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The synthesis of GW710936X to support the development of potent PPARγ agonists

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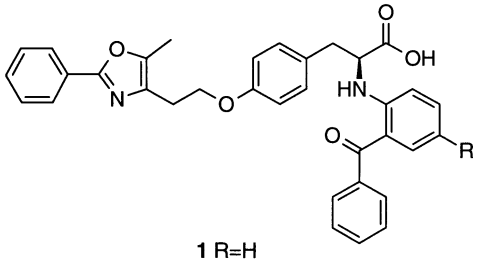
Abstract—(2*S*)-[(2-Benzoyl-4-hydroxy-phenyl)amino]-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propanoic acid has been synthesised from *N*-Cbz-L-tyrosine methyl ester utilising a copper(I) catalysed *N*-arylation as the key coupling step. The synthetic route was designed to be convergent and to facilitate ease of isolation of the unstable product that had proven to be unobtainable by concentration of extracts from biological assays.

1. Introduction

N-(2-Benzoylphenyl)-L-tyrosine derivatives form a novel and potent class of antihyperglycemics that were discovered and optimised from a L-tyrosine-derived screening hit using in vitro assays of peroxisome proliferator-activated receptor γ (PPARγ) activity.[1–3] In particular, compound **1** was shown to have antidiabetic activity when dosed orally to rodent models of Type 2 diabetes[1] (Fig. 1).

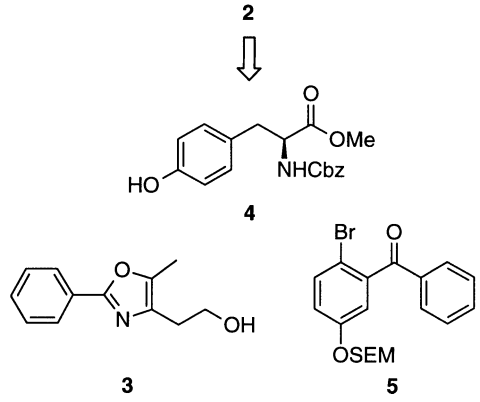
During the course of our effort towards developing molecules with a greater therapeutic efficacy in treating Type 2 diabetes, the synthesis of compound **2**, GW710936X, was required with the primary objectives of providing sufficient material to: (i) elucidate its PPARγ activity and (ii) to serve as an authentic standard for stability and disposition studies.



1 R=H
2 R=OH

Figure 1.

Inspection of the structure of **2** identified oxazole ethanol **3**,[4] tyrosine derivative **4** and unsymmetrical benzophenone **5** as suitable, readily available starting materials that would permit a convergent synthesis (Scheme 1). The key features of the plan involve: (i) a copper(I) catalysed *N*-arylation of the amino acid moiety to attach **5**, the lipophilic portion of the molecule and (ii) the final fluoride mediated deprotection of the phenol with a view towards avoiding any potential degradation problems.



Scheme 1. Synthetic plan for **2**.

2. Results and discussion

The synthesis commenced with the preparation of the unsymmetrical benzophenone **5**. Starting with 2-bromo-5-methoxy-benzoic acid methyl ester **6**, a two step procedure involving Weinreb amide formation followed by the addition of phenyl magnesium chloride was envisaged to afford **7**. However treatment of **6** with *N*,*O*-dimethylhydroxylamine hydrochloride and isopropyl magnesium chloride in

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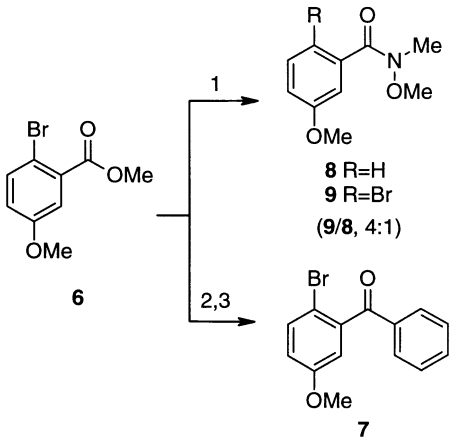
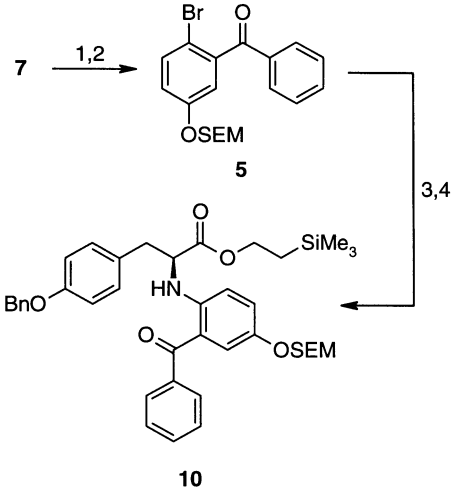


