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The Synthesis of Two Potent β-3 Adrenergic Receptor Agonists

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Abstract:

This contribution describes the initial preparation of two potent β-3 receptor agonists 1 and 2. Subsequent scale up of these two compounds was required for further evaluation and proceeded *via* a common key amine intermediate 24. Synthesis of this key intermediate by way of a Ritter reaction was a vital step in the sequence. Enantioselective Noyori hydrogenation reactions gave access to the chiral epoxides necessary to make the target compounds. Chemistry was developed for the selective dehalogenation of the 2-chloropyridyl group in the presence of a sensitive isoxazole unit to provide access to 1.

Introduction

The use of β-3 agonists for the treatment of a variety of diseases and disorders has been for targeted for many years. In particular, many of the larger pharmaceutical companies have progressed numerous agents into development for obesity and Type 2 diabetes.[1] More recently, groups have targeted β-3 agonists for urinary incontinence.[2] We now wish to report our work to prepare two potent β-3 agonists for the treatment of overactive bladder (OAB). The initial synthesis of these compounds and subsequent scale up is described in detail in the following sections.

Results and Discussion

First-Generation Synthesis. The initial synthesis of the 3-pyridyl derivative **1** is depicted in Scheme 1. This sequence involved preparation of the key intermediate **4** which provided the flexibility to vary both the amide and aryl groups of these molecules. This provided relatively easy access to a large range of analogues in the series enabling rapid compound selection. Tertiary amine **3**[3] was protected to give **4**, which was then coupled with ethyl acetoacetate in the presence of palladium acetate in toluene at 100 °C to give ester **5**. The reaction proceeded *via* the acetoacetate ester which underwent base mediated deacylation under the reaction conditions.[4] Significant amounts of the carboxylic acid derived from **5** and the methyl ketone, formed by hydrolysis and decarboxylation of the acetoacetate intermediate, necessitated purification of the crude product by column chromatography, which proved rather time-consuming and labour intensive on a moderate scale (>20 g).

Deprotection of **5** furnished **6** in quantitative yield, which on alkylation with **7**[5] gave a modest yield of the ester **8**. Attempted optimisation of the reaction conditions with a range of bases, solvents and reaction temperatures failed to improve the reaction profile and yield. Conversion of **8** to the lithium salt **10** was easily achieved by catalytic hydrodechlorination to **9** followed by ester hydrolysis with LiOH. Several coupling reagents were investigated for the crucial amide bond-forming step in this route, the best of which proved to be 1,1′-carbonyldiimidazole (CDI). Since CDI preferentially reacts with the pyridyl nitrogen, optimization of the reagent stoichiometries and reaction conditions was necessary. Further important factors to take into account were both the thermal instability[6] and poor nucleophilicity of 3-amino-5-methylisoxazole. Ultimately, activation of the carboxylic acid **10** with CDI and subsequent treatment with the aminoisoxazole in THF at 45 °C for 60 h provided the amide **11** in acceptable yield. Deprotection of the TBS group with HCl in dioxane produced the desired compound **1**.

A similar sequence as used to produce **1**, provided **2** (Scheme 2). Tosylation of the commercial chiral diol **12** gave the monotosyl compound **13** (with the mass balance composed of starting material and bis-tosylate), which was elaborated to the target compound as depicted in Scheme 2.

Second-Generation Synthesis

Large quantities of both **1** and **2** were required for further studies. The initial priority was to modify the route to enable it to deliver 30 g of each of the target compounds **1** and **2** in the minimal amount of time, hence the route detailed in Scheme 3 was developed. This route is more convergent than the initial synthesis, utilises a late-stage common intermediate, reduces the number of steps and makes use of cheaper, readily available starting materials. This sequence was very high yielding but

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(1) (a) Dow, R. L. *Expert Opin Invest. Drugs* **1997**, 1354. (b) Weber, A. E. *Annu. Rep. Med. Chem.* **1998**, *33*, 193. (c) Lafontaine, J. A.; Day, R. F.; Dibrino, J.; Hadcock, J. R.; Hargrove, D. M.; Linhares, M.; Martin, K. A.; Maurer, T. S.; Nardone, N. A.; Tess, D. A.; DaSilva-Jardine, P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5245.

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(4) Zeevaart, J. G.; Parkinson, C. J.; De Koning, C. B. *Tetrahedron Lett.* **2004**, *45*, 4261.

(5) Dow, R. L.; Paight Jr, E. S. EP 1236723, 2002.

(6) DSC analysis gives an onset temperature of 131°C for this material, and thus, any reaction using it would have to be kept significantly under this temperature.

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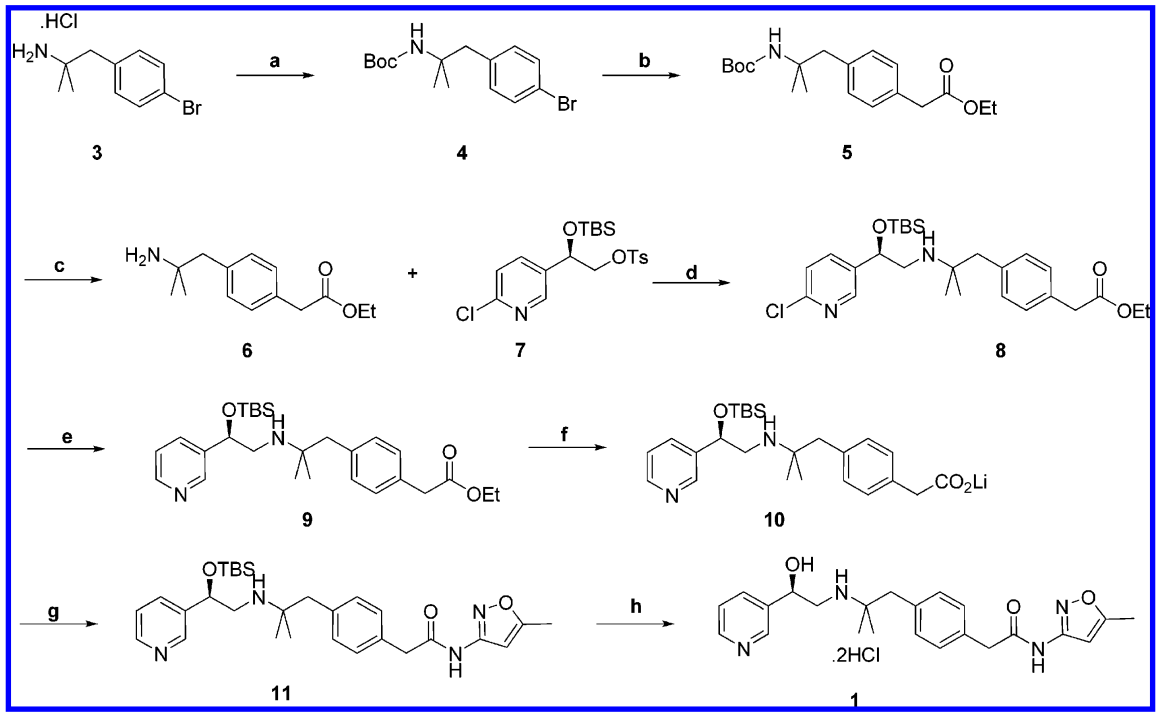
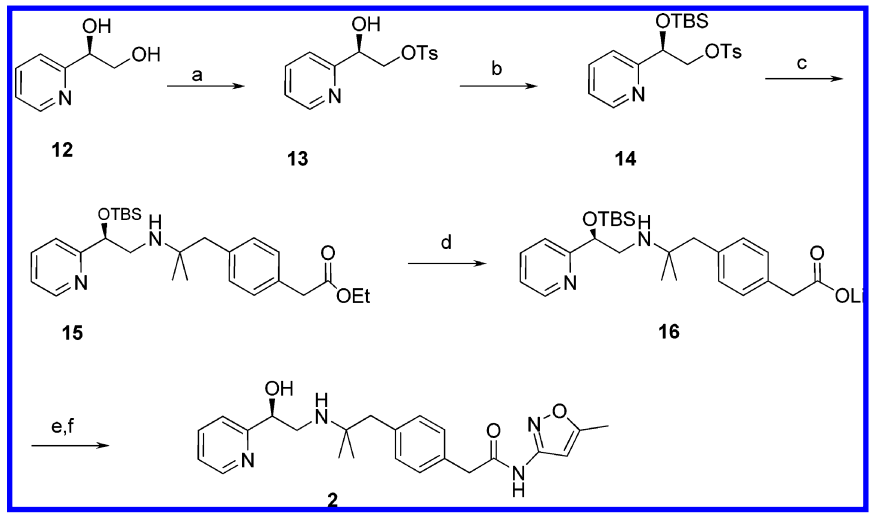
Scheme 1. **Discovery synthesis of the 3-pyridyl isomer 1**[a]



[a] Reagents and conditions: (a) TEA, $(BOC)_2O$, 2-MeTHF, rt, 91%. (b) ethylacetoacetate, K_3PO_4, $Pd(OAc)_2$, 2-(di-*tert*-butylphosphino)biphenyl, PhMe, 100 °C, 65%. (c) 4 M HCl/dioxane, EtOH, rt, 10% aq K_2CO_3, 100%. (d) **7**, K_2CO_3, KI, EtCN, 110 °C, 32%. (e) NaOAc, 5% Pd/C, EtOH, 40 psi, 40 °C, 74%. (f) 1 M LiOH aq, THF/EtOH, rt, 100%. (g) 4 M HCl/dioxane, THF, CDI, 3-amino-5-methylisoxazole, 45 °C, 63%. (h) 4 M HCl/dioxane, dioxane, rt, 87%.

