected].

The urea cleavage procedure was repeated using diastereoisomerically enriched sample **28a** (50 mg, 0.08 mmol). Purification was achieved using preparative TLC (ethyl acetate–methanol 4 : 1) to give the desired product *S*-(−) FIQ2 **26a** (approximately 15 mg, 40%) *ca.* 85% ee. Trace quantities of binder material were detected in the ^{1}H NMR spectrum (0.97 (t), 1.47 (sex), 1.72 (pent), 4.3 (t), 7.53 (dd), 7.72 (dd); $[\alpha_D]_{25}$ −14.2 (*c* 1.2 in $CHCl_3$) was measured but has only qualitative value in view of the unquantified impurity.

Enantiomerically enriched *S*-(−) FIQ2 26b

The previous procedure was repeated using sodium tris(*N*-benzyloxycarbonyl-(*R*)-proline)borohydride. The reaction gave identical selectivity but in favour of the opposite enantiomer (65 mg 27%, 60% ee). The ^{1}H NMR spectrum matched that of (±)-**26**, though trace contamination by pTLC plate binder was detected. The enantiomeric excess was determined by formation of the urea **28b** formed as above. Column chromatography of this product increased the de to 82% by NMR: δ_H(500 MHz) 1.43 (3H, d, *J* 6.8, N-CHCH_3), 2.85–2.91 (1H, m, 8-H), 2.95–3.02 (2H, m, 8-H and 1′-CH), 3.06 (2H, t, *J* 7.5, 2″-H_2), 3.14 (1H, d, *J* 6.9, 13.3, 1′-CH), 3.28 (2H, t, *J* 7.5, 1″-H_2), 3.47–3.53 (1H, m, 7-H), 3.68 (3H, s, OCH_3), 3.71–3.79 (1H, m, 7-H), 3.82 (3H, s, OCH_3), 4.40 (1H, br d, *J* 4.4, NH), 4.91 (1H, br m, N-CH), 5.30 (1H, br m, 5-H), 6.34 (1H, s, 3-H), 6.48 (1H, s, ArH), 6.58 (1H, d, *J* 7.4, ArH), 6.67 (1H, d, *J* 8.1, ArH), 6.98 (1H, s, ArH), 7.16 (2H, d, *J* 7.4, ArH), 7.19 (1H, s, ArH), 7.20–7.24 (2H, m, ArH), 7.27–7.35 (4H, m, ArH), 7.39 (2H, dd, *J* 1.0, 8.1, ArH) [peaks corresponding to the minor diastereoisomer were also observed]; δ_C(125 MHz) 23.0 (α‴-CH_3), 28.8 (CH_2), 28.8 (CH_2), 31.9 (CH_2), 39.8 (br, CH_2), 43.7 (CH_2), 50.2 (CH), 55.8 and 55.9 (2 × OCH_3), 58.6 (CH), 103.0 (CH), 110.0 (CH), 111.1 (CH), 112.5 (CH), 119.4 (CH), 121.7 (CH), 126.0 (2 × CH), 126.4 (CH), 127.0 (CH), 128.6 (2 × CH), 129.1 (2 × CH), 129.8 (2 × CH), 130.8 (C), 131.3 (C), 131.5 (C), 135.6 (C), 144.6 (C), 147.9 (C), 148.7 (C), 153.9 (C), 157.0 (C), 157.1 (C) [missing (1 × C) possibly broadened C=O signal not detected]. The urea cleavage procedure was repeated using the diastereoisomerically enriched samples **28b** (50 mg, 0.08 mmol). Purification was achieved using preparative TLC (ethyl acetate–methanol 4:1) to give the desired product *R*-(+)-FIQ2 **26b** (approximately 15 mg, 40%). Trace quantities of binder material were detected in the ^{1}H NMR spectrum (0.97 (t), 1.47 (sex), 1.72 (pent), 4.3 (t), 7.53 (dd), 7.72 (dd); $[a_D]_{25}$ +19.9 (*c* 1.2 in $CHCl_3$) was measured but has only qualitative value in view of the unquantified impurity.

Acknowledgements

We thank Professor P. Rich for stimulating discussions and EPSRC for a studentship to R. J. P.

References

1 (*a*) P. R. Rich, *Pestic. Sci.*, 1996, **47**, 287; (*b*) P. R. Rich, S. A. Madgwick and T. E. Wiggins, *Biochem. Soc. Trans.*, 1994, **22**, 217; (*c*) P. R. Rich, S. A. Madgwick and D. A. Moss, *Biochem. Biophys. Acta*, 1991, **1058**, 312; (*d*) P. R. Rich, *Biochem. Biophys. Acta*, 1984, **768**, 53.

2 (*a*) P. E. Lindhahl and K. E. Oberg, *Exp. Cell Res.*, 1961, **23**, 228; (*b*) L. Ernster, G. Dallner and G. F. Azzone, *J. Biol. Chem.*, 1963, **238**, 1124; (*c*) D. J. Horgan, T. P. Singer and J. E. Casida, *J. Biol. Chem.*, 1968, **243**, 834; (*d*) T. P. Singer, *Methods Enzymol.*, 1979, **55**, 454.

3 G. von Jagow and T. Ohnishi, *FEBS Lett.*, 1985, **185**, 311.

4 E. C. Slater, *Biochim. Biophys. Acta*, 1973, **301**, 129.

5 C. Fedtke, *Biochemistry and Physiology of Herbicide Action*, Springer-Verlag, Berlin, 1992.

6 M. Ondarroa, S. A. Madgwick, T. E. Wiggins, D. A. Whiting and P. R. Rich, *Abstracts of the Eighth European Bioenergetics Conference*, Valencia, Spain, 1994, p. 59.

7 P. R. Rich, S. Madgwick, S. A. Brown, G. von Jagow and U. Brandt, *Photosynth. Res.*, 1992, **34**, 465.

8 P. C. Levett, D. A. Whiting, J. Cayley, G. S. Cockerill and J. B. Weston, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 505.

9 G. S. Cockerill, P. C. Levett and D. A. Whiting, *J. Chem. Soc.*, *Perkin Trans. 1*, 1995, 1103.

10 We thank Professor P. Rich and coworkers for their collaboration in collecting these data.

11 G. J. S. Doad, J. A. Barltrop, C. M. Petty and T. C. Owen, *Tetrahedron Lett.*, 1989, **30**, 1597.

12 K. Yamada, M. Takeda and T. Iwakuma, *J. Chem. Soc.*, *Perkin Trans. 1*, 1983, 265.

13 (*a*) B. Schönenberger, A. Brossi, C. George and J. L. Flippen-Anderson, *Helv. Chim. Acta*, 1986, **69**, 283; (*b*) B. Schönenberger and A. Brossi, *Helv. Chim. Acta*, 1986, **69**, 1486.

14 N. Brenans and S. Prost, *C. R. Hebd. Seances Acad. Sci.*, 1924, **178**, 1285.

Paper 9/03816G