Scheme 2. *Reagents and conditions*. (1) MeNH(OMe)·HCl, ^{i}PrMgCl, THF, 1 h, −30°C (9/8, 4:1); (2) MeNH(OMe)·HCl, PhMgCl, THF, 1 h, −5°C; (3) PhMgCl, THF, 5 h, −10→25°C (89%, 2 steps).

THF at −30°C according to the procedure of Williams et al. afforded large amounts of the debrominated Weinreb amide **8** resulting from halogen metal exchange with the aryl bromide (Scheme 2).[5,6] This problem could be avoided by using phenyl magnesium chloride to act as the base in the formation of **9** which, following aqueous washing to remove the excess *N*,*O*-dimethylhydroxylamine, underwent a second reaction with the same Grignard reagent to afford the desired phenyl ketone **7** in 89% yield over two steps. It is worth noting that an attempted 'one pot' transformation delivered inferior yields of **7**—presumably due to the competitive addition of the reactive magnesium amide species to the Weinreb amide intermediate **8**.[5] This problem was exacerbated by the requirement of excess (1.5 equiv.) *N*,*O*-dimethylhydroxylamine hydrochloride in order to obtain complete conversion of the methyl ester into **7**.

With **7** in hand, it was deemed prudent to exchange the methyl ether for a more labile protecting group, which requires removal at the end of the synthesis. Thus treatment of **7** with boron trichloride in the presence of tetrabutylammonium iodide cleaved the methyl substituent to give the corresponding phenol (Scheme 3).[7] Subsequent reaction of the crude phenol with 2-(trimethylsilyl)ethoxymethylchloride (SEMCl) in the presence of diisopropylethylamine afforded **5** in 70% yield over two steps.[8] At this stage of the synthesis a trial copper(I) catalysed coupling reaction with a commercially available amino acid was attempted, according to the protocol of Ma et al.[9] Thus treatment of **5** and *O*-benzyl-L-tyrosine with copper(I) iodide and potassium carbonate in DMF at 90°C afforded after 3 days, the *N*-arylated amino acid in 50% yield after chromatography. For ease of characterisation the carboxylic acid was protected as the 2-(trimethylsilyl)ethanol (TMSE) ester **10** in 71% yield by treatment with TMSE, catalytic DMAP and dicyclohexylcarbodiimide (DCC).[10]

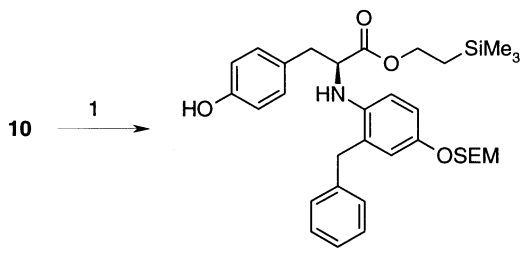


Scheme 3. *Reagents and conditions*. (1) BCl_3, $^{n}Bu_4NI$, CH_2Cl_2, 14 h, −78→25°C; (2) SEMCl, $^{i}Pr_2NEt$, CH_2Cl_2, 18 h, 25°C (70%, 2 steps); (3) *O*-benzyl-L-tyrosine, K_2CO_3, cat. CuI, DMF, 72 h, 90°C (50%); (4) DCC, DMAP, TMSE, EtOAc, 18 h, 25°C (71%).