Scheme 2. **Discovery synthesis of the 2-pyridyl isomer 2**[a]



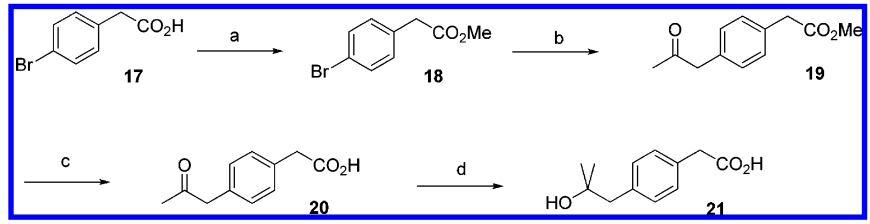
[a] Reagents and conditions: (a) TEA, TsCl, DCM, rt, 47%. (b) TBS-Cl, imidazole, DMF, 99%. (c) **6**, KI, K_2CO_3, EtCN, 110 °C, 47%. (d) LiOH, H_2O, THF/EtOH (1:1), rt, 72 h., 96%. (e) 4 M HCl/dioxane (1 equiv), 3-amino-5-methylisoxazole, DIPEA, HBTU, DMF, rt. (f) TBAF, THF, rt, 25% overall for (e) and (f).

relied on tin reagents in the second step with the associated difficulties of handling, cleaning and disposal of such reagents. For later campaigns, the synthesis of **21** was outsourced to an external vendor who controlled residual tin to an acceptable level (>50 ppb by ICPMS) by use of chromatography. The synthesis involved the Stille coupling of isopropenyl acetate with **18** to provide the keto-ester, **19**. Treatment of the acid **20** (derived from **19**) with excess methyl Grignard affords **21** in high yield.

Coupling of acid **21** with commercially available 3-amino-5-methylisoxazole was achieved using CDI to provide **22**, the substrate for a Ritter reaction (Scheme 4). An article in the literature[7] discusses the thermal stability of this isoxazole as a function of its purity. A thermal explosion and drum failure was attributed to low purity (96%) 3-amino-5-methylisoxazole (contaminated with 5-amino-3-methylisoxazole). The article presents ARC testing data of several batches of varying purity and demonstrates that the isomer 3-amino-5-methylisoxazole is the root cause of the instability. The material sourced by us had a minimum specification of 98% which has a much greater stability as demonstrated in the paper.

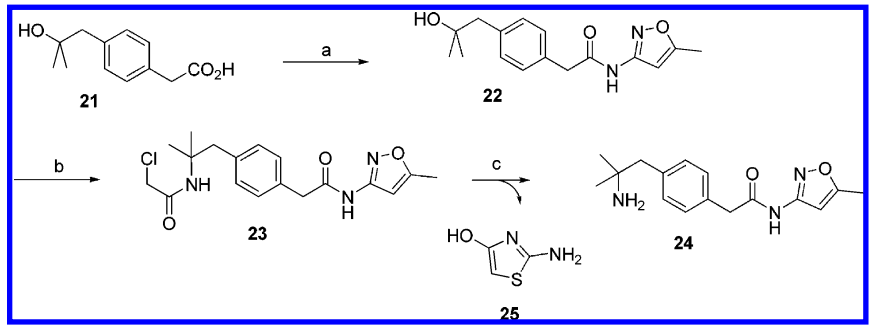
(7) Cardillo, P., *J. Loss Prev. Process Ind.* **1988**, *1*, 46.

Scheme 3. **Initial preparation of the tertiary alcohol 21 via organotin reagents**[a]



[a] Reagents and conditions: (a) AcCl, MeOH, rt, 16 h, 100%. (b) $(Bu)_3SnOMe$, isoprenyl acetate, $Pd(OAc)_2$, $(o\text{-tolyl})_3P$, PhMe, 100 °C, 98%. (c) LiOH (2M), THF, 0 °C, 89%. (d) MeMgBr, Et_2O, THF, rt, 73%.

Scheme 4. **Preparation of the key amine intermediate 24**[a]



[a] Reagents and conditions: (a) 3-Amino-5-methylisoxazole, EtOAc, CDI, 50−55 °C, 80%. (b) $ClCH_2CN$, TFA, 50 °C, 83%. (c) Thiourea, AcOH, MeOH, 60 °C, 81%.

Initially, as speed was one of the highest priorities, little optimisation was performed, and the Ritter step was performed in a 2:1 mixture of TFA: chloroacetonitrile (25 and 12 mol equiv respectively) as solvent, providing **23** in high yield. Deprotection of the chloracetamide, to liberate the free amine, was achieved using thiourea. A protracted workup and a requirement for reverse phase column chromatography, to remove byproduct **25**, were tolerated at this scale (300 g). This key amine fragment, **24**, is common to both targets reducing the amount of effort required to provide the structurally similar molecules.

With delivery of amine **24** achieved, the route was re-evaluated for the feasibility of preparing larger amounts of material (up to 2 kg).

The coupling between 3-amino-5-methylisoxazole and **21** using CDI was investigated, Scheme 4. DMAP catalysis (0.1 mol %) allowed for the reaction to proceed at room temperature; however if the reaction was performed at 50 °C it went to completion in the absence of nucleophilic catalysis. It was found that the charge of CDI had to be carefully monitored as excess reagent resulted in formation of the symmetrical aminoisoxazole-derived urea, which was difficult to purge. Formation of the imidazolide is easily followed by in situ IR and the potency of the CDI can be assessed by use of ^1H NMR. After the reaction and work up, a solvent swap from EtOAc to water results in product precipitation and allows for its collection by filtration.

For the Ritter reaction (**22** to **23**), the amount of chloracetonitrile and TFA were greatly reduced to 1.1 and 1.5 equiv respectively, without affecting the reaction rate or profile. Reducing the amount of chloracetonitrile had an added benefit of providing an easier crystallisation process. The reaction was rapid at 50 °C (2.5 h), but was sensitive to water content, so a 'not more than' 1% water specification on the input material was set. Any water above this level had a detrimental effect on the rate of reaction, slowing reaction completion down to 24 h. Post reaction, a distill-and-replace operation into *s*-butanol gave **23** as a readily isolated, crystalline solid.

A major goal for the route development work was to develop an effective purge of the stoichiometric thiohydantoin byproduct **25**, formed as a result of using thiourea to deprotect **23**.[8] For earlier batches, reverse-phase chromatography was required to remove this byproduct, but a more process-friendly method was desired. Conversion of **23** to **24** is effected by refluxing in an acetic acid/ethanol solvent mixture. Precipitation of **25** was observed on cooling the refluxed reaction mixture to ambient, but it was found that cocrystallisation with the product had occurred, and a selective purge of the byproduct was therefore poor. Switching the alcohol cosolvent to methanol resulted in the selective precipitation of **25** on cooling. Residual **25** was removed by basic extraction, and to this end, a distill-and-replace operation into 2-MeTHF was required. A specification of less than 500 ppm was set for **25**, but we routinely produce material using this method that has levels below the limit of detection.

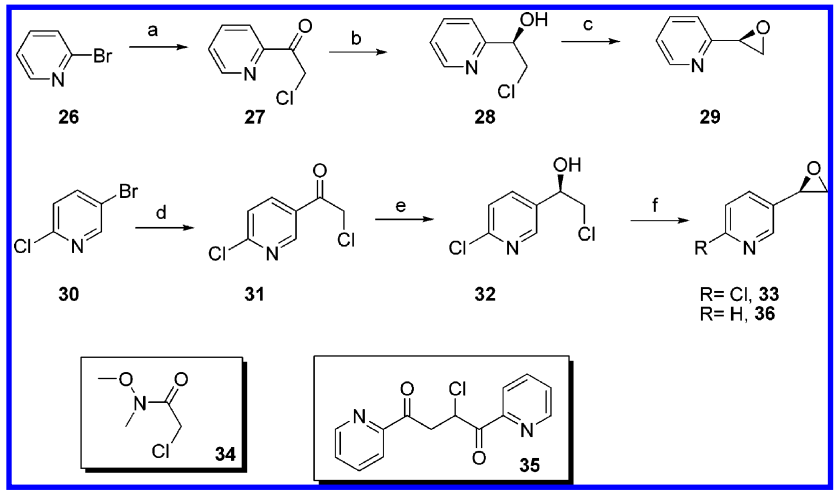
These fairly simple process changes allowed for an event-free synthesis of kilogram quantities of amine **24**.

Preparation of Chiral Pyridyl Epoxides. The routes chosen for the chiral pyridyl fragments (**29** and **33**) were based on literature precedent[9] (Scheme 5). The key issues in these sequences were the cryogenic temperatures required for the preparation of ketone **27** and the relatively low ee (74%) of the chlorohydrin **32**. In order to achieve material of suitable

(8) (a) Sanderson, D. M.; Earnshaw, C. G. *Hum. Exp. Toxicol.* **1991**, *10*, 261. (b) Ridings, J. E.; Barratt, M. D.; Cary, R.; Earnshaw, C. G.; Eggington, C. E.; Ellis, M. K.; Judson, P. N.; Langowski, J. J.; Marchant, C. A.; Payne, M. P.; Watson, W. P.; Yih, T. D. *Toxicology* **1996**, *106*, 267.