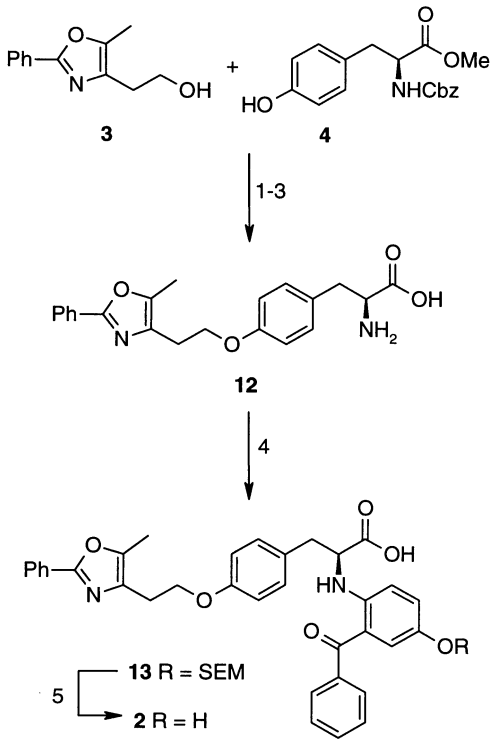
Following the preparation of **10**, which has the carboxylic acid protected and the two phenol moieties differentiated, an alternative route involving debenzylation, Mitsunobu coupling with oxazole ethanol **3** and then fluoride mediated deprotection to afford **2** was considered. However, initial attempts at the removal of the benzyl ether by hydrogenation using catalytic palladium on carbon failed due to competing exhaustive reduction of the ketone to afford **11** (Scheme 4). Thus this approach was abandoned in favour of pursuing a shorter, more convergent strategy.

With evidence that the *N*-arylation seemed feasible, the prior coupling of the oxazole ethanol **3** with the amino acid **4** was investigated. Commencing with *N*-Cbz-L-tyrosine methyl ester **4**, Mitsunobu reaction with **3** using diisopropylazodicarboxylate (DIAD) and triphenylphosphine in toluene at 45°C afforded the coupled product (Scheme 5).[11] Subsequent hydrogenation of the Cbz group using catalytic palladium on carbon followed by saponification of the methyl ester with aqueous sodium hydroxide afforded, after acidification, the amino acid derivative **12** in an unoptimised 55% yield over 3 steps.

The key coupling reaction proceeded by reaction of **12** and **5** using the conditions previously adopted, which, after 4 days, afforded *N*-arylated product **13** in a disappointing 38% yield after chromatography. The lower yield obtained on changing the amino acid component may be a result of the greatly reduced solubility of **12** as compared to *O*-benzyl-L-tyrosine. However, the reaction was deemed capable of generating sufficient material in order to serve the primary purpose of the synthesis. Initial attempts at removing the SEM group using mild conditions such as treatment with TBAF in THF at reflux proved unsuccessful.



Scheme 4. *Reagents and conditions*. (1) Pd/C (10%), EtOH, 25°C (65%).



Scheme 5. *Reagents and conditions*. (1) DIAD, **3**, PPh_3, **4**, toluene, 30 min, 45°C (68%); (2) Pd/C (20%), EtOH, 15 h, 25°C; (3) MeCN/NaOH (aq), 1 h, 50°C (84%, 2 steps); (4) K_2CO_3, cat. CuI, **5** DMF, 96 h, 90°C (38%); (5) TBAF·$3H_2O$, DMPU, 2 h, 110°C (68%).

However, a simple solvent change to *N*,*N*′-dimethylpropyleneurea (DMPU) saw a dramatic increase in rate with complete deprotection being observed within 2 h at 110°C. It is worth noting that DMPU served as an adequate replacement for the highly carcinogenic HMPA which is normally the solvent of choice for this transformation.[12] Isolation and purification by flash column chromatography afforded **2** (in 68% yield). The product was found to decompose rapidly in solution,[13] although storage under nitrogen at −20°C was sufficient to maintain purity, once concentration in vacuo had been achieved.

Disappointingly, closer analysis of the isolated product **2** using chiral HPLC[14] revealed that partial epimerisation of the α-amino acid carbon had occurred to afford a 2.3:1 ratio of enantiomers. The cause of this erosion of e.e. is currently unknown, although Ma et al. carried out a thorough analysis of the *N*-arylated products afforded by their copper iodide promoted coupling reaction, demonstrating no loss of stereochemical integrity.[9] This allows speculation that the final TBAF/DMPU mediated deprotection may be responsible for the observed results. Fortunately, the use of preparative chiral HPLC allowed the isolation of a sufficient quantity of material to support the subsequent biological studies. As a result no further synthetic investigations have been undertaken to establish the cause of the epimerisation.

3. Conclusions

In summary, a short and convergent synthesis of **2** has been accomplished starting from a homochiral L-tyrosine derivative, using a copper(I) catalysed *N*-arylation as the key bond forming reaction. Despite the low yielding coupling step, the synthesis has permitted the generation and isolation of sufficient amounts of an unstable compound in order to meet the requirements for further elucidation of its PPARγ activity.

4. General experimental section

Proton and carbon NMR were recorded on a Bruker DPX400 spectrometer. Infrared spectra were recorded on a Nicolet 20SXC FTIR spectrophotometer and mass spectra run on Micromass Q-TOF, hybrid quadropole time-of-flight MS −/+ve ion electrospray instrument. Reagents and solvents were obtained from commercial suppliers and used as supplied.

5. Experimental

5.1. Data for compounds

5.1.1. (2-Bromo-5-methoxy-phenyl)-phenyl-methanone 7. Phenyl magnesium chloride (2 M in THF, 220 mL, 0.44 mol) was added dropwise to a slurry of the methyl ester **6** (35.5 g, 0.15 mol) and *N*,*O*-dimethylhydroxylamine hydrochloride (21.5 g, 0.22 mol) in THF (300 mL) at −10°C. After stirring for 1 h at −5°C, the reaction was quenched by the addition of 20% ammonium chloride solution (200 mL). The organic phase was separated and washed with water (200 mL), brine (200 mL), dried (Na_2SO_4) and concentrated in vacuo to afford the Weinreb amide **9** (39.2 g, 0.14 mol) as a solid which was used without further purification. *m*/*z* ($C_{10}H_{13}BrNO_3$) $[MH]^+$ 274 and 276 (100%).

Phenyl magnesium chloride (2 M in THF, 300 mL, 0.60 mol) was added dropwise to a solution of the crude Weinreb amide **9** (39.2 g, 0.14 mol) in THF (250 mL) at −10°C. The resulting solution was warmed to room temperature, stirred for 5 h, then quenched by the dropwise addition of aqueous hydrochloric acid (1N, 550 mL), taking care to keep the reaction temperature below 35°C. After cooling to room temperature, the organic layer was separated, dried (Na_2SO_4) and concentrated in vacuo to afford the phenyl ketone **7** (37.4 g, 89%) as a pale brown oil which was used without further purification. R_f 0.37 (*iso*-hexane/diethyl ether, 8:1); ^1H NMR ($CDCl_3$, 250 MHz) δ_H 7.85–7.81 (2H, m, Ar), 7.63–7.56 (1H, m, Ar), 7.52–7.43 (3H, m, Ar), 6.92–6.86 (2H, m, Ar) and 3.79 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ_C 196.0 (*C*=O), 159.2 (*ipso C*–O), 141.8, 136.3, 134.4, 134.2, 130.7, 129.1, 117.8, 114.6, 110.1 (9×Ar) and 56.1 (OCH_3); ν_{max} (film, cm^{-1}) 1673 (C=O), 1594, 1570, 1468 and 1450 (Ar); *m*/*z* 291.0009, $C_{14}H_{12}{}^{79}BrO_2$ $[MH]^+$ requires 291.0021; *m*/*z* Low Res: 291 and 293 ($[MH]^+$, 100%).

5.1.2. (2-Bromo-5-(2-trimethylsilylethoxy)-methoxy-phenyl)phenylmethanone 5. Boron trichloride (1 M in dichloromethane, 100 mL, 100 mmol) was added dropwise over 15 min to a solution of phenyl ketone **7** (11.6 g,

40 mmol) and tetrabutylammonium iodide (35.4 g, 96 mmol) in dichloromethane (200 mL) at −78°C. After warming to room temperature, the reaction was stirred for 14 h, then ice/water (~200 mL) was added and the resulting mixture stirred vigorously for 1 h. Saturated sodium bicarbonate solution (200 mL) was then added, the aqueous phase separated and re-extracted with dichloromethane (2×200 mL). The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo to afford a pale brown oil (~11.0 g) which was used in the subsequent step without further purification.