(9) Tanis, S. P.; Evans, B. R.; Nieman, J. A.; Parker, T. T.; Taylor, W. D.; Heasley, S. E.; Herrinton, P. M.; Perrault, W. R.; Hohler, R. A.; Dolak, L. A.; Hester, M. R.; Seest, E. P. *Tetrahedron Asymmetry* **2006**, *17*, 2154.

Scheme 5. **Preparation of the 2- and 3-pyridyl chiral epoxides (29 and 33)**[a]



[a] Reagents and conditions: (a) *i*-PrMgCl, THF, **26**, −25 °C, **34**, rt, THF, 73%. (b) $(RuCl_2(Cymene)_2)_2$, DMF, HCO_2H, TEA, rt, 76%; 96.4% ee. (c) 4 M NaOH, 2-MeTHF, 40 min, rt, 100%. (d) TBME, BuLi, −75 °C, **34**, then −5 °C, 100%. (e) $(RuCl_2(Cymene)_2)_2$, DMF, HCO_2H, TEA, TBME, rt, 42%, 99.6% ee. (f) NaOH, 2-MeTHF, 10 min, 92%.

quality, purification of both chlorohydrins **28** and **32** by normal phase chromatography, was required. In addition, a chiral chromatography step was required to enhance the ee of **32**.

Grignard formation with bromopyridine **26** is facile, and an instantaneous reaction with the commercially available Weinreb amide **34** occurs. It was essential to quench the reaction at 0 °C with water/acetic acid, as a simple water quench results in significant quantities of dimer **35** being formed. The material for this reaction was of sufficient purity to be telescoped directly to the asymmetric reduction as a TBME extract without impacting the yield and stereoselectivity.

For the Noyori reductions in Scheme 5, it was determined that degassing and anhydrous conditions were not required and use of standard grade solvents was adequate, but the reaction was run under an inert atmosphere as standard. DMF is necessary for formation of the active catalyst; however, it was found to be beneficial to keep the quantities of DMF used to a minimum (∼0.5 L/kg ketone). Any DMF carried into the subsequent step results in ring-opening of the epoxide by dimethylamine. The product of this reaction, a dark, malodorous oil, was on average 85−90% pure. Use of this crude material in subsequent steps results in very poor yields. Despite significant efforts to find an alternative, the only purification method was chromatography.

Compound **30** underwent selective lithium−bromine exchange with butyllithium at −75 °C as a suspension in TBME.[10] Lithium−halogen exchange in alternative solvents, notably THF, results in nonselective lithiation. The use of the equivalent Grignard reagent resulted in poor conversion and the generation of several unidentified impurities. Subsequent reaction of the aryllithium with Weinreb amide **34** furnished the product in quantitative yields. The reaction was warmed to 0 °C, and a quench with aqueous acetic acid reduced the amount of 'dimerization' impurities as seen during the quench in the synthesis of the 2-pyridyl ketone **27**. Acetic acid and bromobutane were removed from the crude product by azeotropic distillation with toluene. Compound **31** was then reduced to the chiral alcohol, **32**, albeit in disappointing ee (74%) *via* Noyori hydrogenation. Alternative reductions including homogeneous asymmetric hydrogenations, CBS-type reductions, and DIP-Cl were attempted but without any improvements.[11,12] For these campaigns (200 g target compound), material was once again purified by use of chromatography, as no suitable alternative was found.

Finally, to complete the headgroup synthesis, a very fast, high-yielding conversion of halohydrins **28** and **32** to the corresponding epoxides **29** and **33** was achieved under modified Schotten−Bauman conditions.

Conversion to Final Products. In order to complete the synthesis, the coupling of the epoxide headgroups (**29** and **33**) with the amine fragment **24** was required.

In the case of **2** (Scheme 6), insolubility of the product resulted in the formation of a thick slurry that was difficult to stir. The reaction rate is dependent on the solvent used, with water proving to be the most advantageous. Trials with other polar solvents such as DMF, DMSO, or aqueous alcoholic solvents did not offer improved results. The reaction requires a 1.3 fold excess of the epoxide **29** to achieve full consumption of **24**.

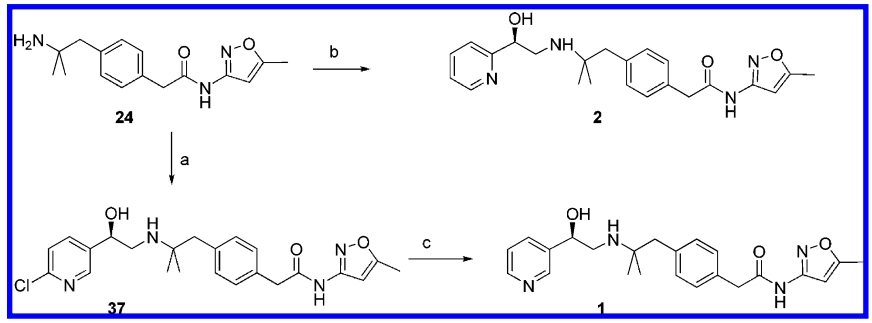
The highly insoluble nature of the product and the uncontrolled manner by which it precipitates from the reaction mixture led to difficulties in isolation of the product by filtration (long

(10) Scott, R. W.; Fox, D. E.; Wong, J. W.; Burns, M. P. *Org. Process Res. Dev.* **2004**, *8*, 587.

(11) Some of the poor selectivity in these alternative reductions can be attributed to the reducing agent used. Depending on the supplier, borane−tetrahydrofuran complex is stabilised by different additives. Thus, for example, Aldrich adds <0.005 M $NaBH_4$ as stabiliser. Experiments have shown that even small amounts of the $NaBH_4$ have a dramatic impact on the selectivity of the asymmetric reduction with (*R*)-Me-CBS-oxazaborolidine, and hence, when using stabilised batches from Aldrich, the proportion of unwanted *S*-enantiomer was 17 to 20%. Under the same conditions using BH_3/THF from Fluka (contains no $NaBH_4$ stabiliser) only 3 to 4% of the unwanted *S*-enantiomer was obtained; however, the yield was low (∼60%).

(12) (a) Nettles, S. M.; Matos, K.; Burkhardt, E. R.; Rouda, D. R.; Corella, J. A. *J. Org. Chem.* **2002**, *67*, 2970. (b) Fu, X.; McAllister, T. L.; Thiruvengadam, T. K.; Tann, C. H.; Su, D. *Tetrahedron Lett.* **2003**, *44*, 801. (c) Duquette, J.; Zhang, M.; Zhu, L.; Reeves, R. S. *Org. Process Res. Dev.* **2003**, *7*, 285.

Scheme 6. **Conversion to final products**[a]



[a] Reagents and conditions: (a) **33**, MeOH, 60 °C, 48 h, 86%. (b) **29**, H_2O, 70 °C, 48%. (c) Zn, AcOH/H_2O/MeOH 10:10:1, rt, 6 h, 93%.

Table 1. **Extract of crystallisation screen for the final purification of 2**

solvent	anti solvent	ratio	**2** (%)	**24** (%)	other impurities	recovery (%)
	Crude API spec.		81.5	6.1	12.3 (multiple peaks 1−2%)	
DMF	water	19:1	95.9	2	2.1	70
DMSO	EtOAc	19:1	98.5	0.5	1	70
DMSO	water	3:1	98.4	0.5	1.1	85

filtration times), as well as difficulties in achieving the high purity required for the final product and a consistent physical form. It was found that recrystallisation from DMSO/water (3:1) gave a good impurity purge, balanced by good recovery of material (see Table 1) with an increase of particle size made possible by temperature cycling.

The final isolation of **2** on scale was achieved by extraction of the aqueous slurry with warm (40 °C) ethyl acetate/methanol, which on concentration to dryness afforded a pale-brown solid. This avoided the very long filtration times that were expected following lab trials of directly filtering the aqueous reaction. The material was recrystallised from DMSO/water (3:1), and the resulting white solid was collected by filtration and dried under vacuum.

Due to the increased lipophilicity provided by the chlorine atom of epoxide **33** aiding its solubility, the coupling reaction between this fragment and **24** could be effected in methanol (Scheme 6). The reaction, carried out at reflux, was complete in 48 h, and on cooling, the product crystallised from the reaction solution and was collected by filtration, providing very pure product.. It is during this reaction that the role of the 2-Cl substituent on the pyridine unit becomes clear. In order for the reaction to occur, elevated temperatures are requiredn and the nonfunctionalised pyridine **36** (Scheme 5) shows significant instability at temperatures above 50 °C. In essence, the Cl-atom stabilises the epoxide by removing electron density from the pyridine ring. Thermal hazard screening of the 2-pyridyl epoxide **29** indicated that the compound had a much higher exotherm onset temperature than **36** and hence was much more stable in the alkylation reaction with **24**.