SEMCl (7.1 mL, 40 mmol) was added dropwise to a solution of crude phenol (~40 mmol) and diisopropylethylamine (13.9 mL, 80 mmol) in dichloromethane (200 mL) at room temperature. After stirring for 18 h, saturated sodium bicarbonate solution (200 mL) was added and the mixture extracted with diethyl ether (2×200 mL). The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography eluting with *iso*-hexane/diethyl ether (8:1) afforded the SEM acetal **5** (11.3 g, 70%) as a pale brown oil. R_f 0.42 (*iso*-hexane/diethyl ether, 8:1); ^{1}H NMR ($CDCl_3$, 250 MHz) δ_H 7.86–7.83 (2H, m, Ar), 7.65–7.59 (1H, m, Ar), 7.55–7.45 (3H, m, Ar), 7.09–7.04 (2H, m, Ar), 5.22 (2H, s, OCH_2O), 3.75 (2H, t, J=8.0 Hz, CH_2CH_2O), 0.94 (2H, t, J=8.0 Hz, CH_2CH_2O) and 0.00 (9H, s, Si(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ_C 196.9 (*C*=O), 158.1 (*ipso C*–O), 142.9, 137.4, 135.4, 135.2, 131.7, 130.1, 120.6, 118.3, 112.2 (9×Ar), 94.5 (OCH_2O), 68.0 (CH_2CH_2O), 27.1 (CH_2CH_2O) and 0.00 (Si(CH_3)$_3$); ν_{max} (film, cm^{-1}) 1676 (C=O), 1595, 1567, 1467 and 1450 (Ar); *m/z* 407.0661, $C_{19}H_{24}{}^{79}BrO_3Si$ $[MH]^+$ requires 407.0678; *m/z* Low Res: 424 and 426 ($[MNH_4]^+$, 100%).

5.1.3. (2*S*)-[(2-Benzoyl-4-(2-trimethylsilylethoxy)methoxyphenyl)amino]-3-(4-benzyloxyphenyl) propionic acid 2-trimethylsilylethyl ester 10. DMF (4.5 mL) was added to a mixture of *O*-benzyl-L-tyrosine (0.67 g, 2.40 mmol), aryl halide **5** (1.00 g, 2.40 mmol), potassium carbonate (0.51 g, 3.70 mmol) and copper iodide (0.05 g, 0.24 mmol) under nitrogen. The reaction mixture was heated at 90°C for 72 h, then cooled to room temperature, diluted with ethyl acetate (50 mL) and water (30 mL) and acidified to pH 3 by the addition of 2 M aqueous hydrochloric acid. The aqueous layer was separated and extracted with ethyl acetate (2×20 mL), then the combined organic phase was washed with 10% lithium chloride solution (3×30 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography eluting with ethyl acetate/*iso*-hexane (1:3→1:1) along with ~0.1% acetic acid afforded arylamine (0.72 g, 50%) as a yellow oil.

DCC (0.24 g, 1.17 mmol) was added portionwise to a solution of carboxylic acid (0.71 g, 1.17 mmol), DMAP (15 mg, 0.12 mmol) and 2-trimethylsilylethanol (0.14 g, 1.17 mmol) in ethyl acetate (2.5 mL) at room temperature. After stirring for 18 h, the precipitate was removed by filtration and washed with ethyl acetate (30 mL). The organic phase was washed with 20% ammonium chloride solution (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography eluting with *iso*-hexane/ethyl acetate (10:1→8:1) afforded the fully protected adduct **10** (0.58 g, 71%) as a bright yellow oil. R_f 0.30 (*iso*-hexane/ethyl acetate (8:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.55 (1H, d, J=7.5 Hz, N*H*), 7.65 (2H, dd, J=8.5, 1.5 Hz, Ar), 7.54–7.33 (8H, m, Ar), 7.28–7.22 (3H, m, Ar), 7.16 (1H, dd, J=9.0, 3.0 Hz, Ar), 6.93 (2H, m, Ar), 6.64 (1H, d, J=9.0 Hz, Ar), 5.04 (4H, s, ArCH_2O and OCH_2OAr), 4.33 (1H, q, J=7.0 Hz, C*H*N), 4.26–4.14 (2H, m, $CO_2CH_2CH_2Si$), 3.70 (2H, t, J=8.0 Hz, CH_2OCH_2), 3.22 (1H, dd, J=13.5, 6.0 Hz, C*H*HCHN), 3.11 (1H, dd, J=13.5, 7.5 Hz, CH*H*CHN), 0.99–0.87 (4H, m, 2×SiCH_2), 0.04 (9H, s, Si(CH_3)$_3$) and 0.00 (9H, s, Si(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 200.0 (*C*=O), 174.4 (O*C*=O), 159.3, 148.2, 147.5, 141.5, 138.5, 132.5, 131.8, 130.6, 130.4, 130.0, 129.5, 129.4, 128.9, 126.6, 124.6, 120.0, 116.3, 114.5 (18×Ar), 95.7 (OCH_2OAr), 71.4 (CO_2CH_2), 67.3 (CH_2OCH_2O), 65.0 (ArCH_2O), 60.0 (*C*HN), 39.6 (CH_2CHN), 19.5 (SiCH_2), 18.8 (SiCH_2), 0.00 (Si(CH_3)$_3$) and −0.08 (Si(CH_3)$_3$); ν_{max} (film, cm^{-1}) 3321 (N–H), 1739 (OC=O), 1632 (C=O), 1611, 1577, 1511 and 1453 (Ar); *m/z* 698.3315 $C_{40}H_{52}NO_6Si_2$ requires $[MH]^+$ 698.3333.

5.1.4. (2*S*)-[(2-Benzoyl-4-(2-trimethylsilylethoxy)methoxyphenyl)amino]-3-(4-hydroxyphenyl) propionic acid 2-trimethylsilylethyl ester 11. A solution of **10** (83 mg, 0.12 mmol) in ethanol (1 mL) was added to a suspension of 5% palladium on carbon (moist, 10 mg) in ethanol (2 mL) under an atmosphere of hydrogen. After stirring for 3 h the catalyst was removed by filtration through Celite® and the filtrate was concentrated in vacuo. Purification by flash column chromatography eluting with *iso*-hexane/ethyl acetate (4:1) afforded phenol **11** (46 mg, 65%) as an oil. R_f 0.14 (*iso*-hexane/ethyl acetate (8:1); ^{1}H NMR ($CDCl_3$, 250 MHz) δ_H 7.29–7.09 (5H, m, Ar), 6.87–6.81 (3H, m, Ar), 6.75 (1H, d, J=3.0 Hz, Ar), 6.62 (2H, d, J=8.5 Hz, Ar), 6.47 (1H, d, J=8.5 Hz, Ar), 5.16 (1H, br s, N*H*), 5.09 (2H, s, OCH_2OAr), 4.18–3.98 (3H, m, C*H*N and $CO_2CH_2CH_2Si$), 3.80 (2H, s, ArCH_2Ar), 3.72 (2H, t, J=8.5 Hz, CH_2OCH_2), 2.92–2.87 (2H, m, CH_2CHN), 0.96–0.81 (4H, m, 2×SiCH_2), 0.00 (9H, s, Si(CH_3)$_3$) and −0.02 (9H, s, Si(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ_C 175.2 (O*C*=O), 155.9, 151.3, 141.1, 140.5, 131.8, 130.1, 130.0, 129.8, 128.7, 127.7, 121.5, 116.8, 116.7, 113.8, (14×Ar), 95.3 (OCH_2OAr), 67.2 (CH_2OCH_2O), 64.8 (CO_2CH_2), 59.9 (*C*HN), 39.2 (CH_2CHN), 27.1 (ArCH_2Ar), 19.4 (SiCH_2), 18.7 (SiCH_2), 0.00 (Si(CH_3)$_3$) and −0.15 (Si(CH_3)$_3$); *m/z* ($C_{33}H_{48}NO_5Si_2$) $[MH]^+$ 594 (100%).

5.1.5. (2*S*)-2-Amino-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)-ethoxy]phenyl}propionic acid 12. A solution of DIAD (3.30 mL, 16.8 mmol) in toluene (3 mL) was added dropwise to a solution of *N*-Cbz-L-tyrosine methyl ester **4** (4.44 g, 13.4 mmol), oxazole ethanol **3** (3.00 g, 14.8 mmol) and triphenylphosphine (4.41 g, 16.8 mmol) in toluene (30 mL). After complete addition the reaction was heated at 45°C for 30 min, then cooled to room temperature and concentrated in vacuo. Purification by flash column chromatography eluting with dichloromethane/methanol (98:2) afforded oxazole amino acid (4.70 g, 68%) as a foam. R_f 0.67 (dichloromethane/methanol, 95:5); *m/z* ($C_{30}H_{31}N_2O_6$) $[MH]^+$ 515 (100%).

A solution of oxazole amino acid (4.70 g, 9.14 mmol) in

ethanol (50 mL) was added to 5% palladium on carbon (1 g). The reaction was then placed under a hydrogen atmosphere and stirred for 15 h at room temperature. After purging the reaction vessel with nitrogen, the catalyst was removed by filtration through Celite® and washed with ethanol (100 mL). Concentration in vacuo afforded the crude amine as a gum. *m/z* ($C_{22}H_{25}N_2O_4$) $[MH]^+$ 381 (100%).