To access the final compound **1** it was necessary to perform a selective pyridyl dechlorination reaction in the presence of an isoxazole ring, which are themselves known to be generally labile under reductive conditions. A search of the literature revealed no relevant precedent for this selective reduction. Indeed, more than 40 reductive reactions (hydrogenations, silyl hydride, transition metal reductions, magnesium reductions, etc.) were investigated, but most resulted in concomitant chloropyridyl reduction and cleavage of the isoxazole N−O bond. The only conditions that were found to be successful for this transformation were Zn/AcOH. Addition of water (10%v/v) to the reaction mixture accelerated the reaction significantly, and furthermore, addition of a small quantity of MeOH (0.5% v/v) was then required to ensure complete conversion to the product **1** (Scheme 6). On removal of the halogen, the product precipitated from the reaction mixture. In this case, it was possible to isolate the product by filtration of the reaction mixture due to significantly faster filtration times vs that seen with **2**. This material was sufficiently pure that it did not require any further treatment.

Conclusions

This contribution highlights the synthesis and subsequent scale up of two potent β-3 agonists to multihundred gram scale. A simple method to convert a keto-acid to its corresponding tertiary alcohol, without the need for protection was applied for the synthesis of **21**. Chemistry was developed for the very mild dechlorination of a pyridine ring in the presence of a sensitive isoxazole ring. A further feature of this work was the selection of a late-stage common intermediate which provided for an efficient synthesis of both target molecules.

Experimental Section

General. All starting materials are available commercially or described in the literature. Flash column chromatography was carried out using Merck silica gel 60 (9385) using either standard glass, Biotage, or ISCO columns. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 plates (5729). Melting points were determined using a Gallenkamp MPD350 apparatus and are uncorrected. ^{1}H NMR was carried out using either of the following instruments: Varian-Unity Inova 400 MHz NMR spectrometer, Varian Mercury 400 MHz NMR spectrometer, Varion Oxford 300 MHz or a Bruker Ultrashield Plus 400 MHz spectrometer. ^{13}C NMR was carried out using a Bruker Ultrashield spectrometer at 100.5 MHz. Mass spectroscopy was performed using a Finnigan Navigator single quadrupole electrospray mass spectrometer or a Finnigan aQa APCI mass spectrometer.

IR was carried out using a ThermoNicolet Avatar 360 FTIR spectrometer. Optical rotation was performed using a Perkin-Elmer Polarimeter 341. Combustion analyses were performed by Exeter Analytical (U.K.) Limited, Uxbridge, and Middlesex, U.K., or Warwick Analytical Service, University of Warwick Science Park, The Venture Centre, Sir William Lyons Road, Coventry CV4 7EZ, U.K.

***tert*-Butyl [2-(4-bromophenyl)-1,1-dimethylethyl]carbamate (4).** Triethylamine (3.82 g, 37.80 mmol) was added to a stirred suspension of the amine **3** (10.0 g, 37.80 mmol) in 2-MeTHF (115 mL) and the mixture cooled with the aid of an ice bath for 10 min. Di-*tert*-butyl dicarbonate (9.90 g, 45.40 mmol) dissolved in 2-MeTHF (15 mL) was added and the suspension stirred for 18 h at room temperature. The mixture was diluted with water (100 mL) and ethyl acetate (50 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (50 mL), and the combined organic extracts were washed with 5% aqueous citric acid (100 mL), dried over $MgSO_4$, and evaporated *in vacuo* to leave a pale-brown oil. Heptane (30 mL) was then added and the resulting solid collected by filtration and dried to give the title compound **4** (11.33 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (s, 6H), 1.44 (s, 9H), 2.92 (s, 2H), 4.19 (br s, 1H), 6.98 (br d, J = 8.2 Hz, 2H), 7.36 (br d, J = 8.2 Hz, 2H); LRMS *m*/*z* (ES^+) 272, 274 [MH − isobutylene$^+$]; Found: C, 54.70; H, 6.75; N, 4.20. $C_{15}H_{22}BrNO_2$ requires C, 54.85; H, 6.70; N, 4.25%.

Ethyl (4-{2-[(*tert*-Butoxycarbonyl)amino]-2-methylpropyl}phenyl)acetate (5). A suspension of anhydrous K_3PO_4 (77.6 g, 0.37 mol) in toluene (250 mL) was degassed and purged with N_2. The bromide **4** (20.0 g, 60.90 mmol), palladium(II) acetate (684 mg, 3.05 mmol), 2-(di-*tert*butylphosphino)biphenyl (1.82 g, 6.09 mmol), and ethyl acetoacetate (18.2 g, 140.00 mmol) were then added, and the mixture was degassed and purged with N_2. The reaction mixture was heated at 100 °C overnight with vigorous stirring and then cooled to room temperature. The mixture was filtered through arbocel and the cake washed with ethyl acetate (200 mL). The filtrate was evaporated *in vacuo*, azeotroped with ethyl acetate (2× 200 mL), and then redissolved in ethyl acetate (700 mL). The organic solution was washed with water (2× 400 mL) and brine (400 mL) and dried over $MgSO_4$ and evaporated *in vacuo* to give a brown oil (22.5 g).

Purification by flash column chromatography on silica (400 g) eluting with ethyl acetate/heptane (1:5) gave the title compound **5** as an orange oil (13.37 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.24 (m, 9H), 1.45 (s, 9H), 2.95 (q, 2H), 3.57 (m, 2H), 4.12 (q, J = 7.2 Hz, 2H), 4.24 (br s, 1H), 7.09 (br d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H); LRMS *m*/*z* (ES^+) 280 [MH − isobutylene$^+$]; Found: C, 67.95; H, 8.73; N, 4.05. $C_{19}H_{29}NO_4$ requires C, 67.97; H, 8.65, N, 4.17%.

Ethyl [4-(2-Amino-2-methylpropyl)phenyl]acetate (6). HCl (4 M) in dioxane (30 mL) was added to a stirred solution of the ester **5** (3.75 g, 11.18 mmol) in ethanol (30 mL) and the mixture stirred at room temperature overnight. The reaction mixture was evaporated *in vacuo* and 10% aqueous potassium carbonate added until the pH of the mixture reached 8. The mixture was extracted with ethyl acetate (3× 150 mL), and the combined extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give the title compound **6** as a yellow oil (2.72 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.10 (s, 6H), 1.24 (t, J = 7.2 Hz, 3H) 2.64 (s, 2H), 3.58 (s, 2H), 4.16 (q, J = 7.2 Hz, 2H), 7.15 (br d, J = 8.2 Hz, 2H), 7.22 (br d, J = 8.2 Hz, 2H); LC/MS R_t = 0.73 min, *m*/*z* (ES^+) 236 [MH^+].

Ethyl[4-(2-{[(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(6-chloropyridin-3-yl)ethyl]amino}-2-methylpropyl)phenyl]acetate (8). Anhydrous potassium carbonate (7.34 g, 53.10 mmol) was added to a stirred mixture of the ester **6** (4.17 g, 17.71 mmol) and the tosylate[5] **7** (7.83 g, 17.71 mmol) in propionitrile (85 mL). Potassium iodide (2.94 g, 17.71 mmol) was then added and the mixture heated at 110 °C with stirring for 18 h. The cooled reaction mixture was evaporated *in vacuo* and water added. The aqueous material was extracted with ethyl acetate (3× 300 mL), and the combined organic extracts were dried over $MgSO_4$ and evaporated *in vacuo* to give an orange oil (16.0 g). Purification by flash column chromatography on the ISCO system, (120 g cartridge), eluting with heptane/ethyl acetate (8:2) to (1:1) gave the title compound **8** as a yellow oil (2.83 g, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: −0.13 (s, 3H), 0.03 (s, 3H), 0.84 (s, 9H), 0.97 (s, 3H), 1.02 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H), 2.56−2.68 (m, 3H), 2.81 (dd, J = 11.3 and 7.4 Hz, 1H,) 3.57 (s, 2H), 4.16 (q, J = 7.2 Hz, 2H), 4.75 (dd, J = 7.4 and 4.3 Hz, 1H), 7.05 (br d, J = 8.2 Hz, 2H), 7.17 (br d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.2 Hz, 1H), 7.64 (dd, J = 8.2 and 2.3 Hz, 1H), 8.36 (d, J = 2.3 Hz, 1H); LC/MS R_t = 1.27 min, *m*/*z* (ES^+) 505 [MH^+]; Found: C, 64.15; H, 8.10; N, 5.55; Cl, 7.05. $C_{27}H_{41}ClN_2O_3Si$ requires C, 63.65; H, 8.30; N, 5.90; Cl, 6.90%.

Ethyl4-(2-{[(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-pyridin-3-ylethyl]amino}-2-methylpropyl)phenyl]acetate (9). Sodium acetate (1.27 g, 15.50 mmol) was added to a solution of chloro compound **8** (2.70 g, 5.30 mmol) in ethanol (40 mL). Palladium (5 %) on carbon (250 mg) was then added and the mixture hydrogenated at 40 psi at 40 °C overnight. The reaction mixture was cooled and filtered on arbocel. The ethanolic filtrate was evaporated *in vacuo* and water added. The aqueous suspension was extracted with ethyl acetate (3× 100 mL), and the combined extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give a yellow oil (2.60 g).