Aqueous sodium hydroxide (2.5 M, 15 mL) was added to solution of the crude amine in acetonitrile (15 mL) and the mixture heated at 50°C for 1 h. After cooling to 0°C, the solution was acidified to pH 8 by the dropwise addition of aqueous hydrochloric acid (2 M, ~20 mL). The precipitate was collected by filtration, washed with ice cold water then dried in a vacuum oven at 60°C for 16 h to afford oxazole amino acid **4** (2.80 g, 84%) as a white solid. ^{1}H NMR (D_2O/DCl, 400 MHz) δ_H 7.72 (2H, d, *J*=8.0 Hz, Ar), 7.47 (1H, t, *J*=7.5 Hz, Ar), 7.36 (2H, m, Ar), 6.95 (2H, d, *J*=8.5 Hz, Ar), 6.72 (2H, *J*=8.5 Hz, Ar), 4.07 (2H, t, *J*=6.0 Hz, CH_2OAr), 4.02 (1H, *J*=6.5 Hz, C*H*NH_2), 2.97–2.83 (4H, m, CH_2CH$_2$OAr and ArCH_2CHN) and 2.20 (3H, s, Me); ^{13}C NMR (D_2O/DCl, 400 MHz) δ_C 171.4 (*C*O_2H), 157.6, 135.0, 131.0, 130.0, 127.6, 126.0, 125.7, 120.3, 115.7 (9×Ar), 65.8 (*C*H_2OAr), 54.2 (*C*HN), 34.9 (*C*H_2CHN), 22.9 (*C*H_2CH$_2$OAr) and 9.6 (*C*H_3); ν_{max} (nujol mull, cm^{-1}) 2570 (NH_3^+), 1601 (CO_2^-), 1555, 1513, 1486 and 1462 (Ar); *m/z* 367.1651, $C_{21}H_{23}N_2O_4$ $[MH]^+$ requires 367.1658; *m/z* Low Res: 367 ($[MH]^+$, 100%).

5.1.6. (2*S*)-[(2-Benzoyl-4-(2-trimethylsilylethoxy)methoxyphenyl)amino]-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl} propionic acid 13. DMF (20 mL) was added to a mixture of oxazole amino acid **4** (2.50 g, 6.80 mmol), aryl halide **5** (2.77 g, 6.80 mmol), potassium carbonate (1.42 g, 10.3 mmol) and copper iodide (0.13 g, 0.68 mmol) under nitrogen. The reaction mixture was heated at 90°C for 94 h, then cooled to room temperature, diluted with ethyl acetate (30 mL) and water (15 mL) and acidified to pH 3 by the addition of 2 M aqueous hydrochloric acid. The aqueous layer was separated and extracted with ethyl acetate (2×20 mL), then the combined organic phase was washed with 10% lithium chloride solution (3×30 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography eluting with ethyl acetate/*iso*-hexane (1:3→1:1) along with ~0.1% acetic acid afforded arylamine **12** (1.80 g, 38%) as an orange foam. ^{1}H NMR (d_6-DMSO, 400 MHz) δ_H 13.02 (1H, br s, CO_2H), 8.35 (1H, d, *J*=8.0 Hz, N*H*), 8.00–7.98 (2H, m, Ar), 7.69–7.56 (8H, m, Ar), 7.28 (1H, dd, *J*=9.0, 3.0 Hz, Ar), 7.18 (2H, d, *J*=8.5 Hz, Ar), 7.14 (1H, d, *J*=3.0 Hz, Ar), 6.91–6.87 (3H, m, Ar), 5.08 (2H, s, OCH_2O), 4.60–4.55 (1H, m, C*H*N), 4.26 (2H, t, *J*=6.5 Hz, CH_2OAr), 3.67 (2H, t, *J*=8.0 Hz, SiCH$_2$CH_2), 3.21 (1H, dd, *J*=14.0, 5.5 Hz, ArC*H*H), 3.09 (1H, dd, *J*=14.0, 6.5 Hz, ArCH*H*), 2.96 (2H, t, *J*=6.5 Hz, CH_2CH$_2$OAr), 2.40 (3H, s, CH_3), 0.87 (2H, t, *J*=8.0 Hz, SiCH_2) and 0.00 (9H, s, Si(CH_3)$_3$); ^{13}C NMR (d_6-DMSO, 100 MHz) δ_C 199.0 (*C*=O), 174.7 (*C*O_2H), 159.8 (*ipso C*–O), 158.5 (*ipso C*–O), 147.4, 146.8, 146.7, 146.5, 140.9, 134.1, 132.7, 131.8, 131.4, 130.5, 130.2, 130.0, 129.6, 128.6, 126.9, 123.3, 119.0, 115.7, 115.2 (19×Ar), 95.0 (O*C*H_2O), 67.5 (*C*H_2OAr), 66.4 (SiCH$_2$*C*H_2), 57.9 (*C*HN), 37.9 (*C*H_2CHN), 27.0 (*C*H_2CH$_2$OAr), 18.8 (*C*H_2Si), 9.73 (CCH_3), 0.01 (Si(*C*H_3)$_3$); ν_{max} (nujol mull, cm^{-1}) 3253 (N–H), 2500 (br, CO_2H), 1725 (OC=O), 1631 (C=O), 1610, 1576, 1533, and 1510 (Ar); *m/z* 693.2994, $C_{40}H_{45}N_2O_7Si$ $[MH]^+$ requires 693.2996; *m/z* Low Res: 693 ($[MH]^+$, 90%), 322 (100%).