Purification by flash column chromatography on the ISCO system (330 g cartridge), eluting with heptane/ethyl acetate (1:1) to ethyl acetate/methanol/0.88 ammonia (95:5:0.5) gave the title compound **9** as a colourless oil (1.85 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: −0.15 (s, 3H), 0.02 (s, 3H), 0.83 (s, 9H), 1.01 (s, 3H), 1.04 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H), 2.58−2.74 (m, 3H), 2.84 (dd, J = 11.1 and 8.0 Hz, 1H), 3.56 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 4.79 (dd, J = 8.0 and 4.1 Hz, 1H), 7.09 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H), 7.22−7.26 (m, 1H), 7.67 (d, J = 7.8 Hz, 1H), 8.51 (m, 1H), 8.58 (d, J = 7.8 Hz, 1H); LC/MS R_t = 1.14 min, *m*/*z* (ES^+) 471 [MH^+]; Found: C, 68.25; H, 9.05; N, 5.85. $C_{27}H_{42}N_2OSi\cdot 0.25H_2O$ requires C, 68.15; H, 8.95; N, 5.90%).

[4-(2-{[(2*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-pyridin-3-ylethyl]amino}-2-methylpropyl)phenyl]acetate Lithium Salt (10). Aqueous lithium hydroxide solution (1M, 7.65 mL, 7.65 mmol) was added to a stirred solution of the ester **9** (1.80 g,

3.80 mmol) in 1:1 THF:ethanol (20 mL) at room temperature and the mixture stirred for 18 h. The reaction mixture was evaporated *in vacuo* to give a white solid which was dissolved in ethyl acetate and filtered through an Isolute phase separation cartridge to give the title compound **10** as a white solid (1.67 g, 100%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: −0.12 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 0.89 (s, 3H), 0.93 (s, 3H), 2.63−2.69 (br m, 1H), 2.75−2.82 (br m, 1H), 3.11 (s, 2H), 3.30 (s, 2H), 4.79 (m, 1H), 6.93 (d, J = 8.2 Hz, 2H), 7.06 (d, J = 8.2 Hz, 2H), 7.35 (m, 1H), 7.75 (m, 1H), 8.46 (m, 1H), 8.56 (m, 1H); LRMS m/z (ES$^+$) 441 [M − H]$^-$.

2-[4-(2-{[(2*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-pyridin-3-ylethyl]amino}-2-methylpropyl)phenyl]-*N*-(5-methylisoxazol-3-yl)acetamide (11). A stirred solution of the carboxylic acid lithium salt **10** (380 mg, 0.85 mmol) in THF (10 mL) was treated with 4 M HCl in dioxane (0.21 mL, 0.85 mmol) and the reaction mixture stirred at room temperature for 2 min. 1,1′-Carbonyldiimidazole (343 mg, 2.12 mmol) was added and the mixture stirred at room temperature for 1 h. 3-Amino-5-methylisoxazole (91 mg, 2.96 mmol) was then added and the reaction mixture heated at 45 °C (internal temperature) for approximately 60 h. The cooled mixture was poured into sat. aqueous sodium bicarbonate (100 mL) and extracted with ethyl acetate (3× 75 mL). The combined extracts were dried over $MgSO_4$ and evaporated *in vacuo* to give a yellow oil (712 mg). Purification by flash column chromatography on the ISCO system, (80 g cartridge), eluting with dichloromethane to dichloromethane/methanol/0.88 ammonia (95:5:0.5) gave a colourless oil. The oil was then azeotroped with toluene (3× 20 mL) and ethyl acetate (2× 20 mL) to give the title compound **11** as a colourless glass (277 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: −0.16 (s, 3H), 0.01 (s, 3H), 0.83 (s, 9H), 0.99 (s, 3H), 1.03 (s, 3H), 2.39 (s, 3H), 2.66 (m, 3H), 2.84 (m, 1H), 3.72 (s, 2H), 4.74 (m, 1H), 6.73 (s, 1H), 7.13 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 7.65 (m, 1H), 8.52 (m, 1H), 8.55 (s, 1H), 8.80 (br s, 1H); LRMS m/z (ES$^+$) = 523 [MH$^+$].

2-[4-(2-{[(2*R*)-2-Hydroxy-2-pyridin-3-ylethyl]amino}-2-methylpropyl)phenyl]-*N*-(5-methylisoxazol-3-yl)acetamide Dihydrochloride (1). A stirred solution of the amide **11** (270 mg, 0.52 mmol) in dioxane (7 mL) was treated with 4 M HCl in dioxane (7 mL) and the mixture stirred overnight at room temperature. The resulting white suspension was evaporated *in vacuo* and azeotroped with toluene (3× 30 mL). The white solid was triturated with diethyl ether (20 mL) and excess solvent removed with the aid of a pipet. Evaporation *in vacuo* gave the title compound **1** as a white solid (215 mg, 87%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.19 (s, 6H), 2.31 (s, 3H), 2.97 (s, 2H), 3.21 (m, 1H), 3.38 (m, 1H), 3.62 (s, 2H), 5.21 (m, 1H), 6.55 (s, 1H), 7.15 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 8.00 (m, 1H), 8.57 (m, 1H), 8.82 (m, 1H), 8.93 (s, 1H); LRMS m/z (ES$^+$) 409 [MH$^+$].

A portion of this salt was partitioned between sat. sodium bicarbonate and ethyl acetate to provide a sample of the free base. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.90 (s, 3H), 0.92 (s, 3H), 2.34 (s, 3H), 2.52 (s, 2H), 2.72 (m, 2H), 3.61 (s, 2H), 4.59 (m, 1H), 5.40 (br s, 1H), 6.59 (s, 1H), 7.06 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.2 Hz, 2H), 7.32 (m, 1H), 7.74 (m, 1H), 8.42 (m, 1H), 8.55 (m, 1H), 11.10 (s, 1H); LRMS m/z (ES$^+$) 409 [MH$^+$]; Found: C, 66.47; H, 6.74; N, 13.38 $C_{23}H_{28}N_4O_3 \cdot 0.5H_2O$ requires C, 66.19; H, 6.95; N, 13.43%.

(2*R*)-2-Hydroxy-2-pyridin-2-ylethyl 4-methylbenzenesulfonate (13). To a stirred solution of (1*R*)-1-pyridin-2-ylethane-1,2-diol **12** (1.50 g, 10.78 mmol) in dichloromethane (50 mL) was added triethylamine (2.25 mL, 16.20 mmol) followed by 4-toluenesulphonyl chloride (2.26 g, 11.90 mmol) and the mixture stirred at room temperature for 20 h. The reaction was diluted with dichloromethane (50 mL), washed successively with water (50 mL) and brine (50 mL), dried over $MgSO_4$, and evaporated *in vacuo* to give a brown oil. Purification by flash column chromatography on silica (150 g) eluting with diethyl ether gave the title compound **13** as a slightly coloured oil which slowly crystallised on standing (1.50 g, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.43 (s, 3H), 4.23 (m, 2H), 4.94 (t, J = 7.1 Hz, 1H), 7.24 (m, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.36 (d, 7.4 Hz, 1H), 7.71 (m, 1H), 7.74 (d, J = 8.1 Hz, 2H), 8.51 (d, J = 7.1 Hz, 1H); LRMS m/z (ES$^+$) 294 [MH$^+$].

(2*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-pyridin-2-ylethyl 4-Methylbenzenesulfonate (14). To a stirred solution of the tosylate **13** (1.62 g, 5.52 mmol) in DMF (15 mL) was added imidazole (751 mg, 11.00 mmol) followed by TBS-Cl (1.08 g, 7.15 mmol) and the mixture stirred at room temperature for 3 days. The reaction was diluted with diethyl ether (100 mL), washed with water (100 mL) and brine (50 mL), dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica (200 g) eluting with 10−20% ethyl acetate/pentane to give the title compound **14** as a clear oil (2.24 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: −0.02 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 2.44 (s, 3H), 4.05 (m, 1H), 4.27 (m, 1H), 5.02 (m, 1H), 7.19 (m, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 7.4 Hz, 1H), 7.69 (m, 1H), 7.72 (d, J = 8.1 Hz, 2H), 8.45 (d, J = 7.1 Hz, 1H); LRMS m/z (ES$^+$) 408 [MH$^+$].

Ethyl[4-(2-{[(2*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-pyridin-2-ylethyl]amino}-2-methylpropyl)phenyl]acetate (15). To a stirred solution of the tosylate **14** (1.65 g, 4.05 mmol) in propionitrile (10 mL) was added potassium iodide (0.67 g, 4.05 mmol) followed by potassium carbonate (2.80 g, 20.20 mmol) and finally the ester 6 (0.95 g, 4.05 mmol) in propionitrile (5 mL). The mixture was heated under reflux for 43 h and cooled, and the solvent was removed *in vacuo*. The residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with brine (20 mL), dried over $MgSO_4$, and evaporated *in vacuo* to give a brown oil (2 g). Purification by flash column chromatography on silica (50 g) eluting with diethyl ether containing 0.2% diethylamine gave the title compound **15** as a yellow oil (0.89 g, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.00 (s, 3H) 0.13 (s, 3H) 0.95 (s, 9H), 1.05 (s, 3H), 1.07 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H) 2.68 (m, 2H) 2.98 (m, 2H) 3.65 (s, 2H) 4.23 (q, J = 7.1 Hz, 2H) 4.97 (m, 1H) 7.16 (d, J = 8.1 Hz, 2H) 7.20−7.25 (m, 3H) 7.57 (d, J = 7.4 Hz, 1H) 7.76 (m, 1H) 8.59 (d, J = 7.1 Hz, 1H); LRMS m/z (ES$^+$) 471 [MH$^+$].

[4-(2-{[(2*S*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-pyridin-2-ylethyl]amino}-2-methylpropyl)phenyl]acetic Acid, Lithium Salt (16). To a stirred solution of the ester **15** (0.96 g, 2.05 mmol) in 1:1 THF/ethanol (10 mL) was added lithium

hydroxide (49 mg, 2.05 mmol) as a solution in water (5 mL) and the homogeneous mixture stirred for 3 days. The solvent was removed *in vacuo* and the residue azeotroped successively with toluene and ethyl acetate to give the title compound **16** as an amorphous off-white solid (0.89 g, 96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: −0.01 (s, 3H), 0.11 (s, 3H), 0.92 (s, 9H), 0.97 (s, 3H), 0.99 (s, 3H), 2.90 (m, 2H), 3.21 (s, 2H), 3.38 (s, 2H), 4.84 (m, 1H), 6.99 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 7.34 (m, 1H), 7.53 (d, J = 7.4 Hz, 1H), 7.88 (m, 1H), 8.55 (d, J = 7.1 Hz, 1H); LRMS m/z (ES$^+$) 443 [MH$^+$].

2-[4-(2-{[(2*S*)-2-Hydroxy-2-pyridin-2-ylethyl]amino}-2-methylpropyl)phenyl]-*N*-(5-methylisoxazol-3-yl)acetamide (2). To a stirred solution of the carboxylic acid lithium salt **16** (50 mg, 0.11 mmol) in DMF (2 mL) was added 4 M HCl in dioxane (28 μL, 0.11 mmol). 3-Amino-5-methylisoxazole (11 mg, 0.11 mmol) was then added followed by di-isopropylethylamine (23 μL, 0.11 mmol) and HBTU (50.4 mg, 0.13 mmol). The mixture was stirred for 3 days at room temperature, diluted with water (50 mL), and extracted with ethyl acetate (2× 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica (10 g), eluting with 50% ethyl acetate/pentane to give the intermediate silyl ether. This was dissolved in THF (2 mL), and tetra-*n*-butylammonium fluoride trihydrate (88 mg, 0.28 mmol) was added as a solution in THF (2 mL). The reaction mixture was then stirred overnight at room temperature. Saturated aqueous sodium bicarbonate was added and the mixture stirred rapidly for 10 min. The mixture was diluted with ethyl acetate (10 mL), and the layers were separated. The aqueous layer was re-extracted with ethyl acetate (10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica (5 g) eluting with 95:5:0.5 dichloromethane/methanol/0.88 ammonia to give the title compound **2** as a white solid (11 mg, 25%) after azeotrope with dichloromethane (2× 10 mL). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.09 (s, 6H) 2.36 (s, 3H) 2.73 (s, 2H) 2.91 (m, 1H) 3.15 (m, 1H) 3.70 (s, 2H) 4.78 (m, 1H) 6.68 (s, 1H) 7.12−7.20 (m, 5H) 7.45 (d, J = 8.1 Hz, 1H) 7.67 (m, 1H) 7.95 (br s, 1H) 8.45 (d, J = 7.1 Hz, 1H); LRMS m/z (ES$^+$) 409 [MH$^+$].

Methyl(4-bromophenyl)acetate (18). 4-Bromophenylacetic acid **17** (404.0 g, 1.80 mol) was dissolved in methanol (2 L), and the mixture was cooled using an ice bath to 0 °C. To this mixture was added, under N_2, acetyl chloride (16.0 mL, 0.23 mol) dropwise very slowly, over a period of 30 min (no exotherm observed). The mixture was stirred at 0 °C for approximately 1 h, allowed to warm to room temperature, and stirred at this temperature for 16 h. Methanol was then removed *in vacuo*, and the residue was dissolved in TBME (1.5 L), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title compound **18** as a clear, orange oil (432 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.58 (s, 2H), 3.70 (s, 3H), 7.17 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H); LRMS m/z (ES$^+$) 229, 231 [MH$^+$].

Methyl[4-(2-oxopropyl)phenyl]acetate (19). To a solution of the bromide **18** (200.0 g, 0.87 mol) in anhydrous toluene (2 L) was added tributyltin methoxide (302 mL, 1.05 mol), isopropenyl acetate (144 mL, 1.31 mol), and tri(*o*-tolyl) phosphine (5.32 g, 17.50 mmol). The reaction mixture was evacuated and purged with nitrogen 4 times before adding palladium acetate (1.96 g, 8.73 mmol). The mixture was stirred under N_2 at 100 °C (internal temperature) for 7 h and then treated with an aqueous 4 M potassium fluoride solution (1 L) and stirred for 1.5 h. The black suspension was filtered through a pad of arbocel topped with a layer of silica and washed through with toluene. The filtrate and washings were concentrated *in vacuo to* 2 L and placed in a separating funnel, and the organic layer was washed with water (1.5 L). The organic layer was dried over Na_2SO_4 and evaporated *in vacuo* to afford a dark-orange oil. The residue was partitioned between acetonitrile (1.5 L) and heptane (1 L). The layers were separated, and the acetonitrile phase was further washed with heptane (2 × 1 L). The acetonitrile solution was then evaporated *in vacuo* to give the title compound **19** as an orange oil (178 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.15 (s, 3H), 3.62 (s, 2H), 3.69 (s, 2H), 3.70 (s, 3H), 7.16 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H); LRMS m/z (ES$^+$) 207 [MH$^+$].

[4-(2-Oxopropyl)phenyl]acetic Acid (20). The ester **19** (178 g, 0.86 mol) was dissolved in THF (890 mL) and the solution cooled to −5 °C using an ice−acetone bath. To this reaction mixture was added dropwise aqueous 2 M lithium hydroxide solution (475 mL), over a period of 45 min. After the addition was complete, the reaction mixture was left to stir at around 0 °C for approximately 2 h. The reaction mixture was concentrated *in vacuo* to afford a creamy solid which was azeotroped with toluene (3 × 200 mL). Acetonitrile was added (5 mL/g), and mixture was left to stir overnight. The resulting solid was collected by filtration, washed with acetonitrile, and dried to afford a white powder. The powder was partitioned between ethyl acetate (900 mL) and 1 M HCl (900 mL), making sure the aqueous phase was strongly acidic. The organic solution was dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound **20** as a cream-colored solid (148.2 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.16 (s, 3H), 3.65 (s, 2H), 3.69 (s, 2H), 7.18 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H); LRMS m/z (ES$^+$) = 191 [M − H]$^-$.

[4-(2-Hydroxy-2-methylpropyl)phenyl]acetic Acid (21). In a 5 L three-necked flask fitted with an overhead stirrer was added THF (500 mL) under an N_2 atmosphere. Methyl magnesium bromide [3 M solution in diethyl ether (406 mL, 1.22 mol)] was then added, and the mixture was cooled to 8 °C using an ice bath. A solution of **20** [78.0 g, 0.41 mol in THF (500 mL)] was added dropwise over 2.5 h, keeping the reaction temperature between 8 and 13 °C. As the addition proceeded, the reaction mixture thickened, necessitating the addition of an additional amount of THF (500 mL). After the addition was complete, the reaction was allowed to warm to room temperature. After 3 h the reaction mixture was cooled to 5 °C using an ice bath before quenching cautiously with dropwise addition of water (40 mL). After effervescence was no longer observed, 2 M HCl (700 mL) was added to the system portionwise followed by ethyl acetate (1 L). The mixture was stirred for 10 min and transferred to a separating funnel (5 L). The organic layer was washed with brine (2 × 700 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford a light-brown solid. TBME (∼550 mL) was added to the solid which was

stirred for approximately 1 h. The suspension was filtered and the resulting solid dried to afford the title compound **21** as an off-white powder (61.4 g, 73%). ^{1}H NMR (400 MHz, acetone-d_6) δ: 1.15 (s, 6H), 2.72 (s, 2H), 3.58 (s, 2H), 7.20−7.21 (m, 4H); LC/MS R_t = 2.54 min, *m/z* (ES$^+$) 207 [M − H]$^-$.