5.1.7. (2*S*)-[(2-Benzoyl-4-hydroxyphenyl)amino]-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl} propionic acid 2. TBAF·3H_2O (1.4 g, 3.6 mmol) was added in one portion to a solution of the SEM acetal **13** (1.0 g, 1.4 mmol) in DMPU (10 mL). After stirring for 2 h at 110°C, the reaction was cooled to room temperature, diluted with ethyl acetate (100 mL), washed with 10% citric acid solution (3×60 mL), water (3×60 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography eluting with ethyl acetate/*iso*-hexane (2:1, 2 column lengths) followed by acidification of the eluent [ethyl acetate/*iso*-hexane (2:1) along with 0.1% acetic acid] afforded the metabolite **2** (0.55 g, 68%) as an orange foam which was stored under nitrogen at −20°C. R_f 0.42 (ethyl acetate/*iso*-hexane, 2:1 plus 0.1% acetic acid); ^{1}H NMR (d_6-DMSO, 400 MHz) δ_H 12.84 (1H, br s, CO_2H), 8.82 (1H, s, O*H*), 8.11 (1H, br s, N*H*), 7.92 (2H, dd, *J*=8.0, 2.0 Hz, Ar), 7.66–7.49 (8H, m, Ar), 7.12 (2H, d, *J*=8.5 Hz, Ar), 6.98 (1H, dd, *J*=9.0, 2.5 Hz, Ar), 6.83–6.81 (3H, m, Ar), 6.74 (1H, d, *J*=9.0 Hz, Ar), 4.45–4.40 (1H, br s, C*H*N), 4.15 (2H, t, *J*=6.5 Hz, CH_2OAr), 3.12 (1H, dd, *J*=14.0, 5.5 Hz, ArC*H*H), 3.00 (1H, dd, *J*=14.0, 6.5 Hz, ArCH*H*), 2.90 (2H, t, *J*=6.5 Hz, CH_2CH$_2$OAr) and 2.33 (3H, s, CCH_3). ^{13}C NMR (d_6-DMSO, 100 MHz) δ_C 198.1 (*C*=O), 174.0 (*C*O_2H), 158.7, 157.4, 146.7 145.4, 143.8, 140.2, 133.0, 131.3, 130.7, 130.4, 129.4, 129.1, 128.9, 128.6, 127.5, 125.8, 124.2, 119.4, 118.4, 114.6, 114.3 (21×Ar), 66.4 (*C*H_2OAr), 57.1 (*C*HN), 37.0 (*C*H_2CHN), 25.9 (*C*H_2CH$_2$OAr) and 10.2 (*C*H_3); ν_{max} (film, cm^{-1}) 3330 (OH and NH), 1714 (OC=O), 1633 (C=O), 1611, 1552, and 1511 (Ar); *m/z* 563.2166, $C_{34}H_{31}N_2O_6$ $[MH]^+$ requires 563.2182; *m/z* Low Res: 563 ($[MH]^+$, 12%), 322 (100%).

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13. In an aqueous/organic solution **2** was found to decompose with a half-life of approximately 7 h. In dry acetonitrile at −20°C under nitrogen it appears stable for at least 2 days.
14. Chiral HPLC was carried out using a Chiralcel OD-R (0.46 cm i.d.×0.25 cm) eluting with acetonitrile/water (3:1, containing 1% formic acid).