2-[4-(2-Hydroxy-2-methylpropyl)phenyl]-*N*-(5-methylisoxazol-3-yl)acetamide (22). To a suspension of the carboxylic acid **21** (1.50 kg, 7.21 mol) in ethyl acetate (7.5 L) was added 1,1′-carbonyldiimidazole (1.22 kg, 7.49 mol) portionwise and the reaction mixture stirred at 25−30 °C for 15 min. 3-Amino-5-methylisoxazole (>98% purity,[7] 1.41 kg, 14.41 mol) was then added in one portion and the reaction mixture stirred at 50−55 °C for 36 h. The mixture was diluted with methyl ethyl ketone (7.5 L) and then washed successively with water (7.5 L) and aqueous 1 M citric acid (2× 7.5 L). The organic liquors were reduced *in vacuo* to approximately 7.5 L, water (7.5 L) was added, and the organic solvent was removed *in vacuo*. The resulting thick aqueous slurry was granulated at 10 °C for 2 h and the resulting solid collected by filtration and dried first under vacuum at room temperature and then under vacuum at 45 °C to give the title compound **22** as a pale-yellow solid (1.67 kg, 80%). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.03 (s, 6H), 2.33 (s, 3H), 2.60 (s, 2H), 3.60 (s, 2H), 4.23 (s, 1H), 6.58 (s, 1H), 7.11−7.14 (d, J = 8.1 Hz, 2H), 7.16−7.19 (d, J = 8.1 Hz, 2H), 11.04 (br s, 1H); ^{13}C NMR (100.5 MHz, CDCl3) δ: 12.69, 29.23, 43.69, 49.33, 70.83, 96.64, 129.25, 131.13, 132.02, 137.18, 158.32, 169.50, 170.04; LC/MS R_t = 7.99 min, *m/z* (ES$^+$) 289 [MH]$^+$.

2-Chloro-*N*-[1,1-dimethyl-2-(4-{2-[(5-methylisoxazol-3-yl)amino]-2-oxoethyl}phenyl)ethyl]acetamide (23). To a solution of chloroacetonitrile (477.7 g, 4.33 mol) in TFA (6 L) was added the alcohol **22** (1.66 kg, 5.75 mol) portionwise over 10 min. The dark red/brown solution was heated at 50 °C (jacket temperature) for 2.5 h. The reaction solution was distilled under reduced pressure removing 3.5 L of solvent, s-butanol (2 L) was added and a further 3 L solvent distilled off under reduced pressure. Further s-butanol (2 L) was added to the mixture, the solution was cooled to 10 °C over 1 h and the resulting thick slurry granulated overnight. The slurry was filtered under reduced pressure and the filter cake washed with s-butanol (1 L). The cake was dried under vacuum at 25 °C for 2 h, then the temperature raised to 45 °C overnight. The title compound **23** was isolated as an off-white crystalline solid (1.74 kg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.37 (s, 6H), 2.39 (s, 3H), 3.03 (s, 2H), 3.74 (s, 2H), 3.94 (s, 2H), 6.23 (s, 1H), 6.74 (s, 1H), 7.11−7.13 (d, J = 8.1 Hz, 2H), 7.26−7.28 (d, J = 8.1 Hz, 2H), 9.56 (s, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 12.69, 26.88, 43.04, 43.62, 44.75, 54.63, 96.67, 129.22, 130.98, 132.31, 136.57, 158.42, 165.39, 169.50, 170.01; LC/MS R_t = 2.60 min, *m/z* (ES$^+$) 364 [MH]$^+$.

2-[4-(2-Amino-2-methylpropyl)phenyl]-*N*-(5-methylisoxazol-3-yl)acetamide (24). The amide **23** (1.73 kg, 4.75 mol) was added in one portion to a stirred solution of thiourea (369.2 g, 4.85 mol) in acetic acid (575.3 g, 9.50 mol) and methanol (8.65 L). The reaction mixture was heated under reflux for approximately 22 h and filtered, and the resulting cake was washed with methanol (1 L). The mother liquors were evaporated *in vacuo*, and 2-MeTHF (6 L) was added. The resulting slurry was treated with 2-MeTHF (8 L) followed by a 1:1 solution of 0.88 ammonia in water (5 L). The organic layer was washed successively with 1:1 0.88 ammonia in water (2 × 5 L) and brine (2 L). The organic solution was then evaporated to dryness *in vacuo* and suspended in isopropyl acetate (4 L) to give a thick slurry. The slurry was warmed to reflux and cooled to 5 °C over 3 h. Heptane (1 L) was added and the resulting solid collected by filtration and dried under vacuum at 45 °C overnight to give the title compound **24** (1.11 kg, 81%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.95 (s, 6H), 2.33 (s, 3H), 2.52 (s, 2H), 3.61 (s, 2H), 6.58 (s, 1H), 7.10−7.12 (d, J = 8.1 Hz, 2H), 7.18−7.21 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 12.68, 30.38, 43.60, 50.12, 50.70, 96.72, 129.03, 130.96, 132.00, 137.64, 158.51, 169.65, 169.93; LC/MS R_t = 5.51 min (ES$^+$) *m/z* 288 [MH]$^+$.

2-Chloro-1-pyridin-2yl-ethanone (27). A solution of isopropyl magnesium chloride in THF (2 M, 174 mL, 0.35 mol) was charged via a cannula to a three-neck round-bottom flask. A solution of 2-bromopyridine **26** (50 g, 0.32 mol) in THF (100 mL) was added dropwise over 45 min to the solution of isopropyl magnesium chloride. The reaction mixture was stirred at room temperature overnight and then cooled down to −25 °C, and a solution of **34** (45.7 g, 0.33 mol) in THF (120 mL) was added dropwise over 45 min. The reaction mixture was then was allowed to warm up to 0 °C and stirred for 3 h. Water (500 mL) was then added carefully followed by acetic acid (200 mL) to pH 7, and the reaction mixture was extracted with TBME (200 mL). The aqueous layer was collected and back extracted with TBME (3× 200 mL). The organic layers were combined, washed with brine (2 × 200 mL), dried over Na_2SO_4, filtered, and evaporated to dryness to afford a brown oil. The oil was purified by flash column chromatography (400 g) eluting with heptane/TBME/triethylamine (90:10:0.2) to give the title compound **27** as a pale-yellow solid (35.9 g, 73%).

A second batch was prepared starting from 60 g of 2-bromopyridine **25** following the exact same procedure. The two resulting batches were combined to give the title compound **27** as a pale-yellow solid (78.6 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.11 (s, 2H), 7.52 (m, 1H), 7.87 (m, 1H), 8.09 (d, J = 7.4 Hz, 1H), 8.65 (d, J = 7.1 Hz, 1H).

(1*R*)-2-Chloro-1-pyridin-2-ylethanol (28). The catalyst for the reaction was freshly prepared by mixing together in solution in DMF (200 mL), di-μ-chlorobis [(*p*-cymene)chlororuthenium(II)] (25.7 g, 42.96 mmol), (1*S*,2*S*)-(+)-*N*-(4-toluenesulphonyl)-1,2-ethane diamine 30.8 g, 84.04 mmol) and triethylamine (12.0 mL, 86.09 mmol). The mixture was stirred at room temperature under nitrogen for 1 h. In parallel, a mixture of formic acid/triethylamine 5:2 [(520.0 mL, 13.76 mol):(780.0 mL, 5.59 mol)] was prepared. To this formic acid/triethylamine solution was added **27** (433.0 g, 2.78 mol) dissolved in tBME (5. 0 L). The preformed catalyst solution was then added to tBME solution and the reaction mixture stirred at room temperature for 12 h. Water (3.0 L) was added over 10 min and the effervescent solution stirred for a further 40 min. The reaction mixture was separated and the organic phase washed with brine solution (20%, 1 L) and evaporated to dryness to afford a black oil (430.0 g). Purification by flash column chromatography (biotage 150 L, 5k g silica) eluting with ethyl

acetate/heptane 7:3 gave the title compound **28** as brown oil, which solidified on standing (332.97 g, 76%,). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.82 (m, 2H), 4.40 (br s, 1H), 4.98 (d, J = 3.2 Hz, 1H), 7.25 (d, J = 7.4 Hz, 1H), 7.42 (d, J = 7.4 Hz, 1H), 7.73 (m, 1H), 8.55 (d, J = 7.2 Hz, 1H); Chiral HPLC (96.4% ee).

2-[(2*R*)-Oxiran-2-yl]pyridine (29). To the solution of the chlorohydrin **28** (48 g, 0.31 mol) in 2-MeTHF (300 mL) was added a solution of 4 N sodium hydroxide (300 mL, 1.22 mol) and the reaction mixture stirred at room temperature for 40 min. The reaction mixture was diluted with water (300 mL) and extracted with 2-MeTHF (2× 300 mL). The combined extracts were washed with brine (100 mL), dried over $MgSO_4$, and evaporated to dryness to afford the title compound **29** as a brown oil (38 g, 100%). ^{1}H NMR (400 MHz, CDCl3) δ: 2.92 (m, 1H), 3.16 (m, 1H), 4.00 (m, 1H), 7.22 (d, J = 7.4 Hz, 2H), 7.66 (m, 1H), 8.54 (d, J = 7.1 Hz, 1H).

2-Chloro-1-(6-chloropyridine-3-yl)ethanone (31). A solution of 5-bromo-2-chloropyridine **30** (500.0 g, 2.60 mol) in TBME (7.50 L) was cooled to −75 °C. Butyllithium in THF (2.5M, 1.14 L, 2.86 mol) was then added to the resulting white precipitate over 1 h whilst maintaining the temperature below −65 °C. **34** (375.28 g, 2.73 mol) in TBME (2.00 L) was then added to the orange suspension over 1 h whilst maintaining the temperature below −65 °C. The reaction was warmed to −5 °C over 1 h, and acetic acid (446.6 mL, 7.79 mol) in TBME (500 mL) was added in a single portion, causing an exotherm to 2 °C. The solution was stirred for 10 min, and water (5 L) was added in one portion. The biphasic solution was stirred for 20 min, and the organic phase was washed with water (1 L) and concentrated to a dark oil. The resulting product was azeotroped with toluene (2 × 2.5 L) to yield the title compound **31** as a beige solid (495.0 g, 100%) which was used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.63 (s, 2H), 7.49 (dd, J = 8.4 and 0.8 Hz, 1H), 8.22 (dd, J = 8.4 and 2.5 Hz, 1H), 8.95 (dd, J = 2.5 and 0.8 Hz, 1H).

(2*R*)-Chloro-1-(6-chloropyridin-3-yl)ethanol (32). Triethylamine (10.7 g, 105.3 mmol) was added over approximately 5 min to a mixture of di-μ-chloro-bis[(*p*-cymene)chlororuthenium(II)] (9.7 grams, 15.8 mmol) and (1*S*,2*S*)-(+)-*N*-*p*-tosyl-1,2-diphenylethylenediamine (11.6 g, 31.6 mmol) in DMF (250 mL) and the resulting mixture stirred vigorously for 30 min at room temperature. Formic acid (605.5 g, 13.2 mol) was added very slowly to rapidly stirred triethylamine (532.5 g, 5.3 mol) at room temperature whilst controlling the exotherm to below 45 °C and off-gassing. The ketone **31** (500.0 g, 2.6 mol) in TBME (1.50 L) was then treated with the activated Ru complex over 5 min followed by slow addition of the salt complex. The reaction mixture was then stirred at room temperature for 3.5 h. Water (500 mL) was added over 10 min, and the effervescent solution was stirred for a further 40 min. The reaction mixture was partitioned between water (500 mL) and TBME (500 mL), and the aqueous phase was extracted with dichloromethane (2 × 1.5 L). The organic layers were combined and concentrated to a black oil (720.0 g). Purification by flash column chromatography on silica (5 kg) using 40% TBME in heptanes gave the title compound **32** as a beige solid (357.0 g, 74% ee). A further quantity of the ketone **31** (200.0 g, 1.05 mol) was subjected to the same reaction under identical reaction conditions, workup, and initial chromatography conditions to give more of the title compound **32** (153.0 g, 74% ee). Both batches of **32** (510.0 g) were purified by preparative chiral chromatography[13] to give the title compound **32** (295.0 g, 42%, 99.6% ee) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.68 (m, 3H), 4.98 (m, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.74 (dd, J = 8.2 and 2.3 Hz, 1H), 8.37 (d, J = 2.3 Hz, 1H); LRMS m/z (ES^+) 192 $[MH]^+$.

2-Chloro-5-[(2*R*)-oxiran-2-yl]pyridine (33). A stirred solution of the chlorohydrin **32** (385.0 g, 2.00 mol) in 2-MeTHF (1.92 L) was treated with 5 M sodium hydroxide (2.0 L, 10.00 mol) in a single portion and the mixture stirred vigourously for 30 min. The two phases were separated, and the organic layer was washed with brine (500 mL). The organic solution was dried over $MgSO_4$ and evaporated *in vacuo* to give the title compound **33** (287.5 g, 92%) as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.79 (m, 1H), 3.19 (m, 1H), 3.88 (m, 1H), 7.30 (d, J = 8.2 Hz, 1H), 7.50 (dd, J = 8.2 and 2.3 Hz, 1H), 8.35 (d, J = 2.3 Hz, 1H); LRMS m/z (ES^+) 156, 158 $[MH]^+$.

2-[4-(2-{[(2*S*)-2-Hydroxy-2-pyridin-2-ylethyl]amino}-2-methylpropyl)phenyl]-*N*-(5-methylisoxazol-3-yl)acetamide (2). A suspension of the amine **24** (209.0 g, 0.73 mol) in water (4.2 L) was treated with the epoxide **29** (92.5 g, 0.76 mol) and the reaction mixture stirred at 70 °C for 5 h. A second quantity of the epoxide **29** (17.0 g, 0.20 mol) was then added, and the reaction mixture was stirred at 70 °C for a further 12 h. Water (2 L) was added to the pale-brown, thick suspension obtained, and this was extracted with warm (40 °C) ethyl acetate/methanol (4:1, 3 L). The aqueous layer was extracted a second time with warm ethyl acetate/methanol (4:1, 1 L). The combined organic extracts were washed with brine (500 mL) and evaporated to dryness to afford a pale-brown solid. The solid was recrystallised from DMSO/water (3:1, 7 L), and the resulting white solid was collected by filtration and dried to give the title compound **2** (142.0 g, 48%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.92 (s, 6H), 2.35 (s, 3H), 2.56 (s, 2H), 2.72 (m, 1H), 2.92 (m, 1H), 3.62 (s, 2H), 4.60 (d, J = 3.2 Hz, 1H), 5.40 (br s, 1H), 6.60 (s, 1H), 7.07 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 7.23 (m, 1H), 7.50 (d, J = 7.4 Hz, 1H), 7.76 (m, 1H), 8.46 (d, J = 7.2 Hz, 1H), 11.10 (s, 1H).

A small sample of the compound (175 mg) was recrystallised from aqueous ethanol (5 mL) to give the title compound **2** (109 mg, 62%, 100% ee) as a white crystalline solid, mp 204−205 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.90 (s, 6H), 2.33 (s, 3H), 2.52 (s, 2H), 2.69 (m, 1H), 2.90 (m, 1H), 3.60 (s, 2H), 4.57 (br s, 1H), 5.36 (br s, 1H), 6.57 (s, 1H), 7.05 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 7.21 (m, 1H), 7.48 (d, J = 7.4 Hz, 1H), 7.74 (m, 1H), 8.45 (d, J = 7.1 Hz, 1H), 11.05 (br s, 1H); LC/MS m/z (ES^+) 409 $[MH]^+$; $[\alpha]^{25}_D$ [c = 0.108 g/100 mL in MeOH/DCM (3:2)] = −29.26° (589 nm); Found: C, 67.55; H, 6.85; N, 13.70. $C_{23}H_{28}N_4O_3$ requires C, 67.63; H, 6.91, N, 13.72%.

(13) Preparative system 1: Varian SD-2 prepstar, Column: Chiralpak-AS-H, 75 mm × 500 mm, 20 μ. 80:20 heptane/IPA at 118 mL/min, 19 min, injection volume/amount: 12 mL at approx. 50 mg/mL crude, injected mass of ~0.90 g (injection pump at 36 mL/min for 20 s), collection: timed, observation at 210 nm and 254 nm). Enantiomers elute at 7.5 and 8.8 min.

2-[4-(2-{[(2*R*)-2-(6-Chloropyridin-3-yl)-2-hydroxyethyl]-amino}-2-methylpropyl)phenyl]-*N*-(5-methylisoxazol-3-yl)acetamide (37). To a solution of epoxide **33** (50.0 g, 161.00 mmol) in methanol (600 mL) at room temperature was added the amine **24** (46.5 g, 170.00 mmol) and the reaction heated under reflux for 48 h. The reaction was cooled to room temperature and the resulting white solid collected by filtration. Recrystallisation from methanol gave the title compound **37** as a white solid (61.6 g, 86%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.89 (s, 3H), 0.90 (s, 3H), 1.38 (br s, 1H), 2.34 (m, 3H), 2.53 (m, 2H), 2.72 (m, 2H), 3.61 (s, 2H), 4.61 (m, 1H), 5.50 (m, 1H), 6.59 (s, 1H), 7.05 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 7.43 (s, 1H), 7.80 (m, 1H), 8.37 (d, J = 7.1 Hz, 1H), 11.10 (s, 1H); LR/MS m/z (ES$^+$) 443 [MH]$^+$.

2-[4-(2-{[(2*R*)-2-(6-Chloropyridin-3-yl)-2-hydroxyethyl]-amino}-2-methylpropyl)phenyl]-*N*-(5-methylisoxazol-3-yl)acetamide (1). The chloropyridine **37** (60.0 g, 0.14 mol) was dissolved in acetic acid (glacial, 500 mL). On complete dissolution, water (50 mL) was added to the solution followed by methanol (2.5 mL). To this solution was added zinc powder (55.2 g, 0.84 mol) and the reaction stirred vigorously for 6 h. Filtration of the reaction mixture to remove the Zn, followed by addition of ammonia (100 mL, SSG = 0.880) led to precipitation of the target compound **1**. The reaction was filtered to collect the product, with no need for purification (55.1 g, 93%, 99.6% ee) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.90 (s, 3H), 0.92 (s, 3H), 2.34 (s, 3H), 2.55 (m, 2H), 2.72 (m, 2H), 3.61 (s, 2H), 4.59 (m, 1H), 5.40 (br s, 1H), 6.59 (s, 1H), 7.06 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 7.32 (m, 1H), 7.74 (m, 1H), 8.42 (m, 1H), 8.55 (d, J = 7.1 Hz, 1H), 11.10 (s, 1H); ^{13}C NMR (100.5 MHz, DMSO-d_6) δ: 12.0, 26.5, 26.7, 42.1, 46.0, 49.7, 52.5, 70.5, 96.2, 123.1, 228.4, 130.3, 132.6, 133.7, 136.9, 139.7, 147.7, 148.0, 158.2, 169.4 LR/MS m/z (ES$^+$) 409 [MH]$^+$; FTIR (ν_{max} cm^{-1}) 720, 790, 925, 1070, 1430, 1485, 1625, 1710.

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